Daniel Mathieu (Ed.)

Handbook on Hyperbaric Medicine

Springer

HANDBOOK ON HYPERBARIC MEDICINE

ЗНАНИЕ

Handbook on Hyperbaric Medicine

Edited by

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Springer

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FOREWORD

The Co-operation On Science and Technology (COST) programme is a European initiative with the objective of implementing and improving cooperation between European research teams in the fields of Science and Technology. Thanks to the efforts of our Belgian colleagues, a specific Action was launched in December 1998 – specifically devoted to Hyperbaric Oxygen Therapy (Action COST B14). The participants included nineteen European countries, members, or associates of the European Union. The main objectives of COST B14 were to expand the knowledge-base for the rational use of HBO; to issue guidelines for the implementation and development of clinical HBO centres; and to provide scientifically sound recommendations for HBO in the treatment of various diseases and conditions.

This Action has since been completed and the Management Committee decided to publish this Handbook to introduce the outcome of COST B14 as well as to incorporate the results of experimental and clinical research performed over the last 6 years. This Handbook is intended as a reference document for researchers and clinicians alike – to be used both in the research laboratory and in everyday hyperbaric clinical practice; it also provides support material for teachers and will assist students in obtaining European Committee for Hyperbaric Medicine (ECHM) level II and III qualifications in hyperbaric medicine.

Contributors to this handbook have to be thanked for their enthusiasm and efforts. We also wish to express our gratitude to our English reviewers, Martin Hamilton-Farell and Frans Cronje; to Audrey Degeldere for her excellent secretarial work; to Springer for its great assistance; and to the COST secretariat for their strong and continuous support of our efforts.

The Management Committee considers this Handbook both a reference and benchmark – the culmination of the COST B14 action. We hope this Handbook will be welcomed and avidly used by the international scientific community.

Prof D. Mathieu
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Hyperbaric Oxygen Therapy

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PREFACE

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On the second day of my surgical residency in the end of 1968, under professor Boerema in the "Wilhelmina Gasthuis" in Amsterdam, I found myself in the hyperbaric chamber, supervising the treatment of a patient with gas gangrene.

When I witnessed the sudden awakening of a very serious victim of carbon monoxide poisoning, in the middle of the night two nights later, I was definitively won over to the side of Hyperbaric Medicine.

These, together with palliative surgical procedures in small children (until 1972), were practically the only indications we had at that time.

The role of hyperbaric oxygen was investigated in many different diseases, and also experimentally; but these three were the most successful clinical indications (besides decompression illness and gas emboli).

A lot has changed since then. Many supposed indications have come and disappeared again; a few have stayed and proved to be successful, and new indications have been found. The situation in Europe was that every physician with a chamber at his or her disposal treated the indications he or she believed in and had experience with. Every four, and subsequently three, years we gathered at the hospital or university of one of our colleagues and discussed what we had done in the previous years. This was established as the International Congress on Hyperbaric Medicine (ICHM) in 1963. A great deal of scientific and clinical work was done; and the Proceedings of these Congresses are witness thereof. If you take the opportunity to read these books carefully, you will be surprised by the good scientific work that was done in those days. It is a pity that much of it has been forgotten or duplicated in later years.

An example of the thoroughness of the work is that in almost every animal experiment a control group was included; this, unfortunately, was lacking in most clinical series. The reason was that "experience-based" and

"consensus-based" medicine were the rule rather than the exception. Many of the young investigators who presented their work later became giants in their respective medical fields.

This is the reason that the International Congress on Hyperbaric Medicine is looking for funds to reprint these old Proceedings.

The Undersea Medical Society (UMS later the UHMS, Undersea and Hyperbaric Medical Society, established in 1967) was the first society that selected a Hyperbaric Oxygen Therapy Committee, to identify and classify the various clinical indications on the basis of the scientific evidence that existed. The first Committee Report was published in 1977 and many followed in later years. Gradually, over the years, the insurance companies took these reports as a guide for payment for the treatment of patients with the recommended indications.

The situation in Europe at that time was that we followed more or less the indications from the UHMS Committee Report. The contacts between the different hyperbaric centres were rare and restricted to the occasional symposium or congress.

Contacts with the Soviet Union and the far east were, if they existed, extremely rare. Also the different languages were a big problem (Russian and Chinese for example).

An example of this is the Proceedings of the VIIth International Congress on Hyperbaric Medicine, held in Moscow in 1981, which were published in 1983 completely in Russian without any translation.

This situation changed in 1989 when the necessity of founding a committee, with the goal of raising the quality and profile of Hyperbaric Medicine, emerged during an informal discussion in Milan. The three editors of this new book were all present on that occasion, as was the author of this Preface.

The first informal meeting took place in November 1989; and this date can be considered the initiation of the European Committee for Hyperbaric Medicine (ECHM).

The first Plenary Meeting with all diving and hyperbaric representatives from the different European countries took place in Amsterdam in August 1990, during the Joint Meeting on Diving and Hyperbaric Medicine (of the International Congress, the Undersea and Hyperbaric Medical Society, and the European Undersea and Biomedical Society, EUBS).

The official founding of the ECHM took place again in Milan, in 1991.

The goals for the Committee were defined as:

1). Studying and defining common indications for hyperbaric therapy; research and therapy protocols; common standards for therapeutic and technical procedures; equipment and personnel; cost-benefit and cost-effectiveness criteria.

2). Acting as a representative body for the European Health Authorities of the European Union (EU) in Brussels (Belgium).
3). Promoting further cooperation among existing scientific organisations involved in the field of Diving and Hyperbaric Medicine (for instance the European Undersea Biomedical, later Baromedical, Society, which was originally established in 1965).

The most important mission of the ECHM was to define European Standards for Hyperbaric Medicine practice regarding indications, patient care and quality assurance, equipment and quality control, personnel and training policies and research.

This all was very much in line and at the same time as the rise of the Evidence-Based Medicine (EBM) movement (in Canada) and the Cochrane Library for meta-analyses of randomised trials, and the weighing and determining of the evidence.

This was not an easy task for many of us, as experienced clinicians with many years of clinical practice behind us. We had to get used to another way of looking at our results and a different way of planning of our clinical scientific work. This no longer included retrospective studies or retrospectively studied large cohorts of treated patients, but rather inclined towards prospective, randomised, placebo-controlled and blinded trials, the so-called randomised controlled trials (RCT's), which were considered the 'gold standard'.

In some indications, where we already had large clinical experience and we had already treated many patients, trials were considered unethical; and gradually it became clear that extensive experience was also evidence, but less convincing than the RCT 's.

I think we struggled and succeeded well with these changes; and we showed that Hyperbaric Medicine is a modern and effective therapeutic modality, judged by the standards of 2005. Of course things can always be done better; and we must strive continuously to determine the best evidence. We have that in common with many other medical specialists, some of whom have not made as much progress as us.

We started our work on indications (among many other matters) in 1991; and we organised the "First European Consensus Conference on Hyperbaric Medicine" in Lille (France) in September 1994.

A list of indications, accepted in most countries in Europe, was judged by an independent Jury, applying the rules of evidence-based medicine.

This list proved to be very important because the practitioners of Hyperbaric Medicine in Europe now had a European list of approved indications for their own clarity and to discuss with the various insurance companies for treatment reimbursement. Moreover we had decided together for which indications more evidence was needed before we could accept

them (indicating more study); and, not the least important, we had defined what were not indications for hyperbaric oxygen treatment.

This work on indications is still going on with regular Symposia, Workshops and Consensus Conferences (the latest in Lille again, in December 2004).

As a result of this work, a Handbook on Hyperbaric Medicine was published by Springer in 1996 under the editorial supervision of Giorgio Oriani from Milan (Italy), Alessandro Marroni from Roseto degli Abruzzi (Italy) and Francis Wattel from Lille (France). This was the first comprehensive book that appeared in Europe on hyperbaric medicine, a major achievement. Besides the physiology and patho-physiology of oxygen and hyperbaric oxygen, the various clinical indications were described. Also, organisational aspects of hyperbaric therapy, and the treatment of diving accidents, were reviewed. A view to the future, and possible future indications, were given in the stimulating section 'New Frontiers'. One of the innovations which made us proud was that so many different doctors and scientific investigators from so many European countries worked together so harmoniously. Naturally, this book sold out rather quickly. The plans for a new and updated European Handbook were quickly made, but the execution of this plan took some time. Fortunately, about five years ago, the COST B14 action was started. Sponsored by the European Union, many hyperbaric specialists were able to meet in various cities of Europe, discussing and developing protocols for treatment and for scientific investigations in the field of Hyperbaric Medicine. In presenting and discussing the results of this action with the authorities, it became soon clear that we were offered the possibility of writing and publishing a book on Hyperbaric Medicine.

It is the great merit of Daniel Mathieu (President-elect of the ECHM) and Francis Wattel (past President) that they realized immediately the possibilities that were offered here.

In the framework of the COST action, however, it was necessary to publish the book in August/September of this year, 2005. The authors of the various chapters had to be colleagues who had taken part in the COST action's work.

Without any hesitation, the editors of this book started working; selecting authors, encouraging them, setting deadlines for contributions and doing all the work necessary for the writing of the manuscript.

Looking at the content of the book nothing has been done in haste. We find well considered contributions in a logical order to set out and explain the whole field of Hyperbaric Medicine.

Part One starts with the physical and patho-physiological bases of hyperbaric oxygen therapy under the trusted editorial guidance of Martin Hamilton-Farell, Beatrice Ratzenhofer-Komenda and Juha Niinikoski from Finland. Contributions on the physics of increased pressure and on the influence of hyperbaric oxygen on DNA and DNA-repair are present.

Part Two describes the various recommended, optional and controversial indications. This is mainly the result of all the work done for the Lille Consensus Meeting. Editors are Daniel Mathieu, together with Jörg Schmutz from Switzerland and Frans Cronje from South Africa, all experienced clinicians and investigators from the outset of the era of modern hyperbaric medicine.

The 50 pages devoted to controversial and non-indications do not represent so much the importance of these indications, but more the thoroughness with which the authors have studied and weighed the evidence and drawn their conclusions.

It is extremely important to know what not to treat and on what basis of evidence. The lack of this in the past has caused us a lot of trouble and problems with fellow scientists and clinicians, and also the health authorities in some countries.

Part Three is devoted to the practice of hyperbaric oxygen (HBO) therapy. Jacek Kot from Poland, Armin Kemmer from Germany and Peter Germonpre from Belgium write and edit contributions on chamber building and equipment, the organisation of a centre, selection of patients for treatment and monitoring them in the hyperbaric chamber, training of personnel, safety in the hyperbaric environment and the economic aspects of HBO, aspects which are often misunderstood or underestimated, complications, research in HBO and the organisation of Hyperbaric Medicine in Europe at this moment.

The publication of this new Handbook on Hyperbaric Medicine is indeed again a major achievement and another highlight in the history of the European Committee for Hyperbaric Medicine. The editors and the contributors can be congratulated with all their work in writing this book.

I sincerely hope that this book will be disseminated initially all over Europe, but also that it reaches colleagues in other parts of the world. I trust that it will be carefully studied and followed in the directions that it offers.

If anything changes (science is always moving ahead), the European Committee will address it in a future Symposium, Workshop or Consensus Conference and in cooperation with our sister organisations.

Let this first edition be sold out very quickly.

A HISTORY OF HYPERBARIC MEDICINE

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1. A HISTORICAL OVERVIEW

Hyperbaric Medicine goes back a long way, since its history derives from the history of diving which dates back to ancient times.

The history of Hyperbaric Medicine has been closely linked with the development of technology for underwater activities and the advance in knowledge about the physical laws and physiological mechanisms of breathing oxygen at pressures above atmospheric pressure.

Three periods can be distinguished:

a time for discoveries: from the Renaissance to the Age of Enlightenment;

a time for hyperbaric therapy: from the middle of the 19th century to the beginning of the 20th century;

the practice of Hyperbaric Medicine on a scientific basis: since the second half of the 20th century.

1.1 A time for discoveries

Science and technical knowledge flourished from the very beginning of the Renaissance.

These are the main areas of scientific progress: in 1644 Torricelli invents the barometric tube; in 1653 Pascal confirms the variation of barometric pressure with altitude and establishes the laws of hydrostatics; Boyle (1661) and Mariotte (1676) both state the law relating the volume and pressure of

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 1–11.

an ideal gas; in 1755 Black discovers carbon dioxide; in 1775 Priestley discovers oxygen; and in 1789 Lavoisier describes oxidation phenomena.

Diving activities had been limited to snorkelling, restricted in time by the duration of apnoea and in space by poor underwater vision. However, from the 16th century onwards, an enormous variety of ideas and projects flourished, such as a breathing tube between diver and surface, which was taken up by Leonardo da Vinci and, after some changes, by Borelli. In 1690 Edmund Halley suggested a system with a diving bell where the air was changed by means of a leather pipe using the air contained in weighted barrels sunk to the seabed. In London, at about the same time (1662), Henshaw was the first to think of using atmospheric pressure as a therapeutic modality. Denis Papin suggested using bellows to inject fresh air continuously into the diving bell. In 1791, Smeaton, an English engineer in charge of repairing bridge piers in Hexham, had the first chamber built in cast steel and fed it with compressed air from a pump on a boat. This 18th century-derived pressure chamber is still in use nowadays. During the same period, Fréminet developed a full-pressure suit and helmet with compressed air supplied through a pipe from bellows on the surface.

1.2 A time for hyperbaric therapy

The therapeutic use of hyperbaric oxygen (HBO) grew in France between the middle of the 19th and the beginning of the 20th centuries. In 1834, Junod described the beneficial effects of high-pressure oxygen on man. Pravaz in Lyon, and Tabarie in Montpellier, both described the positive effects of immersion in compressed air for various ailments. In 1876, Fontaine had a mobile operating theatre built which Péan used for 27 operations. From 1860 onwards, an amazing number of centres were opened in Europe (Amsterdam, Baden-Baden, Brussels, Haarlem, London, Malvern, Milan, Moscow, Munich, Odessa, Stockholm, Vienna, among others); and the first chamber was built in Canada, at Ashawa. The largest was built in 1927 in Cleveland, USA, by Cunningham. This was 6 storeys high and comprised 72 rooms. It was a failure because patients were not selected on proper scientific or clinical grounds.

Among all the people with an influence on the history of hyperbaric medicine, the most famous is certainly Paul Bert. His work “La Pression Barométrique” (1878) is universally known and is one of the foundations of Hyperbaric Medicine. He studied the effects HBO, discovered its toxic effects on living organisms and insisted on the risk of convulsions. He concluded that to avoid harmful effects, oxygen should not be inhaled at a concentration above 60% at 1 ata. The toxic effect of oxygen on the nervous system was later to be named “Paul Bert effect”. Shortly afterwards, Lorrain Smith in Edinburgh described the effects of oxygen on the lungs. At around

the same time, in 1895, Haldane was carrying out an experiment on the effects of carbon monoxide on oxygen tension, recommending as a result the use of HBO for the treatment of carbon monoxide poisoning.

1.3 Practicing Hyperbaric Medicine on a scientific basis

1.3.1 Over recent decades, progress has taken many directions

The increased number of experiments on the animal model, for instance, has brought about an improved understanding of the effects and physiological consequences of HBO: its capacity to increase oxygen delivery to the tissues, its effects on vascularisation and on anaerobic bacteria, its activity as a means of defence against infection and its contribution to wound healing.

The indications for HBO have been determined more precisely, as much for critical conditions as for long-term or chronic disease, and listing only those which have been validated by clinically controlled research following the criteria of Evidence Based Medicine (EBM).

There has been emphasis on increased safety and improved care for patients in hyperbaric chambers, including those who are critically ill and requiring continuous intensive care.

Lastly, the necessary means of education have been brought into play to promote the development of Hyperbaric Medicine as a speciality.

Looking back, progress has not been linear: the 1950's marked the pioneering decade. During the next 20 years, Hyperbaric Medicine underwent an intense phase of development: over 60 indications were listed. Between 1980 and 1994, there was a phase during which the usefulness of HBO underwent doubt and suspicion. The last decade (1994 - 2004) has been a phase of rigorous scientific.

Who's who in the development of HBO?

The first real scientifically based therapeutic approaches were made by Boerema in Amsterdam (1959) in the field of cardiac surgery with the asystolic heart, and Brummelkamp (1961) in the increasingly frequent treatment of gas gangrene. Since then the contribution of the Dutch school has been central in research on infections causing soft tissue necrosis, and their treatment by HBO. Ledingham in Britain, and Jacobson in the USA, were also among the pioneers of HBO.

It is worth noting that in different countries physicians in various fields of medicine and surgery were intent from the start in making progress in Hyperbaric Medicine.

In France, following the suggestion of L. Barthélémy from the Toulon naval Medical Institute, intensivists were the first to introduce HBO.

M. Goulon, A. Larcan, J.M. Mantz, Ph. Ohresser, C. Voisin, L. Lareng and J. Ducailar contributed to determining the indications of HBO for critically ill patients.

In the United States, the influence of surgery can be found from the start, including G. Hart and M. Strauss (indications for HBO in traumatology and plastic surgery); J. C. Davis and T. K. Hunt (problem wounds and HBO) and R. E. Marx (mandibular osteonecrosis and HBO).

In Italy, it was mostly anaesthetists/intensivists who took charge of HBO from the start including A. Gasparetto, A. Gismondi, A. Sparachia and others. In Spain, Internal Medicine specialists initiated Hyperbaric Medicine, including J. Desola who has done excellent work in coordinating centres there.

Where research on diving accidents is concerned, it is mostly those countries with a strong tradition of diving for military purposes which have made the greatest contribution to establishing diving profiles and recompression tables. These tables have quickly been used for treating recreational diving accidents.

1.3.2 What are the reference institutions for Diving and Hyperbaric Medicine?

On the one hand, there are the national and European scientific societies; and on the other, there is the European Committee for Hyperbaric Medicine (ECHM).

- *The Scientific Societies*

Their duties are to promote knowledge in the fields of Diving and Hyperbaric Medicine, organize scientific meetings and annual conferences and publish study reports. Among the oldest are the “Société de Physiologie et de Médecine Sub-Aquatiques et Hyperbares de Langue Française” (MEDSUBHYP), along with the two Italian societies, one created by the National Society for Anaesthesia and Intensive Care (SIAARTI), and the other specifically geared towards Hyperbaric Medicine (SIMSI). German (GTUM) and Dutch (NVD) societies are more involved with Diving Medicine. The Swiss society (SUHMS) and the British Hyperbaric Association (BHA) are involved in both aspects, whereas in Spain this role is taken by the Coordination Committee of Hyperbaric Centres. However, before 1989 there was not much cohesion between the various European countries. There was also a lot of activity in communist Eastern Europe; but we did not know much about that since even the Proceedings of the Moscow meeting of the International College on Hyperbaric Medicine (ICHM) in 1981 appeared only in the Russian language.

The European Undersea Biomedical Society (EUBS) was founded in 1965. The main goal of the EUBS was diving and underwater medicine. In 1993, the EUBS changed its name to European Undersea and Baromedical

Society in order also to include clinical Hyperbaric Medicine. This meant the start of a very fruitful cooperation and even integration between Diving and Hyperbaric Medicine. The same developments were seen in the USA, where the Undersea Medical Society (UMS), founded in 1967, changed its name to the Undersea and Hyperbaric Medical Society (UHMS) in 1986.

- The ECHM

The European Committee is not a learned society but an organization for the promotion of Undersea and Hyperbaric Medicine on a European scale. It is recorded that "during an informal and friendly discussion between some distinguished gentlemen involved in Hyperbaric and Diving Medicine, the necessity of founding a committee to improve the level of quality and acknowledgement of Hyperbaric Medicine emerged in February 1989 in Milan, Italy". The next step was a first informal meeting between the above-mentioned gentlemen (the founding members) in Lille, in November of the same year. The founding members (D. J. Bakker, J. Desola, A. Marroni, D. Mathieu, G. Oriani, P. Pelaia, J. Schmütz, F. Wattel (elected President) and J. Wendling) decided to act as the Executive Board of the Committee. The first plenary meeting (with representatives of all European countries) was held in Amsterdam in August 1990. This occurred during a joint meeting between the ICHM, the UHMS and the EUBS, the first in history. The official founding, according to all necessary rules and regulations, of the European Committee took place in Milan in 1991.

The goals for the Committee were defined as:

- Studying and defining common indications for hyperbaric therapy, research and therapy protocols, common standards for therapeutic and technical procedures, equipment and personnel, cost-benefit and cost-effectiveness criteria.
- Acting as a representative body for the European health authorities of the European Community (EC) in Brussels (Belgium).
- Promoting further cooperation among existing scientific organisations involved in the field of Diving and Hyperbaric Medicine like Divers Alert Network (DAN); Confédération Mondiale des Activités Subaquatiques (CMAS); the European Diving Technical Committee (EDTC); the UHMS, which acts as an international society although it is American; the Japanese Undersea and Hyperbaric Medicine Society; the South Pacific Underwater Medical Society; and the South African Undersea and Hyperbaric Medical Society.

One of its main activities is the organization of European Consensus Conferences and Workshops. Four workshops and seven Consensus Conference have been organized over ten years. The last one took place in Lille in December 2004 in order to review all the documents and literature published since the first Conference in 1994. The ECHM list of accepted

indications was up-dated, and guidelines for organization, safety, education and research in Hyperbaric Medicine were issued, for the next 10 years.

2. STATE OF THE ART IN HYPERBARIC MEDICINE

The main aspects defining hyperbaric medicine today deal with indications, design and safety requirements for HBO chambers and medical equipment, staff training and continuing education requirements and research protocols.

2.1 Current justified indications for HBO

An agreement was reached on indications during the Consensus Conference which was held by the ECHM in Lille in September, 1994, and updated 10 years later in Lille in December, 2004. To be deemed acceptable, an indication had to be based on experimental and clinical studies carried out with strict methodology and producing significant positive results.

In fact, one of the ways of assessing the efficiency of HBO is by referring to the best data available from basic research, animal studies with control groups and human studies following EBM procedures. This approach involves: prospective, controlled, randomized clinical studies; quantified results; collection of results through the Cochrane collaboration; and meta-analysis of the various clinical studies.

The Jury issued its recommendations using a three-grade scale according to the strength with which each recommendation has been evaluated.

Type 1 - *Strongly Recommended:* the Jury considers the implementation of the recommendation of critical importance for final outcome for the patient/quality of practice/future specific knowledge.

Type 2 - *Recommended:* the Jury considers the implementation of the recommendation as positively affecting final outcome for the patient/quality of practice/future specific knowledge.

Type 3 - *Optional:* the Jury considers the implementation of the recommendation as optional.

The Jury also reported the level of evidence supporting the recommendations.

Level A - recommendation supported by level 1 evidence (at least 2 concordant, large, double-blind, controlled randomized studies with little or no methodological bias).

Level B - recommendation supported by level 2 evidence (double-blind controlled, randomized studies but with methodological flaws; studies with only small samples, or only a single study).

Level C - recommendation supported only by level 3 evidence (consensus opinion of experts).

Table 1. Accepted indications for HBO therapy (7th ECHM Consensus Conference, Lille, 2004)

CONDITION	ACCEPTED		
	Level of Evidence		
	A	B	C
Type I			
CO poisoning		X	
Crush syndrome		X	
Prevention of osteoradionecrosis after dental extraction		X	
Osteoradionecrosis (mandible)		X	
Soft tissue radionecrosis (cystitis)		X	
Decompression accident			X
Gas embolism			X
Anaerobic or mixed bacterial anaerobic infections			X
Type II			
Diabetic foot lesion		X	
Compromised skin graft and musculocutaneous flap			X
Osteoradionecrosis (other bones)			X
Radio-induced proctitis/enteritis			X
Radio-induced lesions of soft tissues			X
Surgery and implant in irradiated tissue (prophylaxis)			X
Sudden deafness			X
Ischemic ulcer			X
Refractory chronic osteomyelitis			X
Neuroblastoma Stage IV			X
Type III			
Post anoxic encephalopathy			X
Larynx radionecrosis			X
Radio-induced CNS lesion			X
Post-vascular procedure reperfusion syndrome			X
Limb reimplantation			X
Burns >20 % of surface area and 2nd degree			X
Acute ischemic ophthalmological disorders			X
Selected non-healing wounds secondary to inflammatory processes			X
Pneumatosis cystoides intestinalis			X

2.2 Hyperbaric equipment

Over the last decades, efforts regarding equipment have dwelt on **safety and reliability**. The rules and regulations enforced on manufacturers and users are stringent, particularly regarding fire hazards. Further progress has been made through the **medicalisation of chambers**: there is more room, and entry is made easier by rectangular doors. Nowadays, intensive care can be provided just as efficiently in a hyperbaric chamber as in an ICU.

- A therapeutic hyperbaric chamber shall be considered as a medical device according to the European Council Directive 93/42 “Medical Products”.
- The performance, testing and safety requirements of new therapeutic multiplace chamber systems shall conform with the new European norm prEN 14931 CEN TF 127. All new chambers will be CE marked. Existing chambers should strive to reach the same safety levels as required by that norm.
- Quality assurance should be implemented in hyperbaric centres.
- Approval of medical devices for hyperbaric use is a worldwide problem. With a few exceptions, there is a lack of CE marked medical devices for use in the hyperbaric chamber. A risk evaluation according to the European norm ISO 14971 should be performed before bringing medical equipment into the chamber. Publishing and sharing experience and information on risk analyses between European HBO centres are recommended. The manufacturers shall be encouraged to extend the CE approval of their medical devices for hyperbaric use.

The range of indications for HBO has led to the idea of **equipment functionality**. To avoid treating a patient in critical condition and an out-patient in the same chamber, it is useful to have a series of chambers linked together with airlocks. One chamber is kept for emergency and intensive care indications, another for programmed therapy of chronic diseases. Lastly, there are chambers with specific equipment for performing function testing for divers, hyperbaric workers or patients requiring HBO.
- The Jury strongly recommends that the European Code of Good Practice for Hyperbaric Oxygen Therapy (ECGP) be the minimum requirement to be fulfilled by European hyperbaric centres, as it was established by strong consensus between internationally recognized European experts.
- The operations must be conducted under standard operation procedures described in a specific manual. Each hyperbaric centre must develop emergency procedures in the same way. The staff must review these regularly, and should be trained in these procedures.

2.3 Staff training

2.3.1 Physicians

Medical professionals in Hyperbaric Medicine, whether physicians or paramedical staff, require specific training. Medical training in this field began over ten years ago in some European countries, but varying approaches were made regarding training contents, organization, duration, diplomas and their recognition.

Aware of this disparity, fruitful cooperation between the Training and Education Committee of the ECHM and the Medical Committee of the EDTC has led to the drawing up of a proposal for common objectives, which will provide guidelines for harmonizing training between the different countries in Europe, and which could gain official recognition. It is within the duties of the European College of Baromedicine to make this possible. Requirements include :

- a curriculum drawn up for different categories of hyperbaric personnel, describing the levels of competence according to profession,
- a core curriculum of modular teaching, applicable to all hyperbaric personnel (medical and non-medical),
- education based on a modular system obtainable in different teaching institutions throughout Europe, with mutual recognition of core standards, and with a system of credits based on minimum duration and emphasis of teaching elements. Entry criteria for the education of hyperbaric medical personnel will depend on the competency ultimately required for the professional category.
- the European College of Baromedicine, as supported by the ECHM, should provide validation and accreditation for education and training in European countries.

2.3.2 Paramedical staff

To this day, France, under the aegis of the Ministry of Work, is the only country where a certificate of capacity for working in hyperbaric conditions is compulsory for paramedical professionals. This certificate bears various indications depending on the person's profession, and different categories depending on the pressure authorized.

A programme for the education and training of non-medical hyperbaric personnel has now been developed by an association of non-medical professionals (for example EBASS) in collaboration with the ECHM.

2.4 Research

During recent decades, many studies have been carried out both on professional and recreational diving medicine. Oil exploitation in the North Sea has provided a stimulus to teams working in Aberdeen, NUTEC scientists in Trondheim and COMEX in Marseille. The world-wide development of recreational diving has generated an increase in the number of studies on diving capacities and therapy procedures for decompression accidents. In the meantime, there has been an increase in the number of fundamental and clinical studies, wherever possible prospective, controlled and multi-centre.

In 2001, updating the report J. Schmutz presented at the First Consensus Conference in Lille in 1994, D. Mathieu drew up a status report of research, by analyzing the Medline database for the years between 1996 and 2000. He reported that the mean annual number of publications remained constant, research teams were few, but their number remained the same; that there was a large proportion of experimental studies, but this was decreasing; and that there was a great increase in clinical research. He also noted the appearance of prospective, randomized, controlled and in some cases double-blind studies.

Comparing the type of publications referenced in the Medline database between 1996 and 2000 in the fields of Hyperbaric Medicine, Intensive Care and Surgery produced the following results: the number of publications varied between 1 and 20 with regard to Intensive Care, and between 1 and 300 with regard to Surgery. Clinical studies were about the same in the three fields; but the proportion of prospective randomized controlled studies, equal in Hyperbaric Medicine and Intensive Care, was half that amount in Surgery.

This leads us to the conclusion that hyperbaric physicians are developing high quality and pertinent clinical research.

As for research networks, it is to be noted that many studies are carried out by local teams in temporary collaboration with local laboratories. This explains why experimental studies are a majority; but it is in itself a handicap for clinical research because each centre will have only a few cases of the rarer diseases. The answer to this problem is the development of multi-centre research networks.

Still, the experimental research performed in the last few years has provided an understanding of the mechanical effects of HBO, offering new perspectives. These concern the ischemia-reperfusion phenomenon, and the effects of HBO on the leukocyte/endothelium interaction, inflammatory reactions, defence mechanisms against oxidization and apoptosis, as well as the impact of HBO on auto-immune diseases.

The Action B14 of the COST programme is an appropriate vehicle to promote clinical research in Hyperbaric Medicine. Launched in 1998, it involves 18 European countries. Its activities are based on working groups guided by a steering committee, led by D. Mathieu. Among other projects, methodology guidelines for research and a code of good practice for Hyperbaric Medicine have been developed. Various clinical research protocols involving multiple centres have been defined and initiated: sudden deafness, femoral head necrosis, diabetic foot lesions, glioblastoma radiosensitivity, bone regeneration in irradiated bones. A website “Oxynet” ensures coordination (www.oxynet.org).

3. CONCLUSION

On June 19th, 1997 a first careful attempt was done to compare the European Committee indications with those of the HBO Committee of the UHMS. Not only indications were discussed but also recommended protocols, pressures and threshold treatment levels. The conclusion was that similarities were far greater than differences, and that in the future the two tables should be harmonized. Conditions not on both lists were to be evaluated to resolve differences as soon as possible. It was also planned to include the levels of recommendation for the ECHM indications as in the HBO Therapy UHMS Committee Report. A joint meeting took place during the Annual Meeting of the UHMS in Sydney in 2004; but a lot more work is required, involving both the UHMS Committee and the ECHM .

At the beginning of the 3rd millennium, Hyperbaric Medicine appears to be a grown-up field of medicine world-wide with its own approved and accepted methods of evaluation of the efficacy and cost-effectiveness of therapy following EBM methods. For Hyperbaric Medicine to gain complete recognition as such, ethical and ecological considerations must be paramount in clinical practice, research and training. For this, imagination and creativity are more than ever a necessity.

PART I

PHYSICAL AND PATHOPHYSIOLOGICAL BASES OF HYPERBARIC OXYGEN THERAPY

Editors: B. Ratzenhofer-Komenda, J. Niinikoski,
M. Hamilton-Farell

Chapter 1.1

PHYSICS OF HYPERBARIC PRESSURE

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Abstract: Within the scope of this book, a review is presented regarding general characteristics of gases: constants, pressure and density, composition of air, and characteristics of oxygen, nitrogen and carbon dioxide as major components of air. Relevant information is given regarding the basic gas laws of Boyle and Amontons, the universal gas equation, the gas laws of Dalton and Henry and the laws of diffusion (Fick). In addition the principle of adiabatic processes (Joule-Thomson effect and adiabatic decompression) is described

Keywords: mol, molecular weight, Avogadro's number, Loschmidt's number, Avogadro's law, pressure, pressure unit, density, air, oxygen, nitrogen, carbon dioxide, Boyle's law, Boyle Mariotte law, Amontons' law, Graham's law, ideal gas law, universal gas equation, Dalton's law, partial pressure, fraction, Henry's law, Bunsen's solubility coefficient, diffusion, Fick's First Law of Diffusion, Fick's Second Law of Diffusion, adiabatic process, Joule-Thomson effect, adiabatic compression, adiabatic decompression

1. CHARACTERISTICS OF GASES

1.1 Basics

Molecular weight

1 *mole* of a substance (atoms, ions, molecules, or formula units) is defined as the molecular weight of the substance in *grams*, e.g. 1 mole of oxygen (O_2, molecular weight 32), weighs 32 grams.

Avogadro's number

Avogadro's number (6.022×10^{23}) is approximately the number of particles (atoms, ions, molecules, or formula units) contained in 1 mole of a

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 15–23.

substance. In German-speaking countries this constant is also known as *Loschmidt's* number.

Avogadro's law

Avogadro's law states that equal volumes of gases, at the same temperature and pressure, contain equal numbers of molecules. At standard conditions (0°C, 1.013bar) the volume of any gas is 22.42 l/mol.

1.2 Pressure

Pressure is the application of force to a surface, and the concentration of that force on a given area. A finger can be pressed against a wall without making any lasting impression; however, the same finger pushing a thumbtack can easily damage the wall, even though the applied force is the same, because the point concentrates that force on a smaller area. More formally, pressure (symbol: p or P) is the measure of the normal component of force that acts on a unit area.

Table 1.1-1. Pressure units

1 Pa	Pascal *(SI unit)*	=	1	Newton/m² (= N/m²)
1 kPa	Kilopascal *(SI unit)*	=	1,000	N/m²
1 MPa	Megapascal *(SI unit)*	=	1,000,000	N/m²
1 bar	bar *(accepted by SI)*	=	100,000	Pa
			100	kPa
			0.1	MPa
			750.06	mm Hg
			14.5	psi
1 atm 1 ata	physical atmosphere atmospheres absolute	=	1.013	bar
			760	mm Hg
			1.033	kp/cm² (= at)
			14.696	psi
			10.08	metres sea water
			33.07	feet sea water (= fsw)
			33.90	feet fresh water
1 mm Hg	millimetres of mercury	=	133.32	Pa
1 psi 1 psig	pounds per square inch psi gauge pressure	=	0.069	bar

In the literature different pressure units are mentioned even though there have been international agreements regarding standardized nomenclature for many years. Following this international standardization (SI) the units 'Pascal' [Pa], 'Kilopascal' [kPa] or 'Megapascal' [MPa] should be used (SI units), and the unit 'Bar' [bar] is accepted. Nevertheless in hyperbaric medicine you still will find old units (ata) or imperial units (psi, fsw). In many countries, mm Hg is still used for blood pressure and blood gases.

1.3 Density

Density (symbol: ρ = Greek letter 'rho') is a measure of mass per unit of volume. The higher an object's density, the higher is its mass per volume. The average density of an object equals its total mass divided by its total volume.

Practical relevance: Gas density (in addition to viscosity) is an important factor in the resistance to breathing different inspired gases.

Table 1.1-2. Density of different gases and air

Gas	**Density** at 0 °C and 101.3kPa [kg/m³]
helium (He)	0.17868
nitrogen (N_2)	1.25060
carbon dioxide (CO_2)	1.97690
oxygen (O_2)	1.42895
air (mixed gas)	1.29300

1.4 Air

Atmospheric air is a gaseous mixture consisting of different gases (see table below). In hyperbaric practice it is accurate enough to speak of air as a mixture of ~ 21% oxygen + ~ 79% nitrogen (including ~ 1% of the noble gas *argon*, which behaves similarly to nitrogen). The fraction of CO_2 is negligible. CO_2 is only important in expired gas, where the CO_2 fraction at atmospheric (= normobaric) pressure is ~ 4%.

Table 1.1-3. Components of air

Gas	**Vol. % in air**
nitrogen (N_2)	78.1
oxygen (O_2)	20.93
carbon dioxide (CO_2)	0.038 *(see above)*
argon (Ar)	0.93
neon (Ne)	0.0018
helium (He)	0.00053
krypton (Kr)	0.00011
hydrogen (H_2)	0.00005
xenon (Xe)	0.000008
ozone (O_3)	0.000002
water vapour (H_2O)	*(see below)*

Water vapour is a very variable component of air. At higher temperatures air may contain higher amounts of water vapour. The unit '% of relative humidity' is temperature dependent. Like all other gases in the air mixture water vapour produces a gas pressure (pH_2O). At 37°C and 100% of relative humidity (= 100% saturation with water vapour) pH_2O equals 47 mmHg.

1.4.1 Oxygen

Discovered by Joseph Priestley in 1774, oxygen at ambient temperature and pressure is a colourless, odourless and tasteless gas. It consists of a diatomic molecule with the chemical formula O_2, and molecular weight 32. Oxygen is a major component of air and is necessary for aerobic respiration. It is the second largest single component of the Earth's atmosphere (20.947% by volume). Due to its electronegativity, oxygen forms chemical bonds with almost all other elements (which is the original definition of oxidation). The only elements to escape the possibility of oxidation are a few of the noble gases. The most famous of these oxides is dihydrogen oxide, or water (H_2O). Oxygen promotes fire. For more details see later chapters.

1.4.2 Nitrogen

Discovered by Daniel Rutherford in 1772, nitrogen at ambient temperature and pressure is a colourless, odourless, tasteless and mostly unreactive (ie inert) diatomic non-metal gas. It consists of a diatomic molecule with the chemical formula N_2, and molecular weight 28. Nitrogen is the largest single component of the Earth's atmosphere (78.084% by volume). Nitrogen is nearly insoluble in water, which is important for bubble formation in supersaturated tissues in decompression sickness.

1.4.3 Carbon dioxide

First described by Baptist van Helmont in the 17^{th} century, carbon dioxide at ambient temperature and pressure is a colourless, odourless and tasteless gas, with molecular weight 44. CO_2 is a chemical compound with two double bounds (O=C=O). As it is fully oxidized, it is not very reactive and particularly inflammable. CO_2 is very soluble in water (0.145g CO_2 in 100g H_2O). When dissolved in water, about 1% of CO_2 turns into carbonic acid, which in turn dissociates partly to form bicarbonate and carbonate ions. In 2004, the worldwide atmospheric concentration of CO_2 was 0.038 %.

2. GAS LAWS

2.1 Boyle's Law

First described independently by Sir Robert Boyle (1627-1691) and Edme Mariotte (1620–1684), it is also called the 'Boyle-Mariotte Law':

'The product of pressure (p) and volume (V) in a confined amount of gas at equal temperature (T) remains constant.'

$$p \times V = const. \qquad for\ T = const.$$

For a confined amount of gas in two different states, we can say:

$$p_1 \times V_1 \quad = \quad p_2 \times V_2 \qquad for\ T = const.$$

where: $_1$ = state 1 of confined amount of gas
$_2$ = state 2 of confined amount of gas

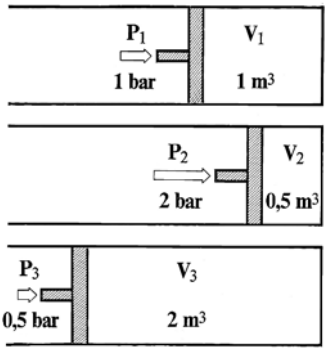

Figure 1.1-1. Principle of Boyle's law (Welslau, 2004)

Practical relevance: Inside hyperbaric chambers any confined gas volume in the human body and in (medical) equipment is subject to this law. In gas filled spaces with rigid walls, this effect has to be accommodated during compression to and decompression from higher pressures. This is most important between 1bar and 1.5bar (100kPa - 150kPa) where changes of pressure cause the biggest relative changes of volume.

2.2 Amontons' law

Discovered by Guillaume Amontons (1663-1705) and published in detail by Thomas Graham (1805–1869), it is also called 'Graham's Law'. In simple words, it states:

'The quotient of pressure (p) and temperature (T) in a confined amount of gas at equal volume (V) remains constant.'

$$\frac{p}{T} = const. \quad for\ V = const. \qquad or \qquad \frac{p_1}{T_1} = \frac{p_2}{T_2}$$

In the above formula, temperature is to be expressed in Kelvin [K]. The Kelvin scale starts at the lowest conceivable temperature (0K = -273°C) and has the same graduation as the Celsius centigrade scale. For conversion from Celsius centigrade [°C] to Kelvin [°K] you just have to add +273 (ie 273°K = 0°C, or 373° K = 100°C).

Practical relevance: During (rapid) compression the compressed gas inside a hyperbaric chamber warms up (see below under *adiabatic compression*). When the target pressure is reached and all valves have been closed, the compressed gas is slowly cooled down to ambient temperature by temperature exchange through the chamber wall. According to Amontons' Law, this is accompanied by a drop in pressure, for which a correction must be made in order to keep the pressure at therapeutic levels.

2.3 Ideal Gas Law

Besides the gas laws of Boyle and Amontons, there are a few more which unfortunately we can not explain here. However, in order to understand the principal relationship between temperature, pressure and volume of gases it is adequate to put the two explained laws together and build a simplified equation of the Ideal Gas Law, also known as Universal Gas Equation.

$$\frac{p \times V}{T} = const. \qquad \text{or} \qquad \frac{p_1 \times V_1}{T_1} = \frac{p_2 \times V_2}{T_2}$$

2.4 Dalton's Law

First described by John Dalton (1766–1844) in 1801, this gas law is also called '*Dalton's law of partial pressure'*. It states that:

> *'The total pressure exerted by a gaseous mixture is equal to the sum of the pressures that would be exerted by the gases if they alone were present and occupied the total volume.'*

$$P_{tot} = p_1 + p_2 + ... + p_n$$

where: $p_1, p_2, \ldots p_n$ represent the partial pressures of each component.

Each gas in a mixture acts as if the other gas was not present, the pressures that come from each gas can simply be added. *Dalton's* law allows calculating the partial pressure of each gas as follows:

'The partial pressure of a gas (p_1) equals the product of total pressure of the gaseous mixture (P_{tot}) and the fraction of the gas (F_1)'

$$p_1 = P_{tot} \times F_1$$

where: *Fraction (F)* is defined as a part of 1; i. e. in air F_{O_2} is 0.21.

Practical relevance: Gases which are non toxic when inhaled at ambient pressure in a certain percentage of a gaseous mixture *(Vol. %)* may become toxic when inhaled at elevated total pressure because the partial pressure, and not the percentage in a gaseous mixture, causes toxicity.

2.5 Henry's Law

First formulated by William Henry (1775-1836) in 1803 this law states:

'The mass of a gas (C) that dissolves in a defined volume of liquid is directly proportional to the pressure of the gas (P) (provided the gas does not react with the solvent)'.

$$\alpha \times \frac{p}{C} = const. \quad for\ T = const.$$

where: p = partial pressure of the gas above the liquid
C = concentration of the gas in the liquid
α = Bunsen's solubility coefficient (specific for gases and liquids)

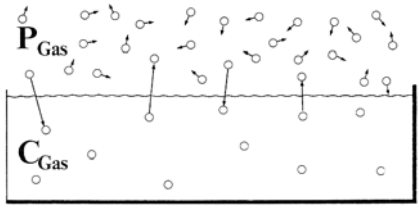

Figure 1.1-2. Principle of Henry's gas law (Welslau, 2004)

The solubility coefficient for gases in liquids α [millilitres of gas/atm/litre of fluid] described by Robert Wilhelm Bunsen (1811–1899) may also be expressed as *Henry's law constant (k)*. As a basic principle, the solubility of gases is greater in cold liquids.

Table 1.1-4. Bunsen's solubility coefficient α for different gases in water

Temp. [°C]	**Air**	**Oxygen**	**Nitrogen**	**Helium**	**Carbon dioxide**
0	29.2	48.9	23.5	9.5	35.4
5	25.7	42.9	20.9	9.2	31.5
10	22.8	38.0	18.6	9.0	28.2
15	20.6	34.2	16.9	8.8	25.4
20	18.7	31.0	15.5	8.7	23.2
25	17.1	28.3	14.3	8.5	21.4
30	15.6	26.1	13.4	8.4	20.0
35	14.8	24.4	12.6	8.3	18.8
40	14.1	23.1	11.8	8.3	17.6

Practical relevance: The pressure dependent solubility of inert gases (e.g. nitrogen) in body liquids and tissues is crucial for the development of decompression sickness (DCS) due to supersaturation of tissues in relation to reduced ambient pressure after exposure.

2.6 Gas diffusion

Fick's Laws of Diffusion were derived by Adolf Fick in 1858. Fick's First Law is used in steady state diffusion. This law gives rise to the formula below, which states the rate of diffusion of a gas across a membrane.

$$Rate\ of\ diffusion = \frac{K \times A \times \Delta P}{D}$$

where:
K = constant (determined by experiment, gas and temperature specific)
A = surface area over which diffusion is taking place
ΔP = difference of gas partial pressure on both sides of the membrane
D = distance over which diffusion takes place, ie membrane thickness

Practical relevance: At various places in the human body partial pressures (or concentrations) of dissolved gases, such as oxygen or nitrogen, depend on diffusion. According to Fick's First Law of Diffusion we can identify the variables for diffusion of gases as size of diffusion area, thickness of diffusion barrier (or distance), and differential gas partial pressure. According to Fick's Second Law of Diffusion, the time needed for diffusion is dependent on size of molecules, allowing smaller gas molecules like helium to diffuse faster than larger ones.

2.7 Adiabatic processes

Adiabatic processes happen without external heating or cooling. In Hyperbaric Medicine, the Joule-Thomson effect and adiabatic compression are of interest.

Joule-Thomson effect

'When letting a gas expand adiabatically (= without external heating), the gas will cool down.'

The Joule-Thomson effect was first described by James Prescott Joule (1818-1889) and Sir William Thomson (1824–1907). During adiabatic decompression, most gases at atmospheric pressure behave like this, the only gas which warms upon expansion under standard conditions being hydrogen.

Adiabatic compression

'When compressing a gas adiabatically (ie without external cooling), the gas will warm up.'

Adiabatic compression describes the opposite effect.

Practical relevance: During compression, the gas inside a hyperbaric chamber warms up. The faster the compression, the more the compressed gas will warm up. Compression of a hyperbaric chamber for treatment of DCS to 280kPa "as fast as possible" (e.g., according to US Navy treatment table 6) may lead to a temperature of 40°C or more. Rapid decompression has the opposite effect.

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Chapter 1.2

BIOCHEMISTRY OF OXYGEN

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Abstract: Oxygen was discovered by Joseph Priestly in 1772. Since then, the chemical characteristics of the molecule have been established, together with its physiological properties relative to the transport and the utilization of oxygen by the cells and tissues. The role of the oxygen free radical, which are toxic reactive species, is important to consider in the practice of hyperbaric oxygen therapy

Keywords: oxygen chemistry, respiratory chain, oxygen free radical, lipidperoxidation

1. HISTORY

It is to Joseph Priestley that one attributes the discovery of oxygen or more exactly the element of 'l'air vital' for the animal kingdom. In 1772, he discovered that the air in a closed chamber where candles had burned until extinction could be regenerated by growing plants inside. He also reported that an atmosphere in which mice had died was regenerated by plants. He had discovered that plants resupplied with oxygen an atmosphere in which a candle had burned or animals had breathed. Thus, Priestley had the genius to gather under the same concept the combustion of a candle and animal's breathing. In 1774 Priestley isolated a new gas from mercury (II) oxide, and called it "air déphlogistiqué", which was in fact oxygen.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 25–30.

2. CHEMISTRY OF OXYGEN

Physical properties	
Formula	O_2
Atomic number	Z = 8
Molar mass	31,999
Volumic mass	$1.429 kg.m^{-3}$
Boiling point	-182.97°C

Oxygen is the eighth element of the periodic table of elements. Its most wide-spread isotope is ^{16}O, which means that its nucleus is constituted by eight protons and eight neutrons. There are two other rare oxygen isotopes: ^{17}O and ^{18}O. Oxygen is a member of group VI according to the periodic table of the elements, which means that it possesses on its external electronic layer six electrons, which renders it avid for two supplementary electrons and explains its properties of electro-negativity. Like the other elemental gases as hydrogen or nitrogen, oxygen appears in the natural state as a molecule of dioxygen O_2 by pooling a pair of electrons between the 2 atoms of oxygen. Thus, the molecule of O_2 possesses a global electronic deficit of two electrons, which exists in form of two unpaired electrons under normal conditions (e.g., room temperature, normobaria, not irradiated). Oxygen usually reacts as a bi-radicals ($^{\bullet}O\text{-}O^{\bullet}$).

3. OXYGEN, THE KEY ELEMENT OF LIVING CELLS

3.1 Transport of oxygen

In normoxic conditions, oxygen is transported to tissues combined with hemoglobin. The biochemistry of this binding has been closely studied; and it is well-known that O_2/CO_2 exchange in both muscle and lung is the result of the differential properties of O_2 and CO_2 binding to hemoglobin under the influence of the surrounding chemistry. This differential affinity of hemoglobin for O_2 and CO_2, ensuring O_2/CO_2 exchange, is responsible for the vital cycle. In fact, under hyperbaric oxygen, hemoglobin being oxygen-saturated, it is as dissolved gas that the extra oxygen reaches tissues.

3.2 Oxygen use

The ultimate consumption of the oxygen is realized within the mitochondrion which is the intracellular organelle responsible for oxidation of end-products of energy substrates (Figure 1.2-1).

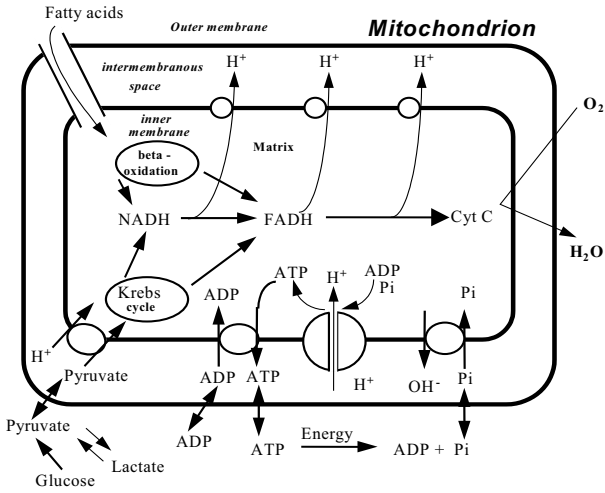

Figure 1.2-1. The mitochondrial respiratory chain and pathways of intermediary metabolism

Indeed, 90% of the oxygen is consumed in the mitochondrion. End-products of energetical substances originating from lipids, carbohydrates and proteins enter the mitochodrion. These substrates, after passing the Krebs' cycle, furnish the carriers (NADH, $FADH_2$) which shuttle electrons and protons to the respiratory chain of the inner mitochondrial membrane. It is at this level that e- and H^+ are transported from NADH and $FADH_2$ to acceptors of the electron transport chain. The process, named oxidative phosphorylation, occurs by means of five multiprotein complexes, known as complexes I to V. Complexes I to IV are involved in electron transfer to oxygen, the final electron acceptor. Complexes I, III, and IV translocate protons across the inner membrane, rising the electrochemical proton gradient (proton motive force) which drives the synthesis of ATP from ADP and P_i by complex V. These five multiproteins of the respiratory chain are: NADH CoQ oxidoreductase, succinate CoQ oxidoreductase, CoQ-Cytc oxidoreductase, Cytc oxidase (also called Cyt a_3) and ATP synthase. Cytc oxidase is notably responsible for the final supply of 4 H^+ and 4 e^- to molecular O_2 to form a molecule of water (H_2O). These enzymatic complexes are coupled with the system which pumps protons towards the intermembranous space, establishing a proton gradient which in turn is used by ATP synthases to produce ATP (adenosine triphosphate), the universal source of energy within the cell (see figure 1.2-1). It is noteworthy for understanding the energetic role of oxygen to compare the energy balance of glucose catabolism between different conditions of oxygen availability. The degradation of glucose (glycolysis) starts first in the cytoplasm, with the goal of forming two molecules of pyruvate. The net energy balance of this first

stage, which does not require oxygen, is two ATP and two NADH molecules.

In presence of oxygen, pyruvate (3C-molecule) penetrates inside the mitochondrion for its decarboxylation to acetyl-CoA (2C-molecule) and the production of NADH. It is at this stage that acetate enters the Krebs cycle to produce two supplementary CO_2, three NADH molecules and one $FADH_2$ molecule per cycle. The energy yield of this first stage is six ATP for one glucose (four from glycolysis + two from the Krebs cycle).

However, the highest energy production is established by NADH and $FADH_2$, which enter the respiratory chain where four H^+ and four e^- are transferred on a molecule of O_2 to form two H_2O. The electron transport chain, by oxidizing the NADH and $FADH_2$, produces energy by transferring H^+ into the intermembranous space; this electrochemical proton gradient creates a proton force which makes them return to the mitochondrial matrix by means of ATP synthases coupling this proton translocation with ATP production. It is at the level of the respiratory chain that the energy production is most profitable because each NADH produces three ATP and each $FADH_2$ produces two ATP. Under aerobic conditions, one molecule of glucose generates 36 molecules of ATP.

In oxygen deprivation, glucose produces two pyruvate molecules and two NADH which bypass the mitochondrion to regenerate the NAD^+. NADH is then regenerated into NAD^+ by transforming pyruvate to lactate. This anaerobic glycolysis, apart from the fact that it produces some lactic acid with well known effects, yields two ATP for one molecule of glucose (produced during the initial glycolysis). This is better than nothing, but markedly less than the 36 ATP obtained under aerobic conditions. This student's description illustrates how much the energy metabolism is dependent on a correct supply of oxygen.

4. THE TOXIC SPECIES OF OXYGEN

4.1 Toxic actors

In the mitochondrion, there is a 'physiological leaking' of partially reduced oxygen species, a phenomenon widely amplified under conditions of insufficient or excessive oxygen supply. Partially reduced oxygen species are produced, namely superoxide radical $O_2^{\bullet -}$, hydroxyl radical $^{\bullet}OH$, and hydrogen peroxide H_2O_2. These diverse chemical species of oxygen are indirectly responsible for the toxic effects of oxygen, their toxicity being related to their high reactivity. This extreme chemical reactivity is notably

deleterious for targets like SH proteins, polyunsaturated fatty acids and nucleic acids.

4.2 Lipidperoxidation

Membrane lipids constitute a main target for reactive oxygen species causing peroxidative damage. Polyunsaturated fatty acids are particularly affected. The process of lipidperoxidation can be divided in three main phases:

- an initiation phase consisting of the formation of a radical of fatty acid by removal of a methylene hydrogen $^{\bullet}H$ (CH_2) from a polyunsaturated fatty acid (RH) by an oxygen radical (mostly $^{\bullet}OH$).

$$RH + {}^{\bullet}OH \longrightarrow R^{\bullet} + H_2O$$

- a propagation phase corresponding to an amplifying process originating from the oxygen which initiates the first hydroperoxide radical:

$$R^{\bullet} + O_2 \longrightarrow ROO^{\bullet}$$

This hydroperoxide radical can in turn react with a nearby fatty acid R'H, generating another hydroperoxide and a radical of fatty acid :

$$ROO^{\bullet} + R'H \longrightarrow ROOH + R'^{\bullet}$$

This reaction self-maintains and propagates to nearby molecules; it is considered that a radical $R^{\bullet}$ can be at the origin of hundreds of hydroperoxide molecules before the phase of termination intervenes by the formation of a stable compound from the association of two radicals.

- a phase of termination, resulting from a reaction of radicals established on a probabilistic basis. There are three sorts of termination reactions, two by biradicalar reaction and one by reaction with an antioxidant :

$$ROO^{\bullet} + ROO^{\bullet} \longrightarrow ROOR + O_2$$

$$ROO^{\bullet} + R^{\bullet} \longrightarrow ROOR$$

$$R'^{\bullet} + AH \longrightarrow R'H + A \quad (AH = \text{antioxidant})$$

The peroxidation of membrane fatty acids, inducing indirect conformational and structural changes of the lipid bilayer, is representative of the radical toxicity of oxygen for membranes and associate proteins such as enzymes, ion channels and receptors. Even though the superoxide radical $O_2^{\bullet -}$ is often cited as the origin of peroxidation, it mainly acts as the precursor of two main initiators of lipid peroxidation: the hydroxyl radical $^{\bullet}OH$ originating from H_2O_2 and the hydroperoxide radical $ROO^{\bullet}$. H_2O_2 results from the dismutation of $O_2^{\bullet -}$, which can be spontaneous but is mainly catalyzed by superoxide dismutases (SODs):

$$2\ O_2^{\bullet -} + 2\ H^{+} \longrightarrow H_2O_2 + O_2$$

The hydroxyl radical ($^{\bullet}OH$), is produced by H_2O_2 and $O_2^{\bullet -}$ through two reactions dependent on iron:

- the Fenton reaction $H_2O_2 + Fe^{2+} \longrightarrow Fe^{3+} + {}^{\bullet}OH + {}^{\bullet}OH$

- The Haber-Weiss reaction $O_2^{\bullet -} + H_2O_2 \longrightarrow O_2 + {}^{\bullet}OH + {}^{-}OH$

Under physiological conditions, most of these toxic species are eliminated by various systems of defence: cellular and extra-cellular enzymes (superoxide dismutases, catalase, glutathione peroxidase) and non-enzymatic substances (ascorbic acid, tocopherol, beta-carotene). In fact, oxygen toxicity occurs when there is an exaggerated production of reactive oxygen species or when the means of defence are overwhelmed. As an example, hemolysis consecutive to bleeding and hematoma formation can be at the origin of a massive delocalization of ionized iron which constitutes an initiator of oxidative processes.

5. OXYGEN AND TISSUES

The physiological concentrations of dissolved oxygen in tissues other than the lung are situated in the range 20-120µM (1Torr = 1.4µM). In reality in organs, tissue O_2 tensions depend on the proximity of arterioles and capillaries as suppliers of oxygen. Oxygen concentrations are the most elevated in the blood of arteries, arterioles and the lowest in venules and veins. The O_2 tension in a given tissue depends on the level of consumption of O_2 by this tissue, on the local blood stream, on the relative distance of the zone considered from the nearest arteriole and capillary. Indeed, O_2 consumption causes pO_2 to fall rapidly between arterioles and veinules. This emphasises the fact that in tissues there is a distribution of oxygen tensions according to a gradient. Such a gradient also exists at the level of the cell such as in the mitochondrion, the terminal place of oxygen consumption where, O_2 concentrations range from 1.5 to 3 µM.

Chapter 1.3

PHYSIOLOGIC EFFECTS OF INCREASED BAROMETRIC PRESSURE

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Abstract: Increased pressure has no effect on solid parts of the body or fluids, but it does on gas filled cavities. Pressure effects directly on the middle ear and indirectly effects on the inner ear are described, with particular reference to equalizing pressures in the middle ear and the development of alternobaric vertigo. Pressure effects on the sinuses, airways and lungs occur only when ventilation is impaired. To understand pressure effects on ventilation, the influence of gas pressures on gas exchange and the concept of oxygen window are described. Changes in ventilation are shown on the basis of the alveolar gas equation and the breathing responses to decreased and increased oxygen pressure. Reasons for toleration of hypercapnia, changes between laminar and turbulent gas flows at different pressures, and variation of ventilation responses at increased pressure are discussed. In the final section, the toxic effects of nitrogen and other inert gases, together with those of carbon dioxide, are described with reference to air breathing at increased pressure

Keywords: Pressure effect, middle ear, inner ear, Eustachian tube, pressure equalization, Valsalva manoeuvre, vertigo, alternobaric vertigo, sinus, ventilation, breathing volumes, breathing gas, oxygen, carbon dioxide, nitrogen, inert gas, water vapour, oxygen window, alveolar gas equation, respiratory centre, chemoreceptor, Haldane effect, hypercapnia, laminar flow, turbulent flow, gas density, gas viscosity, Reynolds's number, flow rate, breathing resistance, flow volume loop, maximum voluntary ventilation, nitrogen toxicity, nitrogen narcosis, carbon dioxide toxicity

1. PRESSURE EFFECTS ON THE BODY

Hyperbaric oxygen therapy is limited by toxic oxygen effects to a maximum pressure of 300kPa (3 bar). For some indications mixed gases are used for treatments up to 600kPa (6 bar). Within this pressure range, all solid

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 31–47.

and liquid parts of the body are practically incompressible and there are no known clinical effects caused by the pressure per se. At therapeutic pressures, effects may only be noticed in relation to gas filled cavities[1].

1.1 Ear

Provided that the auditory canal is not occluded by any means, the middle ear is the only gas filled cavity of the ear which may be affected by pressure changes. Together with the mastoid cells with which it communicates, it forms the only gas filled cavity in the head without a permanent open connection to the rhino-pharynx.

The inner ear with cochlea and vestibular organ is completely filled with perilymphatic and endolymphatic fluid and is thus not directly affected by pressure changes.

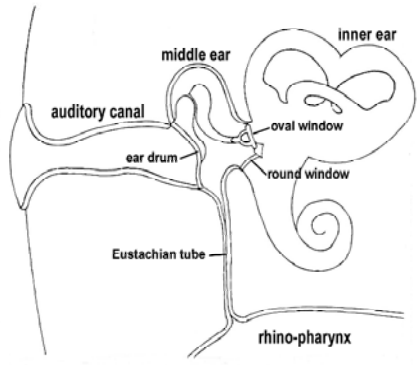

Figure 1.3-1. The human ear (Welslau[2])

1.1.1 Pressure equalization

The *Eustachian* tube, which connects the middle ear and rhino-pharynx, is normally closed. When chewing, swallowing, or yawning *mm. tensores veli palatini & levatores veli palatini* are activated and open the pharyngeal orifice of the *Eustachian* tube, thus allowing different gas pressures in rhino-pharynx and middle ear to equalize. Without conscious actions the tube is opened once every one to four minutes. During rapid pressure changes tubes must be opened actively.

This may be done either by chewing, swallowing, or yawning where pressure is allowed to equalize passively. It may also be done by a *Valsalva*

manoeuvre: mouth and nose are closed and a short forced exhalation attempt against the closed nose causes a rise of rhino-pharyngeal gas pressure, which opens the *Eustachian* tube orifice.

All these methods for pressure equalization depends on normal mucosa situation in the rhino-pharynx and Eustachian tube. When the mucosa is swollen during an upper respiratory tract infection, it may become impossible to equalize pressure in the middle ear.

1.1.2 Alternobaric vertigo

Vertigo is caused by mismatch of information deriving from right and left vestibular organs. In general, vertigo is connected with spontaneous nystagmus, and it may be accompanied by symptoms like nausea, vomiting, sweating and cardiovascular reactions.

In contrast with other less common cause of vertigo in hyperbaric therapy, alternobaric vertigo is caused by a difference of pressure between the two middle ear cavities. If vertigo is noticed during compression, it is called *"alternobaric vertigo of descent"*, an expression which derived from diving medicine. The mechanism of alternobaric vertigo seems to be that different pressures in the left and right middle ear lead to different pressures against the round and oval windows on each sides, causing a differential sensitivity of the two vestibular organs[3].

Vertigo may also happen when a forced *Valsalva* manoeuvre is effective only on one side. It is not clear whether this is a result either of a unilateral sudden change of pressure on the inner ear fluid or of unilateral inner ear liquid oscillation due to rapid movement of the oval and round windows. This cause of vertigo is described as being caused by a *hypermobile stapes*.

If vertigo becomes apparent during decompression, it is called *"alternobaric vertigo of ascent"*. The mechanism here is unilateral blocking of the Eustachian tube with delayed pressure equalization on that side. Animal experiments have shown that increased lymphatic pressure in the inner ear causes increased electric activity of *n. vestibulo-cochlearis*[3].

1.2 Sinuses

Besides the middle ears, there are more gas filled cavities in the head: the main airways (nose, oral cavity, rhino-pharynx), and the paranasal sinuses. As long as their connections with the rhino-pharynx are intact and unclosed, e.g. by swollen mucosa due to an upper respiratory tract infection, pressures will equalize automatically in the sinuses without any problem.

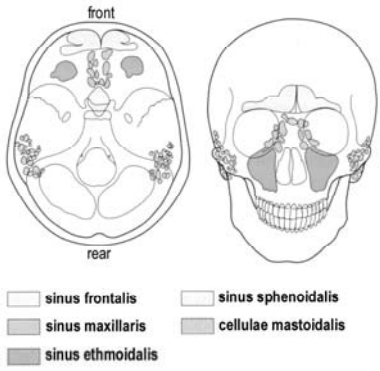

Figure 1.3-2. Location of sinuses (Graphic by J. Mair[4])

1.3 Lungs and airways

Breathing volumes vary enormously depending on height, age, and gender. As an example a young man may have a tidal breathing volume of ~ 0.5l with an inspiratory reserve volume of ~ 3.0l and an expiratory reserve volume of ~ 1.0l, thus having a vital breathing capacity of ~ 4.5l. After deepest expiration he has a residual volume of ~ 1.5l in his lungs and airways which can not be exhaled.

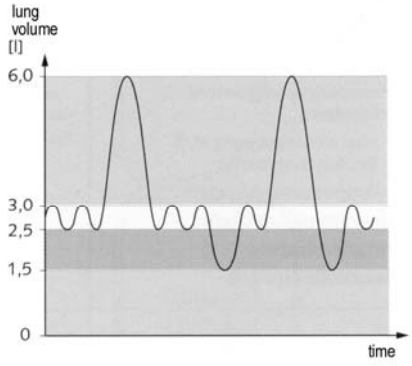

Figure 1.3-3. Breathing volumes (Graphic by J. Mair[4])

As long as breathing takes place continuously and gas is breathed at ambient pressure all the time, there is continuous pressure equilibration between lungs and surrounding atmosphere outside the chest wall. Problems may arise only if breathing is stopped during decompression (e.g. because of

a generalized convulsion due to oxygen toxicity) or if parts of the lung are not ventilated properly in relation to fast decompression (e.g. because of *asthma bronchiale*).

2. PRESSURE EFFECTS ON BREATHING

2.1 Gas pressures

According to *Fick*'s first law of diffusion, the external gas exchange between lungs and blood depends on the partial pressures of inspired gases and on the partial pressures of gases dissolved in the blood. In this respect it is only of indirect importance that O_2 and CO_2 are also transported actively bound to haemoglobin and that CO_2 is, in addition, transported as HCO_3^- ion in the blood. At the site of gas exchange only the physically dissolved gas molecules will play a role in the diffusion process.

When breathing air, in addition to O_2 and CO_2, N_2 and water vapour play a role: N_2 diffuses between lungs and blood like the other gases. Because N_2 is an "inert" gas, in that it does not react chemically in the human body, there is no difference in partial pressure between lungs and blood as long as there is no change in total atmospheric pressure.

Inspired air may contain varying amounts of water vapour which behaves like any other gas and also produces a partial pressure pH_2O. After humidification in the airways the breathing gas in the lungs is saturated with H_2O at 37 °C (ie 100% of relative humidity) and the pH_2O is 47 mmHg.

At this point we start using *mmHg* and leave IS units because in many European countries it is still common to use *mm Hg* for blood gases.

Conversion is as follows:

$$750mm\ Hg \cong 1\ bar = 100kPa \quad \text{and} \quad 760mm\ Hg \cong 1.013\ bar = 101.3kPa.$$

Total atmospheric pressure must be the same for inspired gas, alveolar gas and exspired gas. The gases other than water vapour must share the remaining pressure. For example:

inspired gas: P_{tot} 760mm Hg – pH_2O 6mm Hg = 754mm Hg
alveolar gas: P_{tot} 760mm Hg – pH_2O 47mm Hg = 713mm Hg

So, each inspired gas other than H_2O have to share 754mm Hg and 713mm Hg respectively according to their gas fraction F_{gas}.

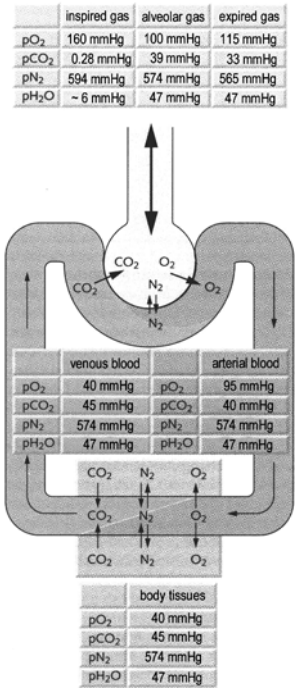

Figure 1.3-4. Gas partial pressures breathing air at 101.3kPa (760mm Hg) (Graphic by J. Mair[4])

2.2 Oxygen window

At atmospheric conditions, the total pressure of gas in the airways (P_{tot}) is 101.3 kPa (1atm, 760mm Hg). Arterial pO_2 and pCO_2 do not exactly equal alveolar partial pressures, because perfusion and ventilation of lungs is never optimal and so, gas exchange between lungs and blood is never complete. Therefore arterial total pressure is slightly inferior to atmospheric pressure (e.g. arterial P_{tot} 756mm Hg). Venous P_{tot} is only 706mm Hg, because pO_2 drops from 95mm Hg to 40mm Hg whereas pCO_2 only rises from 40mm Hg to 45mm Hg[5].

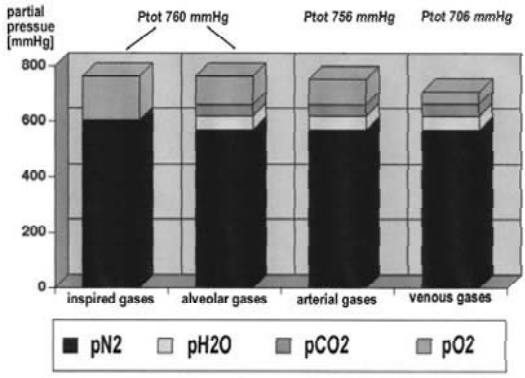

Figure 1.3-5. Breathing gas pressures during air breathing at 101.3kPa (1atm, 760mm Hg), (Welslau[2]; modified from Brian[5])

The difference between barometric ($P_{tot}B$) and venous total pressure ($P_{tot}V$) is called "o*xygen window*" ($P_{tot}B$ 760mm Hg - $P_{tot}V$ 706mm Hg = ΔP_{tot} 54mm Hg). This difference is the reason why confined amounts of gas can not persist in the body under normal conditions. P_{tot} of any amount of gas will equal atmospheric pressure (101.3kPa, 1atm, 760mm Hg) whereas P_{tot} of surrounding tissue – like venous blood – is ~ 706mm Hg. The gas will diffuse into the tissue as dissolved gas until it is reabsorbed completely.

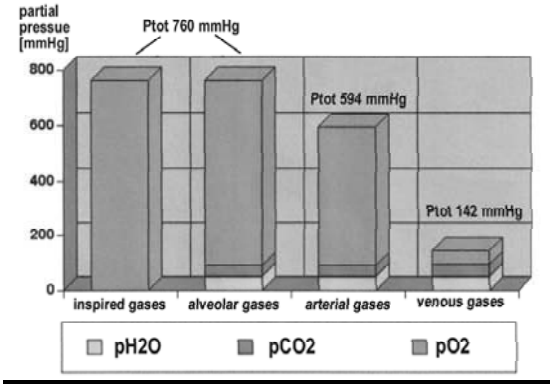

Figure 1.3-6. Breathing gas pressures during 100 % O2 breathing at 101.3kPa (1atm, 760mm Hg) (Welslau[2]; modified from Brian[5])

When breathing 100% O_2 arterial pO_2 rises according to *Fick*'s diffusion laws. In the tissue capillaries, the physically dissolved O_2 is utilized before haemoglobin will be deoxygenized. Hereby intravascular pO_2 drops far more than during air breathing; arterio-venous pO_2 difference is enhanced and the

oxygen window is: P_{totB} 760mm Hg - $P_{tot}v$ 142mm Hg = ΔP_{tot} 618mm Hg. Resolution of free gas will be accelerated[5].

When 100% O_2 is breathed at increased pressure, ie 162kPa (1.6atm, 1216mm Hg), arterial pO_2 and utilization of physically dissolved O_2 in tissue capillaries will rise. In consequence arterio-venous pO_2 difference is further enhanced and oxygen window is: P_{totB} 1216mm Hg - $P_{tot}v$ 150mm Hg = ΔP_{tot} 1066mm Hg. Resolution of gas will be further accelerated.

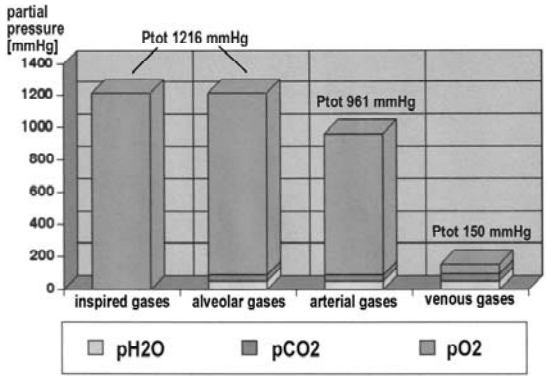

Figure 1.3-7. Breathing gas pressures during 100 % O2 breathing at 162kPa (1.6atm, 1216mm Hg) (Welslau[2]; modified from Brian[5])

2.3 Changes in ventilation

2.3.1 Alveolar gas

With the *alveolar gas equation* we can calculate alveolar partial pressures of O_2 (P_Ao_2) and CO_2 (P_Aco_2). The simplified formula shown below demands a CO_2 free inspiration gas, which will practically cause only minor inaccuracy. The equation shows that under hyperbaric air breathing conditions a significant hypoventilation (ie with P_Aco_2 of 80mm Hg) will not lead to hypoxia. This is because a constant inspiratory O_2 fraction will lead to a rising Po_2 proportional to pressure. The main problem of hypoventilation under hyperbaric conditions is hypercapnia[3].

$$P_AO_2 = P_Io_2 - \frac{P_Aco_2}{R} + \frac{P_Aco_2 \times (1-R) \times F_Io_2}{R} \qquad for: P_Ico_2 = 0$$

where: P_Ao_2 = alveolar O_2 partial pressure [mm Hg]
P_Io_2 = inspiratory O_2 partial pressure [mm Hg]
P_Aco_2 = alveolar CO_2 partial pressure [mm Hg]
R = respiratory quotient (CO_2 / O_2)
F_Io_2 = O_2 fraction in dry inspiration gas

2.3.2 Breathing response to changed oxygen pressures

The response of respiratory centre is modulated by peripheral chemoreceptors at *aa. carotis* and *aorta* and by central chemoreceptors on the floor of the fourth ventricle. Peripheral chemoreceptors mainly respond to a dropping pO_2 below 60mm Hg. Besides this they also respond to dropping pH, rising pCO_2, low blood pressure, increased body temperature and to stimulating agents like nicotine, acetylcholine and CO. Central chemoreceptors mainly respond to increased pCO_2, which is associated with dropping pH in cerebrospinal fluid. About 78% of responses to increased pCO_2 derive from central chemoreceptors. Figure 1.3-8 shows reactions of respiratory system to changes in inspiratory pCO_2 at different pO_2 levels under normobaric conditions[3].

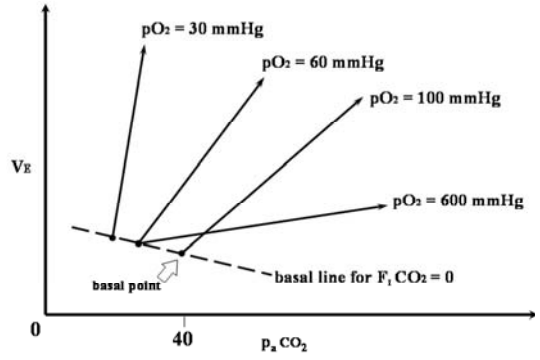

Figure 1.3-8. Reactions of respiratory system to changes of inspiratory pCO_2 at different pO_2 levels under normobaric conditions (Welslau[2]; modified from Flynn[3])

Decreased oxygen partial pressure

Elevating arterial pCO_2 under normobaric conditions by breathing CO_2 enriched gas mixtures will lead to increased ventilation in any case, no matter how high arterial pO_2 is. Ventilation as a function of pCO_2 (ΔV_E /

$\Delta PaCO_2$) will increase more strongly at low levels of PaO_2 than at high levels of PaO_2. At normal PaO_2, increase in ventilation is about 4 l/min/mm Hg $PaCO_2$. If there is no CO_2 in the breathing gas (dashed line in figure 1.3-8), ventilation is increased by low levels of pO_2 as well as by high levels of pO_2. By this mechanism low pO_2 stimulates ventilation via peripheral chemoreceptors[3].

Increased oxygen partial pressure

The mechanism by which increased pO_2 stimulates ventilation is slightly more complex. At increased pO_2 at least one part of cerebral oxygen needs is supplied by physically dissolved oxygen. In this situation less than the normal haemoglobin-bound oxygen is needed. Because haemoglobin with a high oxygen load is not able to bind as much CO_2 as normally (Haldane effect[6]), CO_2 has to be transported to a higher amount as bicarbonate and physically dissolved CO_2. Hereby pCO_2 in venous blood and cerebral tissue is increased. As a result the increased cerebral tissue pCO_2 stimulates ventilation (V_E) and thus leads to the lowering of venous pCO_2 in spite of the unchanged CO_2 production[3].

Under hyperbaric conditions hyperoxia is the most important factor for the development of hypercapnia. When breathing air, nitrox or heliox with a fixed percentage of oxygen, pO_2 increases parallel to rising pressure. Table 1.3-1 shows the effect of hyperbaric hyperoxia on ventilatory responses to increased pCO_2 at rest[7].

Table 1.3-1. Effect of P_IO_2 on ΔVE / $\Delta PaCO_2$ at rest (modified from Lambertsen[7])

$\mathbf{P_IO_2}$ [bar]	$\mathbf{\Delta V_E / \Delta Paco_2}$ [l/min/mm Hg]
0.2	4.5
1.0	3.3
2.0	2.6
3.0	2.0

2.3.3 Tolerated hypercapnia

The maximum amount of ventilation possible per minute is limited. This limit is reduced by increasing the density of the breathing gas. When the necessary ventilation to accomplish physical work approaches this upper limit, it will barely achieve the ventilation rate required to cope with metabolic needs. This will lead to hypercapnia. A similar restriction of ventilation is observed when ventilation work becomes very high at a certain workload. The respiratory centre seems to tolerate hypercapnia easily if this prevents excessive respiratory work[3].

2.3.4 Laminar and turbulent flows

Breathing gas is flowing through the airways following the pressure difference between alveolar pressure *(P_{alv})* and ambient barometric pressure *(P_B)*. When the thorax is widened breathing gas flows into the lungs, and when the thorax is compressed breathing gas flows the opposite direction. The flow of breathing gas is either "turbulent" or "laminar". Laminar flow is found mainly in small terminal airways, whereas turbulent flow is prevalent in the upper airways[3].

Laminar flow

In laminar flows, the flow rate is directly proportional to the driving difference in pressure and to airway radius to the power of four, and it is in reverse proportion to the gas viscosity. Thus, when the airway radius is halved it needs a 16-fold pressure difference to reach the same gas flow.

$$\dot{V} = \Delta P \frac{\pi r^4}{8 L \eta}$$

where: $\dot{V}$ = flow rate
ΔP = driving pressure difference (P_B - P_{alv})
r = airway radius
L = length of airway
η = breathing gas viscosity

Turbulent flow

Turbulent flow occurs when the flow rate is high, and when the quotient of gas density and gas viscosity is large. As a rule of thumb, gas flows are laminar when *Reynold's* number is below 1000, and gas flows are turbulent when *Reynold's* number is over 1500 (see equation below). But turbulent flows may occurr at smaller values of *Reynold's* number at sharp bends and bifurcations, or at irregular surfaces and in varying calibres[3].

$$Re = \dot{V} r \frac{\rho}{\eta}$$

Where: Re = *Reynold's* number
$\dot{V}$ = flow rate
r = airway radius
ρ = breathing gas density
η = breathing gas viscosity

For turbulent flows the equation below shows the relation between driving pressure difference and flow rate. Please note that for laminar flows ΔP is dependent on flow rate $\dot{V}$ to the power of 1, whereas for turbulent flows ΔP is dependent on flow rate $\dot{V}$ to the power of 2. In addition turbulent flows are dependent on gas density.

$$\Delta P = k \times \dot{V}^2 \qquad \text{for: } k \text{ being proportional to } \frac{\rho}{r^5}$$

where: ΔP = driving pressure difference ($P_B - P_{pl}$)
k = constant
$\dot{V}$ = flow rate
ρ = breathing gas density
r = airway radius

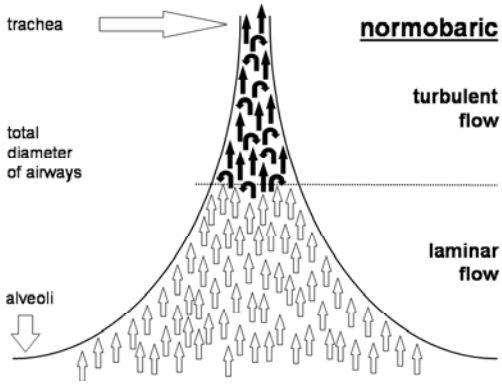

Figure 1.3-9. Total diameter of airways from the trachea to alveolar level, at normobaric pressure gas flow is turbulent only in bigger airways where total diameter is small and gas flow is high. In peripheral airways, where total diameters of airways is bigger and gas flows slower, gas flow is laminar (Welslau[2])

During expiration gas flows from peripheral to central airways. Due to successive reduction of total diameter of airways towards the trachea gas flow is more and more accelerated. Hereby in the larger airways laminar gas flow changes to turbulent flow. During inspiration this happens vice versa. Breathing gas flow in human airways is a mixture of both laminar and turbulent flow[3].

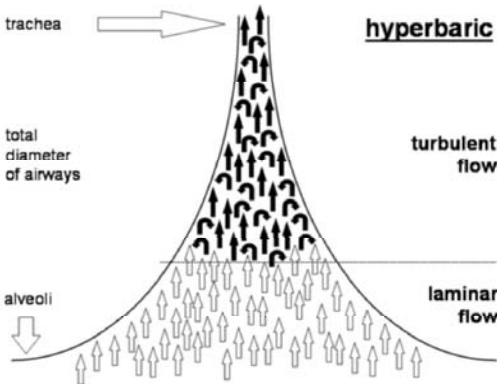

Figure 1.3-10. Total diameter of airways, due to higher gas density at hyperbaric perssure gas flow is turbulent also in more peripheral airways (Welslau[2])

2.3.5 Ventilation response at increased pressure

For a gas with constant composition its density raises proportionally to increasing pressure. Gas flow during expiration always contains a turbulent component, so increasing gas density will always lead to a higher breathing resistance[8]. Because maximum expiratory gas flow at a given lung volume depends on airway resistance, maximum expiratory flow decreases when gas density is increasing. A higher gas density results in diminished maximum inspiratory and expiratory flow volume loops (figure 1.3-11, left side) as well as in more strenuous breathing work, when ventilation has to keep up with physical workload. The higher the gas density, the smaller is the flow volume loop. When drawing expiratory breathing gas flow at a given lung volume (e.g. 60% VC) as a function of increasing gas density, you will notice a reduction of gas flow as shown in figure 1.3-11 (right side)[9].

When inspiratory and expiratory gas flows are reduced by increasing pressure, it is no surprise that maximum voluntary ventilation (MVV) is also reduced by increasing pressure. Ventilation response to increased pCO_2 in inspiration gas at rest will decrease when ventilatory work is increased due to higher gas density[10]. The presumed reason why ventilation response is decreased is that the additional ventilation work requires a stronger CO_2 stimulus. During physical work at increased gas density the breathing frequency is lower and the tidal volume is higher than normal. By this means required additional ventilation work and dead space ventilation are minimized while ventilation volume per minute is maintained[3].

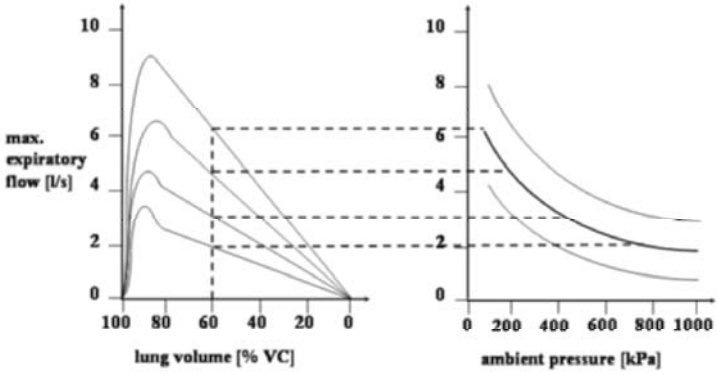

Figure 1.3-11. Reduction of expiratory breathing gas flow as a function of increasing pressure (Welslau[2]; modified from Miller[9])

3. NITROGEN AND CARBON DIOXIDE

3.1 Nitrogen toxicity

3.1.1 Occurrence

Nitrogen intoxication is also called "nitrogen narcosis"[1]. It may occur at pN_2 in excess of ~ 320kPa (3.2bar). When breathing air, this happens at a total pressure of 400kPa (4.0bar). When breathing gas mixtures with reduced nitrogen fraction (F_{N_2}), symptoms will occur at higher total pressure depending on pN_2. Inter-individual susceptibility to nitrogen varies widely. There is also great intra-individual variance for the occurrence of symptoms from day to day. Diverse factors may affect susceptibility to nitrogen narcosis. The list of influential factors is long and the risk of nitrogen narcosis can never be completely ruled out. Nitrogen narcosis will rarely occur in hyperbaric medicine because of limited pressure for standard treatments. But in treatments at higher pressure with mixed gases breathing for special indications (e.g. severe decompression incidents), it may become a problem for air breathing chamber attendants.

3.1.2 Symptoms

Nitrogen affects humans similarly to medical narcotic gases, but to a far less extent. Initial stages of nitrogen narcosis are described to be similar to alcohol or LSD intoxication. Symptoms may not be recognized by the affected individual.

Table 1.3-2. Nitrogen narcosis: enhancing factors and symptoms[1]

Factors enhancing susceptibility to nitrogen narcosis	**Nitrogen narcosis symptoms**
Stress	euphoria / dysphoria
Anxiety	mental concentration impairment
Exhaustion	logical thinking impairment
Inexperience	reaction time slowed down
Alcohol	short time memory impairment
Dope	mental arithmetic impairment
Drugs	competence to judge impairment
Fatigue	Hallucinations *(late)*
Carbon dioxide intoxication	loss of consciousness *(late)*

3.1.3 Pathogenesis

A popular hypothesis explains narcotic effects of nitrogen with its high solubility in lipids, leading to N_2 concentration in the lipophil layers of cell membranes and especially synaptic connections. This is believed to lead to swelling of cell and synaptic membranes with the effect of delayed impulse conduction between nerve cells[11]. One of the alternative explanations is that membrane proteins are the site of action, and that narcosis is the result of neurotransmitter mechanisms[12].

When comparing different inert gases, i.e. gases not taking part in human metabolism, we can state a parallelism between relative narcotic potency and solubility in lipids. Provided the relative narcotic effect of nitrogen is 1, other gases may ranked according to their relative narcotic potency (see table 1.3-3). Solubility of gases in lipids shows that gases with a higher narcotic potency also have a higher solubility in lipids compared with less narcotic gases[13].

Table 1.3-3. Comparison of molecular weight, solubility in lipid and narcotic potency of different gases (modified from Bennett and Elliott[13])

Gas	Molecular weight [gram]	Solubility in lipid [Bunsen coefficient]	Relative narcotic potency [Nitrogen = 1]
Helium (He)	4	0.015	0.24
Neon (Ne)	20	0.019	0.28
Hydrogen (H_2)	2	0.036	0.55
Nitrogen (N_2)	**28**	**0.067**	**1**
Argon (Ar)	40	0.14	2.94
Krypton (Kr)	83.7	0.43	7.14
Xenon (Xe)	131.3	1.7	25.64

3.2 Carbon dioxide toxicity

3.2.1 Occurrence

There are two pathways for the development of CO_2 intoxication: either pCO_2 is increased in inspired breathing gas, or expiration of produced CO_2 is insufficient.

Increased pCO_2 in inspired gas may occur when gas exchange in the hyperbaric chamber is insufficient to keep pCO_2 at physiological level. To prevent raised pCO_2 levels, hyperbaric chambers have to be flushed continuously with breathing gas. The flushing rate has to be adapted to the number of chamber occupants and to the total pressure of chamber atmosphere.

Anxiety can lead to frequent and shallow ventilation and so may cause insufficient expiration of CO_2. Physical exhaustion due to strenuous work and increased CO_2 production may have similar effects. Increased gas density and increased breathing resistance supports this mechanism.

3.2.2 Symptoms

The most common and primarily occurring symptom of CO_2 intoxication is headache. In addition, palpitation, increased blood pressure, or agitation may occur. At pCO_2 over 6kPa (0.06bar) air hunger, tachycardia, and loss of consciousness may occur ("CO_2 narcosis").

Table 1.3-4. Symptoms at different levels of increased pCO_2[1]

pCO_2 in inspiration gas	Symptoms
0.38kPa (0.0038bar)	None (normal atmospheric pCO_2 value)
1.5kPa (0.015bar)	Increased ventilation frequency
2.5kPa (0.025bar)	Headaches, dizziness, vertigo, nausea, air hunger, disturbed vision
6.5kPa (0.065bar)	Loss of consciousness

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Chapter 1.4

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON OXYGEN TRANSPORT AND TISSUE OXYGEN PRESSURE

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Abstract: The mechanisms of oxygen transport, the relationship between oxygen delivery and consumption and determinants of tissue oxygen tension are considered with a brief introduction to the measurement techniques currently available in the clinical setting. An overview of clinical research from the last decade to the present is given with regard to the various organs. Evaluating the effects of hyperoxia at the tissue and cellular level as well as monitoring and titration of oxygen dose will be a challenging field of research in the future

Keywords: oxygen cascade, oxygen transport, oxygen content, oxygen delivery, oxygen consumption, erythrocyte deformability, vasoconstriction, Krogh's model, diving-ergometry, cardiac output, oxygen-supply independency, oxygen-supply dependency, polarography, tonometry, near-infrared spectroscopy, cerebral oxygen consumption, exercise, oxygen measurement methods, diffusion, tissue oxygen pressure, cytochrome c oxidase, VO_2 measurement, cardiac output, central nervous system oxygen pressure, tumour oxygen pressure, soft tissue oxygen pressure, skin oxygen pressure, skeletal muscle oxygen pressure, hyperoxic vasoconstriction

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 49–73.

1. EFFECT OF HBO ON OXYGEN TRANSPORT

1.1 Terminology of oxygen transport

Hyperbaric oxygen (HBO) exerts its effects by elevation of the inspired gas together with an increased proportion of inspired oxygen. The consequences of the latter will be discussed in the present chapter. In this context oxygen has to be considered a drug with its pharmacological properties, indications, contraindications and side effects.

The term "oxygen transport" encompasses the global balance between supply and demand of oxygen. Overall oxygen supply can be determined in the clinical setting whereas the assessment of oxygen demand is much more difficult.

Oxygen moves down a pressure gradient from inspired to alveolar gas, arterial blood, the capillary bed, across the interstitial and intercellular fluid to the sites of utilization within the cell (perioxome, mitochondria, endoplasmic reticulum). Under normobaric conditions, the gradient of oxygen partial pressure (pO_2) known as the "oxygen cascade"[1] starts at 21.2kPa (159mm Hg) and ends up at 0.5-3kPa (3.8-22.5mm Hg) depending on the target tissue.

The pO_2 of the alveolar gas may be calculated by the alveolar gas equation (see chapter 1.3, section 2.3.1).

This equation is applicable for hyperbaric conditions. $PaCO_2$, water vapour pressure and respiratory quotient (RQ) do not vary significantly between 100kPa and 300kPa (1 - 3bar). Thus, for example[2], the inhalation of 100% oxygen at 202.6kPa (2ata) provides an alveolar PO_2 of 1423mm Hg. The alveolar gas equation calculates the "ideal" alveolar gas without consideration of influencing factors like ventilation-perfusion inequalities or pre-existing atelectasis.

In a next step, the alveolar oxygen passes the alveolar-capillary space and diffuses into the venous pulmonary capillary bed according to Fick's Laws of Diffusion. The majority of the oxygen is then transported bound to haemoglobin, whilst a very small amount remains dissolved in plasma which may be quantified and formulated in the "oxygen content equation" (see next page).

There is still controversy about the oxygen-combining capacity of haemoglobin with values ranging between 1.306mL/g to 1.39mL/g in an adult depending on the mode of analysis.

The fraction of oxygen bound to haemoglobin is quantitatively most important whereas the fraction of dissolved oxygen is very small. However, the amount of oxygen dissolved in plasma is mainly responsible for the

availability of oxygen diffusing through the interstitial fluid and the cell membrane. The amount of oxygen dissolved in the blood is determined by Henry´s Law, which states that the concentration of a gas in a fluid (mL of gas dissolved/unit volume of water) is proportional to its pressure and to its solubility coefficient:

$$O_2\ content = \text{Hb-bound } O_2 + O_2 \text{ dissolved in plasma}$$
$$CaO_2 = SaO_2 \times Hb \times 1.34 + 0.003 \times PaO_2$$

where:
CaO_2 = mL O_2/100mL arterial blood;
SaO_2 = percentage of haemoglobin saturated with O_2, expressed as decimal fraction
Hb = haemoglobin content (g/100mL blood)
1.34 = Oxygen-binding capacity of haemoglobin (Hüfner´s number) indicating that 1g Hb may bind 1.34mL O_2 when fully saturated with oxygen
0.003 = solubility constant for dissolved O_2 in plasma corresponding to 0.003mL O_2/100mL plasma/mm Hg PaO_2
PaO_2 = arterial blood pO_2

With air breathing 0.32mL of O_2 are dissolved in 100mL plasma (% by volume) increasing up to 6.8mL O_2/100mL plasma with breathing 100% O_2 at 303.9kPa. This amount equates to the global arterial/mixed venous oxygen content difference ($C_{[a-v]}\ O_2$) which is able to cover the basic metabolic needs of an individual at rest with normal cardiac output. Boerema[3] verified this hypothesis in his fundamental animal experiment "Life without blood" which became a hallmark in hyperbaric medicine research.

Arterial blood pO_2 is influenced by the pulmonary ventilation/perfusion pattern (V/Q ratio) and by the amount of pulmonary venous admixture or right-to-left intrapulmonary or intracardiac shunting. To some extent, exposure to HBO may affect pathologic conditions due to the large increase of PaO_2. Nevertheless, acute or chronic alterations of gas exchange may provide an insufficient level of PaO_2. Therefore, monitoring of blood gases is important to evaluate whether the desired level of oxygen as a therapeutic goal is reached in the hyperbaric environment.

Transport of oxygen from the lung to the cell[1] is achieved by the circulatory system. The quantity of oxygen globally transported to cells is known as "oxygen delivery" which is proportional to cardiac output and arterial oxygen content. Oxygen delivery may be determined according to the following equation:

$$DO_2 = CO \times CaO_2$$

where:
DO_2 = delivery of oxygen (mL/min). CO = cardiac output (mL/min).

According to the Fick principle, the amount of oxygen consumed by the whole body per unit of time (VO_2) is equal to blood flow (i.e., cardiac output), multiplied by the amount of oxygen extracted by the body. This can be calculated as the difference between the content in the arterial blood and that in the mixed venous blood within the pulmonary artery ($C[a\text{-}v]O_2$). Thus, hypothetically, the increased supply of oxygen under hyperbaric conditions could favour an augmentation of oxygen consumption and a better coverage of metabolic demands in conditions where VO_2 depends on DO_2.

Equally, oxygen consumption of any organ can be calculated as the difference between the amount of oxygen delivered by its arterial supply and the amount of oxygen in its venous drainage multiplied by the blood flow:

$$VO_2 = Q \times ([O_2]a - [O_2]v)$$

where:
Q = organ perfusion (L/min)
$[O_2]a$ = CaO_2 arterial blood entering the organ (measured)
$[O_2]v$ = CvO_2 venous blood leaving the organ (measured).

Oxygen extraction ratio (EO_2) is defined as the ratio between consumed and delivered oxygen:

$$EO_2 = \frac{[O_2]a - [O_2]v}{[O_2]a}$$

EO_2 depends on the metabolic activity of each organ and is about 7% in the kidneys, 4% in the skin, 3% in liver, brain and skeletal muscle and 6% in the myocardium. Oxygen extraction may increase up to 9% in exercising muscle[4].

Therefore, with regard to the above equation, oxygen consumption may be increased by either increasing the organ perfusion (Q) or the oxygen extraction ratio or increasing the arterial/venous oxygen content difference.

1.2 The VO_2-DO_2 model

It has been shown in numerous animal experiments that VO_2 is kept stable over a wide range of DO_2 by extraction of oxygen according to the

metabolic needs of the body. In this situation VO_2 does not depend on DO_2. This so called "oxygen-supply independence" is interpreted as evidence of tissue wellness and adequate tissue oxygenation[5]. In the resting subject, DO_2 is approximately twice the VO_2 value to preserve DO_2-independent oxidative metabolism (normal range of DO_2: 500-650 mL min^{-1} m^{-2}). With impaired oxygen supply below a critical threshold as it occurs in pathological conditions, oxygen consumption cannot be kept stable and declines proportionally to delivery which leads to a condition where VO_2 depends on DO_2. This oxygen-supply dependence indicates evidence of tissue dysoxia demonstrated in different mammals, in the whole body[6,7] and in various organ systems such as skeletal muscle[8], the gut[9] and the liver[10].

Assumptions of the VO_2-DO_2 model include that VO_2 demand is constant at all DO_2 values and that DO_2 is equal for all physiologic conditions. Thus, variable muscular VO_2 demand raises problems with strict application of this model. To a certain extent, a physiological oxygen-supply dependence is found in the exercising subject.

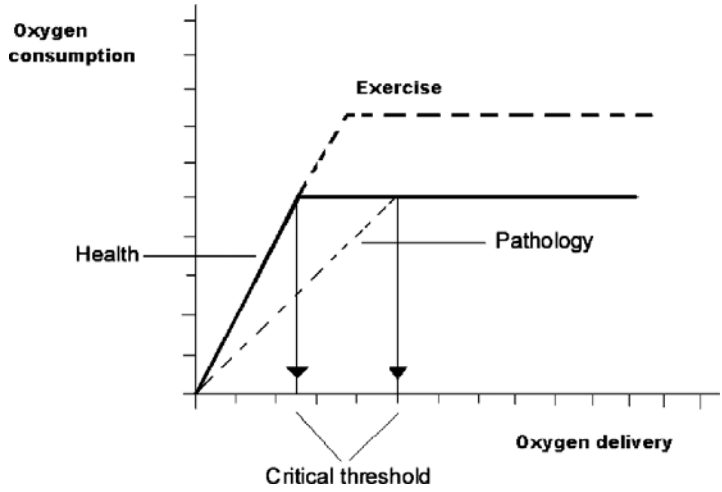

Figure 1.4-1. The VO_2-DO_2 model. Scheme showing the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2).Condition of oxygen-supply independence in health, condition of oxygen-supply dependence at exercise and in case of disease

1.3 Methodology of VO_2 measurement

VO_2 and DO_2 can be calculated from cardiac output determined with the help of a pulmonary artery flotation catheter and from arterial and mixed venous blood gases (reverse Fick method). The development of direct measurements of VO_2 and VCO_2 as a difference in gas concentrations between inspired and expired gases has allowed a non-invasive assessment of whole body metabolism. This has revealed a difference[11-13] between the values derived from thermodilution techniques and those obtained from indirect calorimetry. Indirect calorimetry overestimates the values obtained by the reverse Fick method, which is explained by pulmonary oxygen consumption not assessed by the reverse Fick method of calculation.

Measurement of VO_2 is performed by mass spectroscopy or by paramagnetic oxygen analyzers; measurement of VCO_2 is usually infrared-based. The accuracy of commercially available metabolic monitors is guaranteed up to a normobaric FiO_2 of 0.6.

The hyperbaric environment poses some methodological problems. Arterial blood gases measured under normobaric conditions from samples obtained under hyperbaric conditions need to be interpreted with regard to misleading oxygen tension values, as it is impossible to calibrate blood gas machines accurately for gas tensions higher than ambient barometric pressure. The only way to obtain exact results is to measure blood gases inside the hyperbaric chamber. However, Weaver[14] has shown that normobaric blood gas measurements may provide reliable results in healthy individuals at rest exposed to HBO if a correction formula is used.

1.4 Oxygen consumption during hyperoxia

Administration of HBO increases oxygen delivery, which could hypothetically favour an augmentation of oxygen consumption and a better coverage of the metabolic demands in conditions of oxygen-supply dependence. This hypothesis seems consistent with the findings of Welch[15] showing that normobaric hyperoxia (NBO) improves performance in exercising subjects. In contrast, several authors[16,17] have observed a decrease of VO_2 with NBO. The VO_2 response to NBO reported so far is not uniform and not comparable due to differing study designs and methods of measurement. Above all, the response to HBO has to be judged in context with the basic condition of the subject: conditions of oxygen-supply independence (healthy subject at rest), conditions of oxygen-supply dependence in health (exercise) and in disease (shock state). Apart from the effect of hyperbaric oxygen as a drug, the effect of the altered physical properties (i.e., pressure) of the inspired gas on VO_2 has to be considered.

1.4.1 Effect of hyperoxia on VO_2 of the healthy subject at rest (Condition of oxygen-supply independence)

Whole body VO_2

As opposed to the DO_2-VO_2 relationship in small animals, there is no dependence of oxygen consumption on oxygen delivery in the healthy human subject and in the larger animal, which may explain some of the controversial results obtained.

Normobaric hyperoxia does not alter VO_2 in man[18] ; however, VO_2 can be reduced by anaemia or by autonomic nervous system blockade in the animal experiment[19].

Regional VO_2

Cerebral VO_2 was reported to decrease by 12% at 202.6kPa (2ata) in man[20].

Hepatic oxygen consumption[21] was reported to be moderately elevated with a pO_2 exceeding 100mm Hg. This finding has been interpreted as a sign of borderline hepatic oxygenation under normobaric conditions in the healthy organ but is inconsistent with the autoregulatory capacity of this organ to increase oxygen extraction under hypoxia.

Myocardial oxygen consumption[22] and haemodynamic parameters were determined in ten chronically instrumented conscious dogs during pharmacological autonomic blockade and exposure to HBO at 303.9kPa. Apart from a reduction of left ventricular stroke volume, total coronary blood flow, cardiac output and myocardial oxygen consumption were significantly reduced ($p<0.05$) proportionally to the increased inspired oxygen fraction.

1.4.2 Effect of hyperoxia on VO_2 of the healthy subject at exercise (Condition of physiological oxygen-supply dependence)

Webster[23] did not find an ergogenic effect on subsequent incremental exercise performance or maximal oxygen consumption after a 1-hr exposure to HBO at 202.6kPa (2.0ata).

Controversial observations and interpretations have been made about the quantity of oxygen uptake in the exercising subject: some authors have found an increase of VO_2 max with increased DO_2 in human[24] and animal[25] studies, which has not been observed by others[26,27]. Nevertheless, most authors have observed a better exercise endurance and a decrease of serum lactate levels, suggesting additional hyperoxia-induced metabolic effects.

Regional effects of hyperoxia on oxygen consumption have been most extensively studied in exercising skeletal muscle *in vivo,* and in the isolated muscle model, with contradictory results: There are reports indicating considerable increases[28,29] in muscle oxygen uptake during hyperoxia and others[30-32] without. Wilson[33] showed that the decrease of local blood flow matched the increase of arterial oxygen content during hyperoxia so that a net increase of VO_2 did not occur.

In a rat model, Eynan[34] showed that a 24hr exposure to normobaric oxygen reversed the energy-saving (reduced oxygen consumption) effect of training, in comparison with sedentary animals. Under exposure to NBO, the VO_2 of the trained rats increased by 17% which was similar to the VO_2 of the untrained animals. The authors concluded that prolonged exposure to hyperoxia leads to a reduction of the energy efficiency of the trained rat.

The underlying cause for these opposing observations may be the variety of experimental settings and species, and the modification by autoregulatory mechanisms which are not yet totally defined and predictable.

Hyperoxia interferes with the accuracy of commercially available oxygen consumption measurement devices limiting their use in the hyperbaric environment.

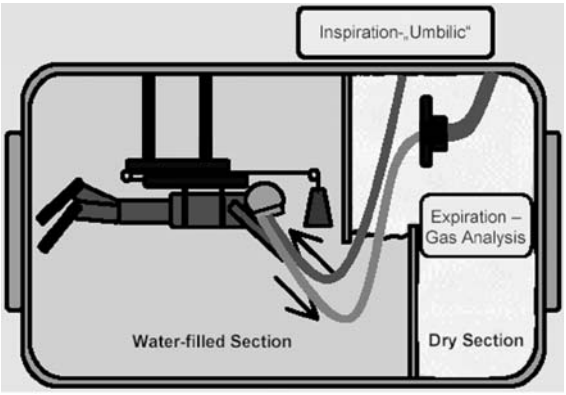

Figure 1.4-2. Diving chamber equipped with the suspended- weights system allowing for fin-swimming in normal swimming position and ergospirometry testing with the semi-open Douglas-bag method (modified from Koch et al.)

Koch[35] devised a set-up for online diving ergospirometry during fin-swimming under realistic diving conditions (Fig. 1.4-2). The divers were tested in a suspended-weights system in normal swimming position where they had to counterbalance increasing weight loads in a ramping protocol. Ergospirometry was performed with the semi-open Douglas-bag method and a tight-fitting full-face mask. In trained subjects there was no significant

difference found in total whole-body oxygen uptake between normobaric cycling, cycling at an ambient pressure of 300kPa (20m depth), as well as fin-swimming (300kPa) at comparable workloads.

1.4.3 Effect of hyperoxia on VO_2 under pathological conditions (Condition of oxygen-supply dependence)

In the healthy individual at rest, VO_2 is kept constant and not confined by oxygen delivery. However, under certain pathological conditions, DO_2 falls below a critical value and induces a concomitant decline of VO_2 which characterizes the period of pathological oxygen supply dependence, and which has been reported in various disease states such as sepsis syndrome, haemorrhage or multi-system organ failure[36]. Even if DO_2 is above the critical threshold, a dependence of VO_2 on DO_2 has been shown, and used as a prognostic outcome index in critically ill patients[37].

Although an increased inspiratory fraction of oxygen (FiO_2) is widely used in clinical practice to improve tissue oxygenation, only a few investigations deal with the impact of hyperoxia on VO_2. An investigation in 20 critically ill (11 septic, 9 non-septic) patients[38] showed a reversible decrease of oxygen consumption by 10%, and maintenance of cardiac index with increasing FiO_2 from 0.4 to 1.0. To the authors, the decrease of VO_2 without decrease of DO_2 was a sign of maldistribution of blood flow and functional oxygen shunting as protection against normobaric hyperoxia.

There is rare data about the effect of hyperbaric hyperoxia on oxygen consumption. Mathieu[39] studied the VO_2-DO_2 relationship in eight critically ill patients undergoing HBO therapy at 253.2kPa (2.5ata) for 90 minutes by indirect calorimetry and by the reverse Fick method. The study aimed at evaluating whether VO_2 would be modified by HBO, and whether the effect of the increase of DO_2 by HBO would be comparable to that of an increased DO_2 by a standardized volume challenge. The fluid loading led to a rise in DO_2 without concomitant increase of VO_2. Hyperbaric oxygen did not induce a rise in VO_2 despite a rise of DO_2.

Cerebral oxygen consumption has been investigated in 37 severely brain injured patients[40]. A maximum of seven treatments per patient had been applied at 151.9kPa (1.5ata) for 60 minutes. Patients were divided into the three categories of reduced, normal or increased pre-session cerebral blood flow. Cerebral blood flow, arterial/venous oxygen content difference, cerebral metabolic rate of oxygen ($CMRO_2$), ventricular cerebrospinal fluid lactate and intracranial pressure values were assessed one hour before, and one and six hours after HBO therapy. $CMRO_2$ increased and lactate levels decreased after treatment, which suggested an improvement of aerobic

cerebral metabolism and showed a prolonged effect of HBO, which did not last, however, until the next hyperbaric session. The authors concluded that more frequent sessions might be beneficial in severely brain-injured patients.

2. EFFECT OF HBO ON OTHER DETERMINANTS OF OXYGEN TRANSPORT

Hyperoxic vasoconstriction

Hyperoxic vasoconstriction does not induce a decrease in oxygen delivery to the tissue, in contrast with catecholamine-induced vasoconstriction. Hyperoxic vasoconstriction causes a reduction of edema formation due to a decrease in capillary transudation. Therefore, HBO therapy is beneficial in the treatment of compartment syndrome, and also in cerebral or medullary edema. It is of paramount importance that this type of vasoconstriction only occurs in hyperoxic tissues as a protection against the development of hyperoxic lesions to decrease the risk of oxygen toxicity. It does not appear in hypoxic tissues where oxygen pressures become normal during exposure to HBO[41]. Vasoconstriction in a healthy area, and blood flow maintenance in an ischemic area, lead to a redistribution of blood flow to the malperfused area. The effect of HBO on features of microcirculation will be discussed in chapter 1.5.

Effect on red blood cells

Red blood cells (RBCs) are concave discs and deformed into any shape, when they pass through the capillary, as the diameter of the capillary is smaller than the RBC diameter. The degree of deformability is an important determinant of blood viscosity. In animal experiments, deformability increases at pressures below 202.6kPa (2ata) and decreases with higher pressures.

In a rat experiment[42], for example, RBC deformabibility was assessed with two different techniques, with the ektacytometer and with micropore filters. Exposure to HBO at 283.6kPa (2.8ata) for 6 hours led to a significant decrease of RBC deformability ($p<0.0001$) with the micropore filter method. This effect was reversible as it was not observed in the group of animals investigated 24 hours after exposure.

An investigation in 70 patients[43] showed an increased deformability after exposure to HBO at 202.6kPa (2.0ata) for 90 min ($p<0.001$) measured by the Stolz method. The decreased viscosity may support blood flow and gas exchange at the capillary level. Elevated ambient pressure per se enhances RBC aggregability which has been studied in

eleven human volunteers[44] during dives to 919kPa (9.19bar, 300fsw). The median RBC aggregate size was significantly increased at depth.

Effect on cardiac output

A decrease of cardiac output has also been observed with normobaric oxygen breathing[45].

Abel[46] investigated the cardiovascular effects of hyperbaric air at 303.9kPa (3ata), HBO at 303.9kPa and NBO in thirteen anesthetized dogs. Heart rate and cardiac output decreased most with exposure to HBO whereas hyperbaric air had only mild effects. The response to NBO was similar but less pronounced. The authors found an imbalance between left and right ventricular performance and concluded that HBO may have a differential impact on the autonomic innervation of the right and left ventricle. This might explain the development of pulmonary edema in patients with congestive heart failure under exposure to HBO.

Cardiac output decreased by 36% and mean heart rate by 10% of the normobaric baseline value studied in a group of 23 healthy Navy divers[47] performing steady state bicycle exercise under normobaric and hyperbaric conditions at 400kPa.

Further effects of HBO on haemodynamics will be discussed in chapter 1.5.

3. EFFECT OF HBO ON TISSUE OXYGEN PRESSURE

3.1 Basic aspects

The last step of the oxygen cascade – transportation of O_2 into the cell – is achieved by convection, i.e. DO_2 (local circulation), and by passive diffusion. The actual tissue oxygen pressure is the result of equilibrium between the amount of oxygen extracted by the individual tissue and the amount of oxygen consumed by the cells[48]. The variables finally defining the level of tissue oxygen pressure are as follows:

a) regional energy expenditure according to tissue metabolism;
b) features of the cardiovascular system and microvascular perfusion;
c) the oxygen-carrying capacity of the blood;
d) features of diffusion from the capillaries to the mitochondria within the target tissue.

Several mathematical models[49,50] have been established for the description of their interactions and performance.

Tissue metabolism

Energy demand varies among the organs. Their microcirculation is well adapted, as tissues with higher metabolic demands like the brain, muscle and the myocardium present with a high density of capillaries.

The skeletal muscle, for example, may increase its energy expenditure eight-fold with exercise compared with rest which is achieved by two mechanisms: by a high number of capillaries increasing blood flow, and by an increase of the oxygen extraction ratio leading to a lower venous pO_2 at exercise compared with an individual at rest.

Features of the cardiovascular system and microvascular perfusion

The cardiac output determines the amount of oxygen delivered to the whole organism. VO_2 may be calculated according to the formula:

$$VO_2 = Q \times (CaO_2 - CvO_2)$$

where: Q = cardiac output (L/ min)
CaO_2 = arterial oxygen content
CvO_2 = mixed venous oxygen content.

The cardiac output in the healthy resting subject is on average 3.5L/m^2 body surface area (BSA) and may increase up to five-fold during exercise or hyperdynamic states like septicaemia. Increased metabolic activity is the main trigger to increase cardiac output, inducing regional vasodilation and favouring increased blood flow in the target organ.

Macrovascular parameters of oxygen utilization do not reflect the distribution of oxygen and its consumption in the various specific organ systems; but microvascular parameters of oxygen utilization are not appropriate for use in the clinical practice

It is essential to understand that limited inferences may be derived from whole body data with respect to individual organ well-being.

In contrast to DO_2, tissue pO_2 provides a direct measure of cellular oxygenation in the tissue measured. Within any organ, tissue pO_2 varies considerably, with some cells being hypoxic and others well oxygenated. These ranges have been described in pO_2 histograms[51]. Mitochondrial oxidative phosphorylation is finally determined by mitochondrial pO_2.

Oxygen-carrying capacity of the blood

It is determined by the concentration of haemoglobin, the affinity of oxygen to haemoglobin and the amount of oxygen dissolved in the plasma.

The haemoglobin level (normal range: 12-15g /100mL blood) is regulated by erythropoetin, a glycoprotein mainly produced by the kidneys. It is secreted into the plasma in response and in direct proportion to the degree of hypoxia.

The relationship between pO_2 and the degree of saturation of haemoglobin with oxygen (sO_2) is non-linear which is of fundamental biological importance. The flat part of the sigmoid-shaped oxyhaemoglobin dissociation curve favours binding of O_2 to haemoglobin over a wide range of pO_2 at the pulmonary level, whereas oxygen dissociates well from haemoglobin in the steep part of the curve in a small range of low oxygen tensions at the tissue level favouring its diffusion into the tissues.

Features of diffusion

At the microvascular level the delivery of oxygen to the tissues is achieved by diffusion. The driving force determining the amount of diffusion is the difference in partial pressures of the blood between the capillary and the mitochondria in adjacent cells. The quantity of diffusing agent per unit time (J) is proportional to the surface of diffusion (F), the absolute temperature (T) and the ideal gas constant (R) and inversely proportional to the viscosity of the solvents (η) and the radius (r) of the diffusing particles. The interrelationship of these parameters is expressed as diffusion coefficient (D) in the equation of Stokes and Einstein as follows: $D = RT / 6\pi r \eta$. The first law of diffusion was established by Fick in 1855:

$$J\,(mol \times s^{-1}) = F \times D\,(dC / dx)$$

where: C = concentration
x = distance of diffusion

Transcapillary diffusion of oxygen can be described by the Krogh cylinder[52], a model introduced by Nobel Laureate Krogh in the last century. This unit structure implies that each capillary section provides oxygen supply to a corresponding cylindrical section of surrounding tissue. Oxygen and other metabolites transported within the oxygenated blood will diffuse from the capillary radially towards the tissue to be consumed by the cells. This model is amenable on the assumptions that

- the Krogh cylinder is an appropriate model for the geometry in a given tissue
- the tissue surrounding the cylinder is homogenous and uniform in its metabolic activities
- the axis of the capillary-tissue cylinder is uniform.

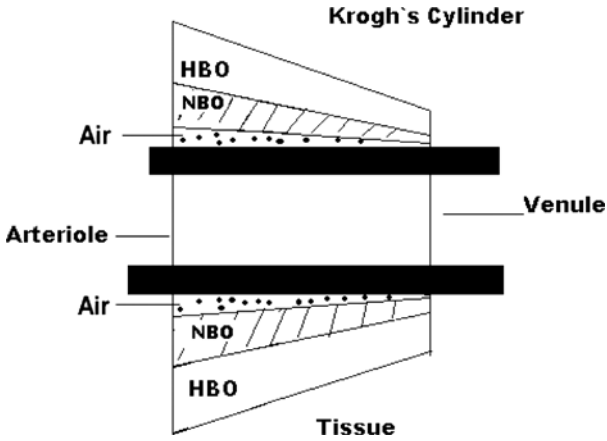

Figure 1.4-3. Cross section of volume of oxygenated areas around the unique capillary under different conditions: with breathing air, normobaric oxygen (NBO) and hyperbaric oxygen (HBO) according to the Krogh's model

This model allows for a deeper insight into tissue oxygenation although it does not consider geometrical features like branches of the capillary bed, alterations of vascular tone which might constrain capillary blood flow or varying local metabolic demands. Nevertheless, on the basis of this model, key variables of tissue oxygenation may be defined which are the *distance between capillaries* and the *transit time* of red blood cells from arteriole to venule.

Thus, the mean distance between capillaries or the mean density of capillaries in a given volume of tissue is a main determinant of tissue oxygenation, which may explain tissue hypoxia despite normal arterial oxygen tension and cardiac output. Above all, the period of time when capillary pO_2 exceeds tissue pO_2 is also a determinant of tissue oxygenation as well. A shortening of transit time diminishes oxygen delivery to the surrounding tissue.

Partial oxygen pressure continuously declines during the transit of the red blood cells from arteriole to venule, and so does oxygenation of the surrounding tissue. Thus, the cells at the venous end of the capillary are least oxygenated and at risk of hypoxia ("lethal angle"). Three thresholds below normal values may be defined. At a venous pO_2 of 25-28mm Hg reactive vasodilation occurs; the PvO_2 of 20mm Hg has to be considered critical to tissue oxygenation; and at a PvO_2 of 12mm Hg the oxygen pressure approximates zero within the mitochondria.

Under normobaric conditions the pO_2 at the arteriole equals the arterial pO_2 of about 100mm Hg, the pO_2 at the venule being about 34mm Hg. The distance of diffusion equals 100µm at the arteriolar and 36µm at the venular

side leading to a diffusion volume with the shape of a truncated cone. In contrast, with exposure to HBO at 303.9kPa (3ata) arteriolar pO_2 equals 2000mm Hg and venular pO_2 to 100mm Hg on the assumption of constant oxygen consumption. The distance of diffusion equals 247μm at the arteriolar end and to 64μm at the venular end of the capillary, leading to a more than ten-fold increase of oxygen diffusion volume. These theoretical considerations have been confirmed by direct measurements of oxygen pressure in various tissues[53].

Nevertheless, the Krogh model remains a simplification because the morphology of the capillaries is not at all uniform, nor the direction of blood flow[54,55].

Intracellular utilization of oxygen is mainly achieved within the mitochondria finally leading to adenosine triphosphate (ATP) generation. The determinant of oxidative phosphorylation is mitochondrial pO_2. The minimum intramitochondrial driving pressure of oxygen to maintain oxidative phosphorylation is considered to be less than 0.5mm Hg[56]. A mean tissue PO_2 of 15mm Hg indicates tissue dysoxia[57]. Diffusion barriers[58] may impair the diffusion from capillary to mitochondria, such as anatomical barriers like abnormal structure and/or thickness of the erythrocyte membrane, arterial/venous shunts, or physical barriers such as altered haemoglobin-O2 affinity or RBC velocity.

3.2 Effect of HBO on tissue PO_2 in various organs

Central nervous system

Polarograhic measurements of tissue pO_2 ($PtiO_2$) in rat central nervous system (CNS)[59] showed a range of 10-34mm Hg with normobaric air breathing. PtiO2 values rise to 452 ± 68mm Hg with breathing pure oxygen at 303.9kPa (3ata), and to 917 ± 123mm Hg with breathing pure oxygen at 506.5kPa (5ata) If CO_2 is added to the inhaled gas, cortical pO_2 increases even further because the vasoconstrictor response to hyperoxia is counteracted. With breathing a gas mixture of 95% O_2 and 5% CO_2, CNS PtiO2 increases to 791 ± 5mm Hg at 303.9kPa (3ata) and to 1540 ± 94mm Hg at 506.5kPa (5ata). Regional variations in PtiO2 depend on neuronal activity cerebral metabolic rate and blood flow. HBO decreases the concentration of NO which is a potent vasodilator, which provides protection against hyperoxic brain damage. In contrast, prolonged hyperoxia and/or higher levels of ambient pressure (506.5-607.8kPa, 5-6ata) led to increased NO production and blood flow, which could not be explained in detail.

Cerebral vasoconstriction, which is a determinant of tissue oxygen pressure, is the result of a sophisticated biochemical cascade of reactions in

response to superoxide anion generation ($O2^-$) induced by HBO. In this context, extracellular concentration of superoxide dismutase (SOD) plays a crucial role in regulating cerebral blood flow in vivo which could be shown in genetically altered mice strains[60]. High concentrations of SOD are found in vessels where NO is important for vascular relaxation.

Daugherty[61] studied the effect of HBO at 1.5ata on cerebral PtiO2, oxygen consumption and mitochondrial function after lateral fluid-percussion injury in rats in comparison to 30% oxygen breathing. HBO was able to restore the reduced post-injury redox potential indicating impaired mitochondrial oxygen metabolism and to increase $PtiO_2$ and brain VO_2.

The impact of HBO on brain oxygenation at 192.5kPa (1.9ata) and 283.6kPa (2.8ata), intracranial pressure and brain glucose/ lactate levels was determined in anaesthetized and ventilated non brain injured pigs[62]. A normobaric increase of the FiO_2 from 0.4 to 1.0 resulted in a rise of brain $PtiO_2$ from 33 ± 14 to 63 ± 28mm Hg. A further increase was observed at 192.5kPa (1.9ata) (F_IO_2 of 1.0) to 151 ± 65mm Hg and at 283.6kPa (2.8ata) to 294 ± 134mm Hg. Intracranial pressure and glucose/lactate levels remained constant.

Tumours

Most tumours contain hypoxic areas so that HBO is a valuable tool to reverse this phenomenon and to act as a radiosensitizer by enhancing the response to irradiation[63,64].

Brizel[65] measured tumour oxygenation in rats who had been implanted R3230Ac mammary adenocarcinomas during breathing NBO, normobaric carbogen, HBO at 303.9kPa (3ata) and hyperbaric carbogen at 303.9kPa (3ata). NBO or normobaric carbogen were not effective but HBO and hyperbaric carbogen improved tumour oxygenation with a rise of median $PtiO_2$ from 8 to 55mm Hg.

Soft tissue

Tissue gas tensions were determined in 6 patients with necrotizing fasciitis and in 3 healthy controls by Korhonen[66]. Samples were taken from healthy distant tissue and in the vicinity of the infected area. Baseline values while breathing room air were 87mm Hg in the healthy brachial subcutaneous tissue and 92mm Hg in the infected area. The mean PO_2 value obtained from the healthy tissue was lower (283mm Hg) than that near the infection site (387mm Hg) during the hyperbaric session at 253.2kPa (2.5ata) for 100 minutes, with a concomitant mean arterial pO_2 of 742mm Hg. This behaviour may be attributed to increased microcirculation enhancing the inflammatory response to infection or due to impaired local oxygen utilization.

Non-healing chronic wounds are often treated with HBO to restore tissue oxygen levels in ischemic areas. Measurements of tissue oxygen pressures permit the correlation of structural changes in the tissue with local oxygen levels. Siddiqui[67] evaluated tissue responsiveness to 14 versus 5 serial HBO treatments in terms of tissue oxygen tensions in the ischemic rabbit ear model. 31 female New Zealand White rabbits underwent selective arterial division at the base of one ear, the other one served as an internal non-ischemic control. Nine of them received only NBO, the others HBO and NBO. Tissue responsiveness was defined as the plateau PtiO2 achieved during NBO exposure. The ischemic rabbit ears receiving 14 daily treatments achieved statistically significant higher tissue oxygen tensions under hyperbaric conditions (253.2kPa [2.5ata], 90minutes) and during HBO exposure than the other groups. On contrary, the behaviour of tissue oxygen tensions during breathing of normobaric air within each group did not differ significantly between baseline values and those after 14 days of HBO treatment. HBO is considered to act as a signal transducer beyond its energy-generating effect in wound healing.

Skin

Reviewing the publications of the past 15 years, transcutaneous pO_2 has been used in combination with HBO treatment as a predictor for the healing of problem wounds[68] or of diabetic ulcers[69] or of final outcome after pedicle musculocutaneous flap transplantation[70,71]. Wound healing and cell division requires a basic tissue oxygen tension of 30mm Hg. Cut-off values have been defined for success or failure of wound healing: Wattel[72] reported the healing of ulcers in patients with arterial insufficiency when the $PtcO_2$ exceeded 100mm Hg during exposure to HBO at 253.2kPa (2.5ata).

Transcutaneous pO_2 values exceeding 400mm Hg during HBO exposure at 253.2kPa (2.5ata) or exceeding 50mm Hg during NBO exposure are considered as good predictors for the healing of chronic foot ulcers in diabetic patients[73].

Other organs

Tissue oxygen tensions have been evaluated, i.e., in the eye[74] and even intracellularly[75]. Nevertheless, data about hyperbaric exposure remain scarce in this context.

Skeletal muscle pO_2 has been measured in patients with gas gangrene who presented with higher $PtiO_2$ values than those with other anaerobic soft tissue infections[76]. Alpha toxin may be responsible for this increase in gas gangrene patients, by destroying cellular membranes and hence pO_2 diffusion barriers.

Medulla oblongata oxygen tension[77] and excitability have been measured in solitary rat neurons exposed to hyperbaric helium to test the effect of pressure per se and to HBO at 253.2kPa (2.5ata) to 344.4kPa (3.4ata). Increased pressure and HBO independently increased excitability in some solitary neurons.

3.3 Methods of tissue PO_2 measurements

The ideal method should fulfill the following criteria: accuracy and reproducibility in a wide oxygen range, easy handling, safe use and non-invasiveness, limited size of the device.

In general, there are two main groups of methods available for the assessment of $PtiO_2$: Polarographic techniques comprising tissue tonometry, transcutaneous electrodes or needle electrodes; and non-polarographic techniques comprising mass spectroscopy, near-infrared spectroscopy (NIRS), magnetic resonance spectroscopy, frozen specimen spectroscopy, positron emission tomography, electron spin resonance, NADH fluorescence, and phosphorescence quenching.

The most common methods in the clinical setting to be used under elevated ambient pressure are transcutaneous measurements, tissue tonometry and NIRS which are briefly described:

Polarography

Based on the discovery of polarography[78] by the Czechoslovakian chemist Jaroslav Heyrovsky in the early 1920s, solid platinum (Pt) microelectrodes were developed 20 years later by Davies and Brink to facilitate in vivo local oxygen pressure measurements. In 1956 Clark presented a rapidly measuring electrochemical cell which has been used in blood gas machines and oxygen monitors since then. In 1972 Huch modified the Clark electrode for non-invasive transcutaneous use[79] which was easy to introduce into the hyperbaric chamber and which became a most valuable monitoring tool in the clinical routine. A Clark oxygen electrode consists of two half cells separated by a salt bridge. A platinum electrode is separated from a solid silver electrode. The electrodes are surrounded by a concentrated potassium chloride solution. The oxygen monitor holds a constant voltage difference between both electrodes so that the platinum electrode becomes the cathode (negatively charged) where electrochemical reduction takes place, and a current flow develops from the silver electrode to the platinum electrode. The current generated by the reduction of oxygen is proportional to the number of oxygen molecules entering the chamber between anode and cathode through a membrane permeable to oxygen molecules.

The electrode is heated in order to obtain more reliable oxygen tension values by vasodilatation and improved diffusion of oxygen out of the tissue beneath. It is attached to the skin by an adhesive ring filled with a contact solution.

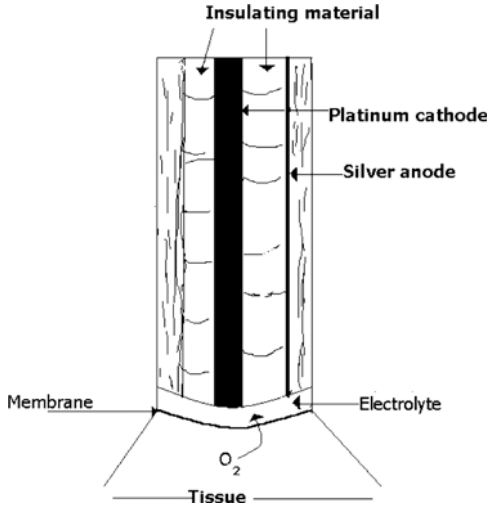

Figure 1.4-4. Schematic view of the oxygen electrode

Tissue tonometry

A miniature tube with a wall permeable to gases is inserted into the tissue and filled with anoxic fluid. The tissue oxygen tension in the fluid becomes gradually equilibrated with the tissue oxygen tension of the adjacent tissue and can be determined after about 5 to 10 minutes of equilibration. Korhonen[80] performed measurements of tissue pO_2 and pCO_2 with an implanted Silastic tonometer and a capillary sampling technique which proved reliable and appropriate for use under hyperbaric conditions. They collected the sample fluids in glass capillary tubes which were sealed and stored on ice until they were measured in a blood gas analyzer. This method is amenable to institutions possessing of a blood gas analyzer and not very costly. It may be considered a drawback that the tissue is slightly injured after insertion, which might influence the values obtained.

Near-infrared spectroscopy (NIRS)

Human tissue contains substances that can be qualified and quantified according to their well-defined absorption spectra at near-infrared wavelengths[81]. The tissue concentrations of oxygenated and deoxygenated

haemoglobin as well as oxidised cytochrome oxidase are proportional to tissue oxygenation and metabolism. Jöbsis[82] was the first to demonstrate that measurements of transmitted light of near-infrared radiation could be used to monitor the extent of oxygenation of certain compounds. According to Lambert-Beer's Law, the absorbance is proportional to the concentration of the compound in the solution and the optical path length:

$$A = log_{10} [Po / P] = a \times c \times d$$

where:
A = absorbance measured in optical densities
P_o = parallel beam of radiation of power Po entering the medium
P = power of radiation transmitted through the medium by absorption
a = specific extinction coefficient of the absorbing compound
c = concentration of the absorbing compound in the solution
d = distance between entrance and leaving points of the light.

Cytochrome c oxidase is located in the mitochondrial membrane and is the terminal enzyme of the respiratory chain. It contains four active redox groups: haem iron centres a and a_3, and copper centres Cu_A and Cu_B. The determination of cytochrome oxidase is more difficult than that of oxygenated haemoglobin due to its low tissue concentration. Oxygen availability within the cell limits the rate of oxygen consumption by cytochrome oxidase, resulting in a higher degree of reduction of the copper centre. The absorbance of near-infrared light by cytochrome oxidase reflects oxygen availability at the cellular level.

A primary goal for monitoring tissue oxygenation is the early detection of cellular respiratory failure. A therapeutic measure to correct tissue hypoxia requires profound knowledge about critical oxygen-supply thresholds of the individual organs. Monitoring oxygenation at the tissue and cellular levels[83] will be important to titrate and to guide the dosage of oxygen during HBO therapy. The quality of sampling, the tissue volume interrogated by any local probe, the localization of the probe, and the distribution of capillaries must be taken into account for the interpretation of results.

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Chapter 1.5

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON HEMODYNAMICS AND MICROCIRCULATION

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Abstract: Hyperbaric oxygen (HBO) in the pressure range used for therapeutic purposes induces haemodynamic changes both at the macro- and micro circulatory levels. In normal subjects, systemic haemodynamic changes mainly concern the heart rate (an effect related to both the barometric and the oxygen pressures). Arterial blood pressure tends to increase slightly. Cardiac output is maintained or moderately decreased due to compensating responses which may fail in patients with pre-existing cardiac failure. At the microcirculatory level, HBO causes vasoconstriction with a decrease in microcirculatory blood flow but with no decrease of oxygen pressure in the tissues. This hyperoxic vasoconstriction does not appear in previously hypoxic areas where the microcirculatory blood flow remains unchanged. Consequently, oxygen pressure in the tissues increase to levels close to normal. The reappearance of cyclic vasomotion seems to indicate an improvement in the local metabolic condition. The haemodynamic and microcirculatory effects of HBO appear to be effective in compensating ischemic conditions, particularly in cases of heterogeneous microcirculatory hypoperfusion

Keywords: haemodynamics, hyperbaric bradycardia, hyperoxic bradycardia, hyperoxic hypertension, cardiac output, regional circulation, cerebral blood flow, coronary blood flow, renal blood flow, hepatosplanchnic blood flow, muscle blood flow, microcirculation, capillary blood flow, hyperoxic vasoconstriction, vasomotion

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Hyperbaric oxygen therapy (HBO) is a therapeutic modality in which oxygen is administered to a patient through his respiratory system at a pressure above atmospheric pressure. The objective is to obtain an increase in pressure of oxygen in the tissues, either to compensate for a deficiency in oxygen supply, or to recruit special effects of oxygen at pressure above normal.

However, delivery of high pressures of oxygen are not exclusively beneficial; toxic effects do occur but are fortunately rare. For the most part, pressures and durations of oxygen exposure used in clinical practice are well off from the limits of toxicity. However, high pressures of oxygen do cause important haemodynamic and circulatory alterations, the most well-known being bradycardia and hyperoxic vasoconstriction. These alterations which have been well demonstrated for healthy subjects, tend to protect tissues from the consequences of hyperoxia.

A number of studies have been published on this subject, with apparently conflicting results. Differences in experimental protocols, populations studied and situations compared make a global synthesis difficult. Here we propose a synthesis of the works available in the literature and our own research in this field.

In the chain of events that brings oxygen from the ambient atmosphere to where it can be used in the cells, there are three basic stages which have long been identified by physiologists :

- Respiration, which involves the entry of oxygen into the body and its distribution in the blood,
- Circulation, which involves oxygen delivery from the small circulation to the capillaries in the tissues,
- Cell oxygenation, the stage where oxygen is brought to the cells where it is to be used.

The period in which this circulation takes place must also be seen as a multi-level process :

- first of all, there is a global macrocirculatory level to consider, where circulation is compared to a circuit of pipes (arteries and veins), pumps (right and left ventricles) and supply reservoirs (lungs and tissues). The effects of HBO on the macrocirculatory level have often been studied by physiologists and clinicians ; here we shall present the effects on *central haemodynamics,*
- a second level in the study of circulation involves blood flow distribution to each organ and even to each part of an organ. This will include a study on the effects of HBO on *regional blood flow*,
- the third level involves *microcirculation* where oxygen is brought to the locations where it is to be consumed.

At each level, high pressures of oxygen produce varying effects. In particular, the final effect varies depending on the condition – normal or pathological – of the body, organ or tissue.

1. CENTRAL HAEMODYNAMIC EFFECTS

On the scale of the whole body, HBO has a multi-facet activity within which it is not easy to distinguish between the actual activity of the high pressures of oxygen and the combined or opposed activity of other environmental factors such as the increase in hydrostatic pressure, variations in temperature or gas densities, etc… Analysing the abundant albeit often contradictory literature enables the following summary of these effects to be made: HBO effects include a decrease in heart rate, an increase in arterial blood pressure, and a tendency to decrease cardiac output[1,2].

1.1 Effects on heart rate

The most well-known effect of HBO on the cardiovascular system is the decrease in heart rate. It has been observed in animals as well as in man, in healthy and diseased patients, at rest and during exercise.

1.1.1 Early works

Shortly after P B reported bradycardia occurring in ducks during diving and the discovery of the bradycardic reflex on immersion of the face, H , Mager & Von Schrötter (1897) described a decrease in heart rate at rest and during exercise in tubing workers exposed to pressures of 2.5 and 3.6 ata. Dautrebande & Haldane (1921), also observed bradycardia in subjects exposed to pure oxygen at 1 ata and 2 ata.

Schilling (1936) performed the first systematic study of this effect and discussed the relative importance of the various factors that could be involved: the increase in pressure of oxygen, density, hydrostatic pressure and inert gas pressure.

1.1.2 Experimental facts

First observed by Dautrebande & Haldane, its importance was made evident by Fagraeus[3]. These authors studied the heart rate and other physiological variables in healthy subjects performing a standardized exercise in various atmospheric conditions: air at 1 ata (A), oxygen at 1 ata (B) and air at 4.5 ata (C). Since pressures of oxygen were the same in

conditions B and C, the effect of the increase in pressure of oxygen could be distinguished from the effect of the other environmental factors. The authors showed that for the four levels of exercise studied, there was a decrease of 12 to 16 beats per minute in condition C, whereas this decease, when it occurred, was only 4 to 7 beats per minute in condition B. They concluded the bradycardia observed in compressed air was mainly caused by high pressures of oxygen, but this only explained in part the bradycardic effect, the part of bradycardia which is not oxygen-dependent being related to other environmental factors.

The relative importance of the oxygen dependent and non-dependent parts was questioned by Shida & Lin[4]. Studying the heart rate of non anaesthetized rats in various atmospheric conditions (O_2-N_2 and O_2-He mixtures) and pressures, these authors showed that, for pressures between 1 and 10 ata this increase in oxygen pressure was the primary cause for the bradycardia. Variations in density, pressure and inert gases produced only marginal effects.

However there are several explanations for the seeming contradiction: beyond the differences in species (man and rats) both the conditions (exercise and rest) and pressures of oxygen differed in range. Fagraeus's study was carried out at a pressure of oxygen of 1 ata whereas Shilda & Lin mostly worked with pressures of 0.6 ata. Kenmure[5] showed the bradycardic effect was close to its maximum at 1 ata oxygen and increasing PO_2 over 1 ata only produced a small effect.

Thus the following conclusion can be made : in the range of pressures used in HBO (1-3 ata, $FiO_2 = 1$), the decrease in heart rate is mostly due to the increase in oxygen pressure, this decrease is nearly completely achieved as soon as normobaric oxygen (NBO) is provided and a higher increase in pressure causes no further decrease in heart rate.

1.1.3 The mechanisms of bradycardia

From the above, it appears that the bradycardia observed in HBO is due to two mechanisms: an oxygen-dependent and a non-oxygen-dependent effect. Many authors have tried to determine the processes involved in both these effects, and particularly whether the autonomic nervous system is involved (Daly & Bonduran[6], Fagraeus & Linnarson[7], Fagraeus[8]). Fagraeus & Linnarson[7] of the autonomic nervous system using anticholergenic and beta-blocking agents in healthy human beings undergoing a standardized exercise testing in various atmospheres (air at 1 ata, O_2 at 1.3 ata and air at 6 ata). Their conclusion was that the oxygen-dependent effect was mainly due to a direct effect of the high pressure of oxygen on the myocardium, combined to a lesser extent with a

parasympathetic effect. The non-oxygen-dependent aspect, on the other hand, was mainly related to a decrease in sympathetic heart tone (i.e., a reduced beta effect).

The relative importance of the direct action on the myocardium and of the indirect action of the autonomic nervous system on oxygen-dependent bradycardia has been evaluated. Doubt & Evans[9] confirmed the direct action of HBO on the myocardium by demonstrating a specifically oxygen-dependent bradycardia, in cats anaesthetized and curarized at a pressure of 31.3 ata (PO_2 = 0.35 ata, PHe = 31 ata). Bergo[10], however, reported the disappearance of the oxygen-dependent bradycardia in rats injected with atropine at 5 ata. In fact, apart from the differences in methods and animal models, it seems possible to reconcile the outcome of both studies in differentiating two HBO effects : (1) the bradycardic effect exerted on heart rate both at rest and during exercise and (2) the bradycardia occurring due to a direct effect on myocardial cells at rest, which is oxygen-dependent, appears quickly, is reversible with atropine, and is therefore probably mainly mediated by the parasympathetic system. This parasympathetic effect is brought into play by the baroreceptors stimulated by the hyperoxia-induced arterial hypertension. The effect is further increased because both the activity of the sympathetic system[11] and the level of circulating catecholamines[12,13] decrease due to the hyperoxia.

Another mechanism that has been proposed is a decreased sensitivity of the chemo-receptors to CO_2 during hyperoxia[14]. However, this is not likely to play a significant role if one considers that the time it would take to develop is much longer than the actually observed onset time for the bradycardia. During exercise, the chemo-receptors are stimulated by the increase in pressure of CO_2 and although this stimulation is weak, it compensates for the vagotonic action. The bradycardia observed is thus mainly of a direct origin.

Finally, it must be emphasized that the oxygen-dependent bradycardic effect is not a sign of oxygen toxicity. As Matalon[15] reported, an increase in heart rate above the baseline takes place before the occurrence of a hyperoxia crisis. Tachycardia rather than bradycardia has long been recognised as a clinical warning sign of an impeding hyperoxic crisis.

1.2 Effects on arterial blood pressure

1.2.1 Experimental effects

The effects of HBO on arterial blood pressure have also been controversial. Although many authors have observed an increase in systolic and diastolic arterial pressure (Whitehorn[16], Alveryd & Brody[17]), other authors found no alteration or non-significant changes (Richards & Barach[18] Behnke[19]). Behnke[20] even considered the increase in blood pressure to be a sign of oxygen toxicity.

In a study including 20 volunteer healthy subjects, Kenmure[21], only observed a small and not statistically significant increase of the mean arterial pressure, but this was combined with a significant 15% increase in systemic arterial resistance. More importantly, the increase in systemic arterial resistance was observed in oxygen at 1 ata and increased only very slightly and insignificantly in oxygen at 2 ata. Dooley & Mehn[22] confirmed these observations. In 11 healthy volunteers randomly breathing either air at 1 ata, O_2 at 1 ata, O_2 at 2 ata and O_2 at 3 ata, they observed a significant increase in mean arterial pressure related to peripheral vasoconstriction (assessed by arm/ankle ratio of arterial pressure) in the group breathing O_2 at 1 ata. However, breathing oxygen at 2 ata or 3 ata did not provide a significant further effect.

1.2.2 Mechanisms of the increase in arterial blood pressure

There is no consensus between authors on the existence of arterial hypertension in HBO, but all agree on the existence of an increase in peripheral vascular resistance, made obvious by calculating systemic arterial resistance[21], or by the arm / ankle arterial pressure ratio[22]. Usually the increase in resistance is related to hyperoxic vasoconstriction.

However because of the localization of the hyperoxic vasoconstriction (arteries of a smaller diameter than the medium- and small-size arteries responsible for the major part of the arterial resistance), of the anatomical and physiological differences related to regional circulation in the organs, of whether the perfused areas are hyperoxic or not, the overall consequences of the vasoconstriction may be very variable. This explains why the effect on arterial pressure can be of variable intensity. Also, systemic arterial resistance is only one of the factors determining arterial pressure. The simultaneous variation in cardiac output also has an influence on arterial blood pressure, which accounts for the apparent contradictory in results of the various studies.

1.3 Effects on cardiac output

1.3.1 Experimental facts

Most authors agree that cardiac output decreases in HBO. Yet the various available studies report contradictory results: exposure to oxygen at 1 ata decreased cardiac output in rats in Torbati study[23]. However, this effect was not observed by Onarheim & Tyssebotn[24], not by Smith in their work on dogs[25], nor by Matalon in their study involving ewes[15]. Cardiac output even increased when manifestations of oxygen toxicity started to occur. In human beings, however, most authors (Eggers[26], Whalen[27], Andersen & Hillestad[28], Kenmure[21]) observed a decrease in cardiac output, but amplitude was small (10-15 %) and the physiological significance uncertain.

1.3.2 Mechanisms of the cardiac output decrease

Nearly all authors agree that the drop in cardiac output in HBO is dependent on the decrease in heart rate (Keys[29], Otis[30], Dripps & Comroe[31], Kenmure[21]). However, Whitehorn[16] have reported a combined decrease in systolic ejection volume (SEV). In patients with myocardial infarction, Cameron[32] also showed a decrease in the SEV. Interestingly, in their patients, cardiac output decreased whereas the heart rate remained the same. Arterial blood pressure rose, indicating a marked increase in systemic arterial resistance. However, these harmful effects on patients with compromised hearts have not been observed by all authors. In fact, several have reported an improvement of heart performance for this type of patient (Smetnev[33], Deepika[34]).

There is little available literature on the ventricular function and the effects of HBO. Savitt[35] observed a decrease in cardiac output, in myocardial oxygen consumption (VO_2) and in coronary output in HBO at 3 ata in anaesthetized dogs, but the changes were proportional so that myocardial contractility remained unchanged. Ishikawa[36] reported an increase of 11% of myocardial contractility when PO_2 was increased to 460 mmHg. They interpreted this increase as the result of a direct beneficial effect of oxygen on the myocardial fibre. However, Ask & Tyssebotn reported a positive inotropic effect related to the barometric pressure itself. But this effect only seems to appear at pressures above those used in HBO[37-39].

In contrast with the findings of Savitt, Kioschos[40] and Abel[41] observed a slight but significant decrease (10-15 %) in the indexes of ventricular performance in anaesthetized animals. This decrease in myocardial contractility was only observed in the left ventricle and Abel[41] made the hypothesis that the relative decrease in left ventricle function combined with a preserved function of the right ventricle could be the cause of spurious cases of pulmonary oedema occurring during HBO exposure.

To clarify this point, we have carried out a study on the global haemodynamic changes induced by HBO (2.5 ata) in 10 critical sedated patients under controlled ventilation[42]. We observed a decrease in heart rate, a moderate increase in systemic and pulmonary blood pressures, and no change in cardiac output. The absence of variation in cardiac output was due to an increase in the SEV mainly related to an increase in ventricular end diastolic volume with the ejection fraction remaining the same.

In our study, no decrease in myocardial contractility was observed. The increase in ventricular afterload due to the hyperoxic arterial vasoconstriction was balanced by an increase in ventricular preload evidenced by an increase in end diastolic filling volume. The increasing effect on preload was mainly related to the hyperbaric pressure rather than to the hyperoxia. These observations are consistent with the finding that hyperbaric pressure rather than hyperoxia increases auricular natriuretic factor release due to an increase in auricular volume[43]. Two mechanisms can account for the increase in preload: the increase in ventricular filling time caused by the bradycardia, and a decrease in ventricular compliance which is made evident by the pressure / volume curves (i.e., Starling curve).

However, these compensatory mechanisms are finite: increasing ventricular work in the presence of pre-existing ventricular dilatation (i.e., a reduction in ventricular compliance) explains why patients with dilated cardiomyopathies or coronary artery diseases may decompensate.

Hence two situations can arise: (1) the myocardium is able to oppose the increase in peripheral resistance by maintaining the systolic ejection volume, either because it has the necessary reserves or because the conditions of hyperoxygenation provide the required oxygen, or (2) the degraded myocardium is no longer able to counter the increase in peripheral resistance and cannot therefore maintain the SEV leading to manifestations of left heart (pulmonary oedema) or cardiac failure during HBO.

If one remembers that it is not so much the body itself but its metabolic requirements - particularly the need for oxygen delivery and CO_2 elimination – that determines cardiac output, it makes sense that the increase in oxygen content by HBO would result in a decrease in cardiac output while peripheral oxygen delivery remains the same.

1.4 Synthesis

Thus the changes in central haemodynamics induced by HBO therapy (2-3 ata) include (1) decreased heart rate, (2) increased peripheral resistance which tends to (3) increase arterial blood pressure and (4) maintain or slightly decrease cardiac output. These manifestations seem to be mainly related to the peripheral action of the high pressure of oxygen which have both a direct vasoconstrictive action on the vessels and an indirect action by bringing into play the chemo- and baroreceptors as well as the autonomic (parasympathetic) nervous system.

2. EFFECTS ON REGIONAL CIRCULATIONS

Thus the effects of high pressures of oxygen on central haemodynamics include a decrease in cardiac output mainly through a decrease in heart rate and an increase in peripheral resistance. However, the way this decrease in blood flow is distributed between the various organs has led to controversy. Once again it should be emphasised that regional blood flow, just like global cardiac output, is regulated by the metabolic requirements of the respective organ system. Experimental protocols can produce great variations in regional blood flow distribution depending on the choice of subjects (small mammals such as rats vs large mammals such as dogs, ewes and human beings) the state of consciousness (conscious or anaesthetized), the drugs administered (type of anaesthesia) and whether subjects are resting or exercising (controlled or spontaneous ventilation).

First we shall analyse the effects of high pressures of oxygen on the various regional circulations, then we shall attempt to describe the mechanisms involved.

2.1 Alterations in regional circulations

2.1.1 Cerebral circulation

As early as 1948, Ketty & Schmidt[44] reported a 13 % decrease in Cerebral Blood Flow (CBF) in normobaric hyperoxia (1 ata, $FiO_2 = 1$) and an 18 % decrease in HBO (2 ata, FiO2 = 1). This decrease has also been observed in anaesthetized dogs under controlled ventilation (Jacobson[45], Bergofsky & Bertun[46]) and in conscious rats in spontaneous ventilation (Hordnes & Tyssebotn[47]). In all these studies, the drop in CBF was equivalent or slightly greater than the drop in cardiac output. In conscious

ewes under controlled ventilation, Matalon[15], observed an increase instead of a decrease in CBF in HBO. However, this increase was only observed when signs of oxygen toxicity occurred and at a time when the global cardiac output itself was increasing.

Alterations in blood flow distribution have been studied within the brain itself. Bergo & Tyssebotn[48] studied CBF distribution to the various areas of the brain in conscious rats in spontaneous ventilation at 1, 3 and 5 ata FiO_2 = 1. At 1 and 3 ata, blood flow only decreased in the areas of the pons, mesencephalon, thalamus and hypothalamus, whereas it decreased in all the areas at 5 ata.

This variation in effects of high pressures of oxygen relative to the application duration of and the pressure itself has also been observed by other authors (Bean[49], Lambertsen[50], Torbati[51]). In conscious rats, Torbati[51] showed how at pressures of oxygen between 1 and 3.5 ata, the drop in CBF was maintained throughout exposure. At 5 ata, FiO_2 = 1, the initial drop in CBF was followed by a secondary increase after 30 minutes. At 7 ata FiO_2 = 1, there was no decrease in CBF, on the contrary, an increase in CBF was shortly followed by a convulsive hyperoxic attack.

In human beings, Torbati[51] confirmed the data of Ledingham[52] by suggesting that the secondary increase in CBF was dependent on an increase in cerebral PCO_2. The vasodilating effect of the latter countered the vasoconstricting effect of the hyperoxia. During moderate hyperoxia (1–3.5 ata, FiO_2 = 1), PO_2 related vasoconstriction limited the increase in tissue PO_2. However, the hyperoxia induced an increase in cerebral PCO_2 by means of (1) alveolar hypoventilation (due to a decrease in respiratory drive) (2) decrease in carbamino-haemoglobin (Haldane effect) (3) decrease in cerebral blood flow due to hyperoxic vasoconstriction, so that vasodilation appeared. This led to an increase in cerebral PO_2 and ultimately toxic manifestations of hyperoxia. The neurological tolerance to hyperoxia is, therefore, related to cerebral vasoregulation which controls PO_2 within a range where anti-oxidizing defences of the cells can compensate for the hyperoxia.

To summarize, the variation in CBF in hyperoxia depends on an interrelationship between various regulating systems in which local PO_2 and PCO_2 seem to play a major role. Thus the state of consciousness, anaesthetic drugs provided, control of ventilation and level of PCO_2 are all important factors to be taken into account when analysing alterations in CBF. Also, Torbati & Carey[53] have emphasised that brain trauma has distinct effects on the vasoconstrictive response to the hyperoxia. This means that whenever HBO is used on cases involving cerebral pathologies, careful monitoring is recommended of: cerebral functions (continuous EEG), jugular venous

pressure and oxygen saturation, jugular arterio-venous gradients for glucose and lactate or of CBF itself.

2.1.2 Coronary circulation

Since the 1970's, many authors have reported that providing oxygen at high pressures causes a decrease in coronary blood flow (with a mean figure of 20 to 30 % for 1-2 ata FiO_2 = 1) (Daniell & Bagwell[54], Podlesch & Herpfer[55], Winter[56]). This was combined with a decrease in myocardial VO_2 of around 20 % and a decrease in lactate extraction.

However, this decrease in coronary blood flow has to be interpreted in the light of a decrease in cardiac output. It is well known the coronary blood flow is closely adjusted to the myocardial VO_2, since the myocardium cannot increase its capacity for oxygen extraction which is already maximal. Hütter[57] has shown how myocardial VO_2 could be approached by the product of systolic arterial pressure by heart rate (SAP*HR). On rats in marked hyperoxia (5 ata, FiO_2 = 1), BREGO[10] reported a 59% decrease in myocardial blood flow at 5 minutes, eventually stabilising at 51% after 60 minutes. In contrast, the external work of the left ventricle was only reduced by 13% after 5 minutes but more importantly, it had returned to normal after 60 minutes. These authors concluded that from the beginning and throughout the exposure to HBO, the coronary output became increasingly inadequate for the amount of ventricular work. This would lead to myocardial ischemia. Yet, the authors were not able to indicate any proof of such hypoxia.

Savitt[35,58] again studied this problem by means of an experimental model in dogs. They showed that at 3 ata FiO_2 = 1, coronary blood flow decreased by 17 ± 10 % myocardial VO_2 decreased by 11 ± 6 % whereas cardiac output decreased by 24 %. Myocardial function, assessed by systolic work remained the same: end diastolic volume curves and the myocardial energetic state as determined by the relationship between myocardial VO_2 and total mechanical energy expenditure (i.e. systolic work of the left ventricle + myocardial internal work) were unchanged. Thus coronary blood flow did not appear inadequate for cardiac output in hyperbaric hyperoxia.

To summarize, there is a decrease in myocardial blood flow in HBO, but this decrease is related to the decrease in myocardial work induced by a decrease in cardiac output.

2.1.3 Renal circulation

In models of anaesthetized (Onarheim[24]) or conscious rats (Hordnes & Tyssebotn[47], Torbati[23]) renal blood flow was decreased in hyperoxia. This decrease seems to be independent of the central nervous system (Norman[59]).

2.1.4 Hepatosplanchnic circulation

Studies on the intestinal blood flow have reported either a moderate decrease in dogs (Bergofsky[46]), in conscious rats (Hordnes[47]), or no change in ewes (Mantalon[15]).

On the contrary, hepatic blood flow in animals has been reported as unchanged[10] or increased[61].

In human beings[62] using indocyanin green clearance, hepatic blood flow has been shown to be maintained even for 16-hour exposures at 1.5 ata FiO_2 = 1.

The preservation and even an increase in hepatic blood flow is remarkable when compared to the nearly universal decrease of blood flow in other organs. It may be accounted for by the fact that the greater part of the hepatic blood flow is of portal venous origin and that the increase in PO_2 in the portal venous blood is much smaller than in the arterial blood. Taking into account the balance between hepatic artery and portal vein where hepatic blood flow is concerned, hyperoxia could cause vasoconstriction of the hepatic artery thus decreasing arterial blood flow into the liver. Portal flow would increase to compensate. Since this involves venous blood, the increase in hepatic PO_2 would be moderate, which could explain that the hepatic blood flow does not decrease.

2.1.5 Muscular circulation

In conscious rats, the blood flow in the striated muscles of the limbs has been found to decrease in hyperoxia[10,60]. In dogs, however, it is hardly affected[46].

Actually, muscular blood flow depends on the level of muscular activity. Thus in conscious rats in spontaneous ventilation, the blood flow in the abdomen and thorax muscles decreases in normobaric hyperoxia and increases in hyperbaric hyperoxia, as well as in hyperbaric normoxia. This increase in local blood flow is probably due to the increase in VO_2 induced by the increase in muscular work caused by an increase in work of breathing due to gas density-related ventilation resistance under hyperbaric condition.

In summary, HBO induces generalized vasoconstriction affecting all organ systems. Global cardiac output decreases and so do the regional blood flows. However, all regional blood flows are not affected equally. Cerebral blood flow seems to decrease in greater proportion to the global cardiac output, and this has a protective effect against the toxic effects of hyperoxia. Coronary blood flow decreases too, but following a decrease in myocardial

work. The other regional blood flows drop proportionally except in the organs where the work is increased by hyperbaric condition (i.e. respiratory muscles) or in the organs that are shielded from hyperoxia by venous admixture (i.e. liver).

2.2 Mechanisms of regional blood flow redistribution

2.2.1 Role of the environmental factors

The effects of the various pressures of oxygen and nitrogen have been studied by Hordnes & Tyssebotn[60]. Cardiac output and regional blood flow were studied using marked microspheres with conscious rats in three conditions: Group 1 : Normobaric Oxygen (NBO) (PO_2 = 1 ata), Group 2 : Hyperbaric air with PO_2 = 1 ata (5 ata, FiO_2 = 0.20), Group 3 : Hyperbaric Nitrox with PO_2 = 0.2 ata (5 ata, FiO_2 = 0.04).

Global cardiac output decreased in the hyperoxic groups but did not change in the normoxic group (i.e., a PO_2 rather than a pressure effect). Cerebral blood flow decreased only in the hyperoxic groups. Myocardial blood flow decreased in the hyperoxic groups whereas it increased in the hyperbaric normoxic group. Respiratory muscle blood flow increased in the hyperbaric groups.

To summarize, regional blood flows were reduced in proportion to cardiac output in the hyperoxic groups with the predominant effect being on cerebral blood flow. Myocardial blood flow was affected inversely by hyperoxia and hyperbaria, as was respiratory muscle blood flow. In a later study, Risberg & Tyssebotn[61] showed that this was actually an effect of hydrostatic pressure (and gas density) and not of the actual pressure of nitrogen.

2.2.2 Role of the central nervous system

Changes in regional blood flow have not yet been explained convincingly. Risberg & Tyssebotn[61] have shown that changes in myocardial output persist even after blocking the beta 1 adrenergic receptors. Savitt[58] et al. have reported a decrease in coronary blood flow after blocking the autonomic nervous system.

Furthermore, the decrease in regional blood flows seems to be unrelated to the decrease in catecholamines observed in hyperoxia[12,13]. Thus the sympathetic nervous system does not appear to be responsible for this redistribution of cardiac output. The very fine adjustment of regional blood

flows within organ systems points toward local (metabolic-related) regulation rather than global humoral or autonomic regulatory mechanisms.

3. EFFECTS ON MICROCIRCULATION

From the above, we can conclude that the precise regulatory mechanisms controlling oxygen and blood supply to organs is related to tissue metabolism. These mechanisms come into play very quickly and are controlled by the respective organs themselves. This is largely independent from the autonomic nervous system and is also unrelated to hormonal regulation via cardio-circulatory adjustment mechanisms (renin-angiotensin system, circulating catecholamines). These features tend to point to regulating mechanisms either at a local level (organs) or rather even at a microcirculatory level.

Thus it is at the microcirculatory level that the action of high pressures of oxygen should be studied.

3.1 Physiology of microcirculation

By microcirculation we mean the part of the vascular network that goes from the pre-capillary arteriole (metarteriole) to the post-capillary venule. Its main functions are to provide nutrients to the tissues and remove cellular waste.

3.1.1 Microcirculation structure[62]

Capillary vessels are very fine structures. Their walls are made of one layer of cells and a basal membrane. This is where nutrient and waste exchanges between tissues and blood take place. In humans there are about 10 billion capillaries with an exchange surface area of between 500 and 700 m^2. Thus anywhere in the body it is rare for a cell to be more than 20 or 30 micrometers far from a capillary.

Generally nutrient arteries divide 6 to 8 times on entering the organs until the diameter becomes small enough for branches to be called arterioles (under 20μm in diameter). The arterioles then divide 2 to 5 times, decreasing to diameters of between 5 and 9 μm, where they end by transferring blood to the capillaries.

The basic structure of microcirculation is the microcirculatory unit where blood enters the capillary network from an arteriole and leaves by a venule. Blood from the arteriole flows through a series of metarterioles (also called

terminal arterioles) whose structure is halfway between that of arterioles and that of capillaries. After leaving the metarterioles, blood enters the capillary network which is made of some wide capillary vessels (called preferential channels) and other smaller ones that are called real capillaries. When blood leaves the capillary network it flows into the venules and returns to the general blood flow.

In their walls, arterioles have a thick muscle layer and thus they can undergo extensive changes in diameter. Metarterioles (terminal arterioles) have no continuous muscle layer but smooth muscle fibres surrounding the vessel at certain points. At the point where capillaries begin from the metarterioles, there is a somewhat thicker mass of smooth muscle fibres surrounding the beginning of the capillary. These muscle fibres are called pre-capillary sphincters. Recent work has shown that they are not organized in a complete ring but rather in a larger mass of cells. Either way, these smooth muscle fibres act like sphincters in that they can open or close the capillaries and their rhythmic activity generates vasomotion. Venules are considerably larger in diameter than arterioles, and their muscle fibre layer is much thinner. Nevertheless, because the pressure in the venous area is much less than in the artery area, venules are also able to contract considerably.

Microcirculation can vary in architecture in the different organs but the general structure is the same. Most of all, metarterioles and pre-capillary sphincters are in very close contact with the tissues they supply. Thus local conditions in the tissues such as nutrient, metabolic end-product and hydrogen ion concentrations can exert direct effects on these structures to control local blood flow in each of microcirculation units.

3.1.2 Capillary blood flow

At any given moment, not all capillaries supplied by a single metarteriole are perfused simultaneously. Similarly, blood flow is not continuous in any given capillary. Thus capillary blood flow is intermittent, with alternating periods of perfusion and periods of collapse every few minutes. This intermittence in capillary blood flow is caused by a phenomenon called vasomotion which is due to intermittent contraction of the metarteriole and of the pre-capillary sphincter.

Despite the intermittence of capillary blood flow, considering the enormous number of capillaries in certain tissues, the function of the capillary network can be assessed by a mean value. Thus mean values of capillary output, capillary pressure and substance transfer through the capillary wall can be determined.

3.1.3 Local control of blood flow

One of the important characteristics of the microcirculation is that it affords each tissue the ability to control its own local blood flow in proportion with its own requirements[62].

This needs-based system of perfusion is vital. Continuous luxury-perfusion to all tissues would have greatly exceeded the mechanical capabilities of the heart. Actually, blood flow in each tissue is usually adjusted to the minimum level which satisfies its requirements. Thus, tissues never lack nutrients and the mechanical workload of the heart is kept at a minimum appropriate level.

Control on local blood flow can be divided into two phases : immediate and long-term control. Immediate control is ensured by swift changes in the diameters of the arterioles and of the pre-capillary sphincters which take place within seconds or minutes to make sure the adequate local blood flow is maintained. Long-term control is responsible for changes in blood flow over periods of several days, weeks or even months. Generally the long-term changes involve the increase or decrease of the number (angiogenesis) and calibre of the blood vessels providing nutrients to the tissues.

3.2 Effects of high pressures of oxygen on microcirculation

3.2.1 Experimental effects

We have long known about the existence of arterial hyperoxic vasoconstriction, particularly in the areas of the brain[44,50], the retina[63], the kidneys[64] or the skeletal muscles[65,66]. However hyperoxic vasoconstriction is not uniform, neither in all organs nor along the arterial axes. Accordingly there is a large number of contradictory studies with varying models and experimental protocols.

Hyperoxic vasoconstriction varies:

- with the location on the artery axis : large diameter arteries (over 80 μm) undergo much less vasoconstriction than finer arteries and terminal arterioles[67,68]. Bertuglia[69] using video-microscopes and Strahler's topographical artery classification[70] showed that the maximum decrease in diameter affected mainly arterioles of the1st and 2nd order, whereas arterioles of the 3rd and 4th order were little affected. However, it must not be concluded that sensitivity of vascular walls to oxygen varies with diameter, since Sullivan & Johnson[71] found no evidence of a variation in constrictive response to oxygen for the various arterial diameters for identical PO_2 in the

environment. Duling[72,73] had made the hypothesis that arteriole vasoconstriction depended on periarteriolar PO_2. Granger[74] showed that vasoconstriction affected vessels of increasing diameters in accordance with the degree of increase in PO_2.

The variation of intensity and location of hyperoxic vasoconstriction was confirmed by Sonny[75] who showed that the greatest amount of vasoconstriction occurred between 1 ata 100% O_2 and 2 ata 100% O_2, but beyond that no significant further changes occurred between 2 ata 100% O_2 and 3 ata 100% O_2 – which agrees with the results of Dooley & Mehm study[22].

- with blood flow : it was observed a long time ago that hyperoxic vasoconstriction affects organs differently. Vasoconstrictive response is stronger in skeletal muscles[76] than in mesenteric vessels[77]. In an arterial segment model it has been shown that an increase in blood flow causes greater vasoconstriction in hyperoxia[78]. Thus, the vasoconstrictive response to oxygen is flow-dependent.

- with the pre-existing arterial contraction : Hoogerwerf[79] et al. have provided evidence of an increase in vasoconstrictive responsiveness in vessels that have previously undergone noradrenergic constriction.

Vasomotion is also affected by hyperoxia: it decreases its frequency and amplitude. Many capillaries seem to be totally closed and only open briefly. Perfusion time decreases and tends towards zero[68,80].

All these phenomena are reversible and microcirculation reverts to a normal condition 15 to 20 seconds after return to normal oxygenation conditions.

3.2.2 Consequences of hyperoxic vasoconstriction on pressures of oxygen in the tissues

The various effects of hyperoxia on arteries depending on their size combine with each other to limit an increase in PO_2. Contractions of the 1st and 2nd order vessels decrease capillary blood flow while the small effect on 3rd order vessels causes an increase in shunted output[69].

Both these phenomena account for the unchanged or moderately increased tissue PO_2 in hyperoxia. Whalen & Nair[81,82] showed in normal rats that cellular pressure of oxygen was approximately 6 mmHg and did not increase significantly when animals breathed NBO_2. Their PvO_2 increased indicating that the full potential for oxygen delivery to cells had not been realized under normobaric conditions: this was therefore not a reflection of what might be achieved under conditions of greater transcapillary oxygen diffusion as might be achieved during HBO.

These experimental effects are important because they show that cellular PO_2 only undergoes limited changes in hyperoxia. Thus the decrease in blood flow due to the hyperoxic vasoconstriction really has a protective effect against the toxic effects of oxygen.

3.2.3 Relation between the onset of vasoconstriction and pressures of oxygen in the tissues

The occurrence of hyperoxic vasoconstriction has often been an argument against the use of HBO in ischemic situations. A decrease in blood flow could induce a further decrease in peripheral DO_2 causing hypoxia in the tissues[83,84]. Furthermore, hyperoxic vasoconstriction of arteries supplying already ischemic areas would also aggravate the hypoxia[72].

However, although this theoretical concern has often been mentioned, no study has reported evidence of an occurrence of tissue hypoxia due to hyperoxia. In fact a number of authors have shown that despite a decrease in blood flow caused by vasoconstriction, the hyperoxygenation of the arterial blood causes an increase in PO_2 in the tissues[85,86].

This is because hyperoxic vasoconstriction is a local vascular response to an increase in PO_2. Although we cannot describe the detailed mechanism, it appears to be the increase in PO_2 at the level of the terminal arterioles or the periarteriolar space that triggers vasoconstriction. So this is a very precise regulation of blood flow to adjust for the requirements of the perfused tissue unit. The hypothesis can thus be made that as long as in a given area, oxygen pressure has not increased beyond a certain threshold, the vasoconstrictive effect does not occur. In support of this hypothesis, we carried out a study on cutaneous microcirculation due to its accessibility and sensitivity to hyperoxic vasoconstriction[42].

Ten patients treated for localized ischemia with HBO 2.5 ata underwent a study in which transcutaneous pressures of oxygen ($TcPO_2$) were measured and microcirculatory blood flow was measured. Using transcutaneous oximetry and Doppler laser flowmetry respectively, the ischemic and controlateral (control) areas were evaluated in 3 different conditions: atmospheric air, NBO and HBO 2.5 ata. Our results showed that cutaneous blood flow decreased in the areas where pressures of oxygen increased beyond normal levels but that this decrease did not take place in areas where the values of pressures of oxygen remained subnormal (Table 1.5-1 - Figure 1.5-1).

	Transcutaneous pressures of oxygen		
Area	*1 ata air*	*1 ata O_2*	*2.5 ata O_2*
Subclavicular	38 ± 15 *	336 ± 94 *	1059 ± 166
Ischemic	23 ± 17 *	75 ± 40 *	405 ± 214
Contralateral	33 ± 22 *	218 ± 75 *	817 ± 192
	Doppler laser blood flow		
Area	*1 ata air*	*1 ata O_2*	*2.5 ata O_2*
Ischemic	17 ± 11 ns	17 ± 9 ns	16 ± 9
Contralateral	15 ± 5 *	12 ± 4 *	9 ± 3

* $p < 0.05$

Table 1.5-1. Transcutaneous pressures of oxygen and amplitude of the Doppler laser flow in various pressures of oxygen in 10 cases of localized ischemia

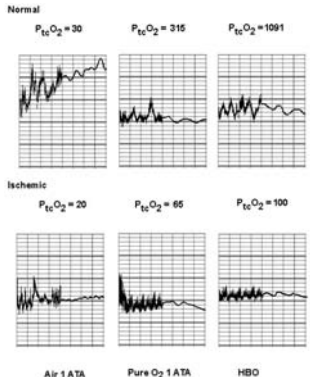

Figure 1.5 -1. Doppler laser flow in ischemic area and normally perfused area in various breathing pressures of oxygen. In the normally perfused area, the Doppler flow decreases whereas $PtcO_2$ increases. In the ischemic area, the Doppler laser flow remains the same whereas $PtcO_2$ does not reach a high level. Note the vasomotion waves in the ischemic areas which are not seen in atmospheric air but appear during HBO.

Inhaled pressure of oxygen

So hyperoxic vasoconstriction is a local phenomenon where local blood flow adjusts to the requirements of the perfused tissues. Even more importantly, the recurrence of vasomotion in ischemic areas shows that the

pace-maker function of the smooth muscle cells is once again at work – demonstrating an improvement in their metabolic condition[87].

Four conclusions can be made from our study: (1) DO_2 in ischemic areas is increased in HBO because there is an increase in the blood oxygen content and because local blood flow does not decrease; (2) hyperoxic vasoconstriction appearing in normally perfused areas is in fact an adjusted response of the vessels reducing the risk of oxygen toxicity; (3) vasoconstriction in correctly perfused areas combined with maintained blood flow in ischemic areas leads to a redistribution of blood flow into the poorly perfused areas. This phenomenon of vascular redistribution can play an important part in the beneficial effects of HBO in cases where perfusion is heterogeneously altered in organs - for instance in reperfusion syndromes; (4) the recurrence of vasomotion proves the improvement of the metabolic condition of the ischemic areas. This could be used as an objective to guide the use of HBO in clinical practice.

3.2.4 Mechanisms of hyperoxic vasoconstriction

Hyperoxic vasoconstriction does not seem to be of reflexive in origin. Differences in regional distribution, the vascular site of action[88] and the decrease in sympathetic activity during hyperoxia[11-13,89] argue against this theory.

All authors agree that hyperoxic vasoconstriction is linked to regulatory mechanisms acting at the level of the microcirculation units. Whalen & Nair[81,82], were the first to show that cellular PO_2 in muscles underwent no change in hyperoxia and that this was due to an adjustment of the microcirculatory blood flow. Duling allocated the action of hyperoxia to the terminal arterioles and the precapillary sphincters[72].

Granger[74] showed that the higher the level of hyperoxia, the bigger the vessels affected by vasoconstriction. Thus, depending on the degree of hyperoxia, the primary control mechanism involves an effort by the microcirculation to limit gaseous exchanges; if this is unsuccessful, a secondary mechanism comes into play involving vasoconstriction of the proximal (resistance) arteries.

The precise mechanisms of hyperoxic vasoconstriction are still not fully understood. Duling[72] showed that oxygen did not have a direct action on vascular smooth muscle cells. The involvement of mediators has been suggested[83]. The idea of prostaglandins being involved has been abandoned because there is no action of the cyclo-oxygenase inhibitors[90,91]. Two mechanisms have been suggested :

- Rubanyi & Vanhoute[92] showed on the coronary artery rings of cats that the superoxide anion had an inhibitive effect on the EDRF released by

the vascular endothelium in response to acetylcholine (which is currently identified as NO) and that hyperoxia encouraged the inactivation. This mechanism can account in part for the vasoconstriction and particularly for the fact that it spreads from the smaller to the larger vessels, but does not fully explain how some terminal arterioles are completely obstructed.

- Jackson[84,93] gave evidence of the vasoconstrictive role of leukotrienes in hyperoxic situations and of their inhibition caused by lipo-oxygenase inhibitors and leukotriene receptor antagonists. The cells which produce these have not yet been identified. It seems that it cannot be the arteriolar wall cells since the signal is generated at a distance[93]. The cells of other vascular walls (venules, capillaries), parenchymal cells or certain blood cells could be producing the leukotrienes. However, the variability in responses depending on the various artery sizes seems to indicate that certain responses must originate from the arteriolar muscle cells.

To summarize, microcirculatory blood flow undergoes a remarkably precise adjustment to oxygenation conditions. Effective protective mechanisms are brought into play to stop pressures of oxygen in the tissues from increasing beyond appropriate levels. There appears to be a hierarchy in these mechanisms, enabling recruitment of defence strategies to vary with the intensity of the hyperoxic challenge. Also they are reversible and discontinue once the hyperoxia ceases. Lastly and most importantly, they do not appear to exceed their objective: i.e., they do not induce paradoxical hypoxia.

4. CONCLUSION

HBO administered in the range of pressures used for therapy induces haemodynamic effects both on a central and on a microcirculatory level.

Changes in central haemodynamics mostly involve a decrease in heart rate (effects of pressure and oxygen). Arterial blood pressure tends to increase slightly and cardiac output is maintained or slightly decreased. These are related to adjustment mechanisms that may be harmful in the case of pre-existing cardiac compromise.

On a microcirculatory level, hyperoxic vasoconstriction only occurs in areas where pressures of oxygen increase above normal levels. In previously ischemic areas the increase in oxygen pressure remains close to normal and is not combined with a decrease in local blood flow. On the contrary, the renewed occurrence of vasomotion suggests an improvement in local metabolic conditions.

Thus HBO appears to effect circulation in a way that is beneficial for conditions of hypoperfusion – particularly when these are heterogeneously distributed. Its effects on tissues and especially on cells still need further study.

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Chapter 1.6

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON MICROORGANISMS AND HOST DEFENCES AGAINST INFECTION

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Abstract: Physiologic effects of hyperbaric oxygen on microorganisms and host defence mechanisms against infection fall into three categories:
- a direct action on anaerobic bacteria
- an indirect action on the microbicidal capability of polymorphonucleocytes and macrophages by raising or restoring normal oxygen pressure within the infected areas.
- an enhancement of the antimicrobial activity of some antibiotics.
These actions have been proven both in vitro and in animal studies and are the basis of the use of HBO in selected infectious processes

Keywords: anaerobic bacteria, oxygen free radical, antioxidant, phagocytosis, bacteriostasis, bactericidal activity, polymorphonuclear leukocyte, antibiotics, infection

1. INTRODUCTION

The use of Hyperbaric oxygen therapy (HBO) against infections started in 1961, when Brummelkamp & Boerema reported on their first successful treatment of gas gangrene in human subjects in Amsterdam[1]. Some years later refractory chronic osteomyelitis became another recognized indication for HBO in infectious pathology[2]. Over the last decades, an enormous amount of experimental and clinical research has been conducted on the effects of high pressures of oxygen on bacteria, on body's defence

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mechanisms and on healing processes, enabling us to reach a better understanding of the therapeutic effects of HBO and to make a more precise assessment of clinical results. In the same time, the awareness and knowledge regarding the toxic effects of oxygen have been improved.

2. EFFECTS OF THE INCREASE IN PARTIAL PRESSURES OF OXYGEN ON BACTERIA

2.1 Susceptibility of bacteria to oxygen

Bacteria can be sorted into the following groups depending on their tolerance to oxygen[3-7]:

1. *strictly aerobic bacteria*: those absolutely requiring molecular oxygen to develop since oxygen is the final obligatory electron acceptor,
2. *microaerophiles*: those able to use oxygen but developing best in concentrations of oxygen lower than in air,
3. *aero-anaerobes or facultative anaerobes*: those developing with or without oxygen since their metabolisms are based either on respiration or fermenting processes (*Staphylococci* and *Enterobacteriaceae*),
4. *aerotolerant anaerobes*: those still able to develop in the presence of molecular oxygen but develop better without oxygen (*Streptococci* and *Enterococci*)
5. *strictly anaerobic bacteria with anoxybiotic metabolism*: those for whom molecular oxygen is lethal. These bacteria use fermenting processes to produce energy (the final electron acceptor is organic or mineral but not oxygen) and most of them do not have any of the usual enzymes of respiratory systems such as superoxide dismutase, catalase or peroxidase. The toxic effects of molecular oxygen vary: some bacteria are Extremely Oxygen Sensitive (EOS) and die after a very short exposure. These can only withstand oxygen concentrations under 0.1 %. EOS bacteria which have been studied on man are commensal bacteria of the digestive tract and of the skin and seem to have no pathogenic effects. Some strictly anaerobic bacteria are unable to develop in concentrations of oxygen above 0.5 % (*C. haemolyticum*). Most of the anaerobic bacteria involved in infectious pathology are moderately anaerobes with an oxygen tolerance of 0.5 to 5 %. These include *B. fragilis*, *C. novyi*, *P. melaninogenica*, *Peptostreptococcus*[4,6,8]. In contrast, other anaerobic bacteria can develop in air but only into very small colonies[3,7] (Table 1.6-1).

It is to be noted that within each group aerotolerance varies widely. The metabolisms of micro-organisms are also different with *in vitro* experimentation than is found in *in vivo* in natural environments[5,8].

Table 1.6 -1. In vitro oxygen susceptibility of strictly anaerobic bacteria (from Loesche[8])

Pressure of Oxygen (mmHg)	0	1	2	3.5	5	8	15	20	30	45	60	75	90
Bacteria													
Clostridium haemolitycum	++	++	++	++	+	0	0						
Peptostreptococcus	++	++	++	++	++	++	+	0	0				
Clostridium novyi	++	++	++	++	++	++	+	0	0				
Bacteroides oralis	++	++	++	++	++	++	++	++	+,V	+,V	0	0	
Prevotella Melaninogenica	++	++	++	++	++	++	++	++, V	++, V	+,V	+,V	0	0
Fusobacterium Nucleatum	++	++	++	++	++	++	++	++	++	++	+,V	0	0
Bacteroides fragilis	++	++	++	++	++	++	++	++	++	++	+,V	0	0

++ : normal development

\+ : development is slowed

V : development varies with strain or incubation duration

0 : no development

2.2 Effects of the increase in partial pressure of oxygen on development and viability of bacteria

These effects have been studied on experimental models of bacterial infections both *in vitro* and *in vivo*.

2.2.1 In vitro

Pressures of oxygen above 4 mmHg are quickly lethal for strict anaerobes. Pressures of oxygen in the range of normoxia (20 % of O_2; PO_2 of 152 mmHg) are lethal after a 2-hour exposure for *Peptococcus magnus*, after 5 hours for *Bacteroides fragilis* and after 10 hours for *Clostridium perfringens*[9].

HBO has bacteriostatic and even bactericidal effects on *Clostridia*. The inhibiting or lethal effect of oxygen varies with the strain of *Clostridium* the bacteria reproduction cycle (development phase) pressures of oxygen exposure duration and culture media. Quiescent spores of *Clostridium perfringens* are not susceptible to oxygen toxicity. *In vitro*, HBO has

bactericidal effects on *Clostridium perfringens C. novyi C. histolyticum* and *C. tetani*, whereas *C. bifermentans* and *C. septicum* are more resistant[10]. Blood or tissue debris impede the effects of oxygen since the catalase they produce destroys the autodestructive peroxides produced in an oxygenated atmosphere by the *Clostridia*[4,10-12].

One of the major benefits of HBO is the inhibiting effect on the development of toxins. This is inhibited at pressures of oxygen above 80 mmHg[13,14]. In contrast, although HBO stops the activity of certain toxins such as theta-toxins, it has no effect on previously produced alpha-toxins[11].

Facultative anaerobes and aerobes survive in hyperoxia (PO2 under 760 mmHg), whereas a 24-hour exposure at 3 ata 100% O_2 has a bactericidal effect on *Pseudonomas aeruginosa Proteus vulgaris* and *Salmonella typhi*[15].

High pressures of oxygen can inhibit or stimulate the development of facultative anaerobes or strict aerobes. Aerobes provide a 2-phase response to an increase in pressure of oxygen. Usually development of aerobic bacteria is stimulated in pressures up to 1.5 ata 100 % O_2, and inhibited at higher pressures[16,17]. A bacteriostatic effect has been observed on *E. coli*[18,19], as well as on many *Enterobacteria*, *Pseudonomas aeruginosa* and *Enterococcus faecalis*[16] after exposure to pressures of oxygen between 1.5 and 3 ata. The bacteriostatic effect has been observed for short exposure durations at 8-hour intervals[20].

2.2.2 In vivo

Most of the experimental research on the activity of HBO in infections involves anaerobic infections. As early as 1972 Holland proved the effectiveness of HBO as monotherapy in a randomized study involving a model of *Clostridium* infection in mice[21]. Demello, comparing surgical debridement, antibiotics and HBO (100 % O_2, 3 ata, 2-hour sessions, 3 times a day on day1, twice on day 2, once on day 3) in a model of experimental gas gangrene in dogs (*Clostridium perfringens*) obtained the best survival rate by combining the three[22]. Hill & Osterhout have shown the effectiveness of HBO in two models of infection in mice (implantable disks, injection of *Clostridium perfringens*)[11.] Later studies have shown that the effectiveness of HBO increased when the delay between inoculation and the administration of HBO was reduced. HBO has also been found effective for treating intrahepatic micro-abscesses involving *Bacteroides fragilis* and *Fusobacterium necrophorum* in mice, the latter with greater effectiveness[23].

In 1986 Thom showed the usefulness of HBO in models of peritonitis in rats induced by inoculations combining *E. coli*, *Enterococci*, *Bacteriodes fragilis* or fecal flora[24]. Using inoculations of *E. coli* and *Bacteriodes fragilis*

in the same model of peritonitis in rats, Muhvich et al also showed the effectiveness of combining HBO, surgery and antibiotics[25]. More recently, Stevens[26] and Hirn[27] confirmed the additional benefit provided by HBO when combined with antibiotics and surgery.

Although there are no controlled studies, the effectiveness of adjunctive HBO on anaerobic soft tissue infections in combination with antibiotic therapy and surgery has been confirmed clinically by a number of research teams over the last 30 years[28].

2.3 Bactericidal activity and bacteriostasis: mechanisms of action

Molecular oxygen is relatively inert but can react with organic molecules, inducing the production of highly reactive intermediates: free radicals or reactive oxygen species (ROS)[29,30]. The development and accumulation of free radicals account for the bactericidal and bacteriostatic effects of an increase in pressure of oxygen. It is generally agreed that bacteria with no defence mechanisms against free radicals are more susceptible to an increase in pressure of oxygen[5,16].

Free radicals are a type of molecule with one or more free electrons. Oxygen molecules include two free electrons on two different orbitals but spinning in parallel. To react with other molecules and accept electrons (oxidation), these must spin inversely – this is why molecular oxygen is not very reactive. But when oxygen molecules accept just one electron, an oxygen superoxide radical ($O_2^{\bullet}$) is formed[30]:

$$O_2 + e^- \rightarrow O_2^{\bullet}$$

Superoxide radicals are mostly produced in the mitochondria during redox reactions. The quantity of $O_2^{\bullet}$ produced increases in proportion to the concentration in oxygen. In aqueous media, $O_2^{\bullet}$ turns into hydrogen peroxide (H_2O_2) by a dismutation reaction:

$$2O_2^{\bullet} + 2H^+ \rightarrow H_2O_2 + O_2$$

Hydrogen peroxide is not considered a free radical because it does not have any free electron. However, hydrogen peroxide passes readily through membranes while radicals like $O_2^{\bullet}$ are charged and therefore do not. The capacity of hydrogen peroxide for deleterious effects is therefore due to its great diffusivity. It becomes reactive when in contact with certain metal ions such as iron or copper. This reaction causes a highly reactive hydroxyl radical ($OH^{\bullet}$) to be produced (Fenton's reaction):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH$$

Neither the superoxide radical anion nor the hydrogen peroxide are particularly cytotoxic per se, but as both can generate hydroxyl radicals they are potentially highly dangerous. The hydroxyl radical reacts very swiftly

with many molecules such as DNA, proteins and carbohydrates. It also destroys membrane lipids in a lipid peroxydation process (chain reaction). Free radicals can encourage the production of secondary messengers such as diacylglycerol or phosphatidic acid by its activity on cell membranes.

2.4 Suceptibility of bacteria to oxygen: mechanisms of defence

The oxygen tolerance of bacteria is related to their defence mechanisms against free radicals: superoxide dismutase, catalase, glutathione peroxidase and NADH oxidase being the main enzymes involved[5,30].

Superoxide Dismutase (SOD) is bacterial main defence against free radicals. This enzyme catalyses the dismutation reaction which eliminates the superoxide and turns it into hydrogen peroxide which is less toxic :

$$2O_2^{\bullet} + 2H^+ \rightarrow H_2O_2 + O_2$$

All SODs are metalloproteins. MnSOD (manganese SOD) is located in the mitochondria, whereas Cu & ZnSOD (copper and zinc SOD) is present in the cytoplasm. These destroy the free radicals produced in the cells where they are located because generally $O_2^{\bullet}$ does not pass through biological membranes. There is also a extracellular form of Cu & ZnSOD[5,30]. Hydrogen peroxide (H_2O_2) is eliminated by the enzymes catalase and glutathione peroxidase – the latter requiring reduced glutathione and selenium. These induce the breakdown of hydrogen peroxide into water and molecular oxygen, thus avoiding hydroxyl radicals from being produced :

$$H_2O_2 \rightarrow 2H_2O + O_2$$

All aerobic organisms with cytochrome systems have superoxide dismutase and catalase, whereas strict anaerobes have no superoxide dismutase, nor usually catalase. Aerotolerant anaerobes have no catalase but do have SOD. Some authors[31] state that the deficit in superoxide dismutase is the main reason for which strict anaerobes cannot tolerate air. However, enzymatic activity has been detected in a number of strict anaerobes. In a study on 22 strains of pathogenic anaerobes, Tally was able to make a correlation between aerotolerance and SOD levels[32]. The latter can be a virulence factor that enables anaerobes to survive in oxygenated tissues until more favourable conditions enable them to start developing again[5]. Most *Bacteroides* have superoxide dismutase and this presence of superoxide dismutase can account for the aerotolerance of *Bacteroides*. However, some bacteria, such as *Lactobacillus plantarum*[33] are without any SOD, catalase or peroxidase, yet tolerate air. Archibald & Fridovich have shown how intracellular manganese is able to trap the superoxide radical anion thus compensating for the absence of the enzymes involved in detoxifying the

oxygen reduction derivatives[34]. NADH oxidase allows NADH to be turned into NAD with the hydrogen combining with oxygen to form water :

$$4\ NADH + O_2 \rightarrow 4\ NAD + H_2O$$

3. EFFECTS OF PRESSURE OF OXYGEN ON HOST DEFENCE MECHANISMS

Faced with an infection, the body brings two responses into play: one is specifically directed at the offending micro-organism and generated by the immune system, whereas the other is non-specific, involving the inflammatory reaction and its consequences. Beyond the direct activity on bacteria we have previously described, HBO enables the defence mechanisms to recover their effectiveness by restoring adequate tissue oxygenation conditions[35]. Bacterial penetration into the body induces an inflammatory reaction generating foci of infection where cellular and humoral mechanisms are essential to eliminate the infective agent.

3.1 Phagocytosis

The function of phagocytes, particularly polymorphonucleocytes, and macrophages is to ingest, destroy and digest micro-organisms. Firstly bacteria stick to the phagocytes. The phagocytes then surround the bacteria with pseudopods and internalize them by invagination into the cytoplasm membrane. A vesicle containing the bacteria develops within the cell : the phagosome. Bacteria are affected by bactericidal effects when free radicals penetrate the phagosome. Phagocytosis is accompanied by an enormous increase in the phagocyte's oxygen consumption (over 30 times the normal figure) called the oxidative burst. NAPDH production by the hexose monophosphate shunt increases greatly and NADPH oxidase penetrates the phagosome. NADPH oxidase reduces the molecular oxygen into superoxide radical within the phagosome. An SOD turns these superoxide ions into highly bactericidal H_2O_2, which is detoxified by catalase, myeloperoxidase or glutathione peroxidase. The most important system in polymorphonucleocytes is myeloperoxidase which produces the highly bactericidal hypochlorite (ClO^-)[36,37]. Along with the oxidative burst, phagolysosome fusion takes place and lysosome contents pour into the phagosome. Fusion starts with the primary granules which contain a large quantity of myeloperoxidase. Then secondary granules fuse to complete the digestive stage where bacterial constituents are eliminated by exocytosis,

letting the bacterial antigens loose and making them available to the immune competent cells of the immune system (specific immune response)[36,37].

3.2 Hypoxia and infection

It has long been recognized that ischemic wounds and tissues are particularly vulnerable to infection. The decrease in local perfusion means the inflammatory reaction cannot develop normally since it reduces the input of oxygen, polymorphonucleocytes and plasma-derived mediators. Hypoxia is the most important factor accounting for the body's inability to destroy bacteria[38]. Since Silver's work, it is known that pressures of oxygen are considerably decreased in the centre of an infective focus, sometimes only reaching 3 mmHg. This hypoxia is a consequence both of the decrease in oxygen input due to the decrease in local perfusion and to the increase in oxygen consumption induced by the inflammatory phenomena and the bacterial invasion[39].

3.3 Consequences of hypoxia on polymorphonuclear microbicidal activity

In vitro and *in vivo* experimental research has largely demonstrated the deleterious effects of hypoxia on phagocytosis. In 1976, Hohn compared the bactericidal activity of cultures of *Staphylococcus aureus* exposed to pressures of oxygen ranging from 0 to 150 mmHg in the presence of normal human polymorphonuclear leukocytes (PMN's) and PMN's from children suffering of Chronic Granulomatous Disease (CGD)[40]. They observed that bactericidal activity in normal PMN's decreased when oxygen pressure dropped under 30 mmHg and this was only half the normal activity in pressures around 0 mmHg, reaching a level similar to that of CGD subjects (Figure 1.6-1). However, the decrease in bactericidal activity of the hypoxic PMN's was reversible when normal conditions of oxygenation were restored in the environment, while those of PMN's of CGD subjects were not. Hypoxia, which is the equivalent of a lack of substrate in terms of the oxidative burst phenomenon, has similar consequences to those of the NADPH oxidase enzyme deficit (i.e., CGD sufferers)[40]. In an hypoxic environment, other authors have also observed a decrease in the bactericidal activity of the PMN's against a number of bacteria commonly found in wounds and abscesses (i.e., *Proteus vulgaris*, *Salmonella typhi murium, Klebsiella pneumoniae*, *Staphylococcus albus*, *Pseudomonas aeruginosa*, *Escherichia coli*, etc)[41-43]. Hence, the production of free radicals by the PMN's is decreased by 90 % in an anaerobic environment when compared to a normoxic environment. Anaerobic conditions prevent the oxidative burst

from occurring *in vitro*, causing an arrest in the production of free radicals in the lysosomes and thus stopping to oxygen-dependent bactericidal activity[40].

In vivo, the extent of the decrease in bactericidal activity of the PMN's in hypoxic conditions has been shown on an experimental model in dogs involving skin and muscle-skin flaps inoculated with *Staphylococcus aureus*[44,45]. This work clearly showed how infectious necrotic lesions developed in hypoxic areas in pressures under 30 to 40mmHg. Radioactive marking of the PMN's confirmed that they continued to migrate but that their bactericidal activity in the hypoxic tissues was affected. Harris has shown how bactericidal activity against *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* decreased in the lungs of mice in hypoxic conditions[46].

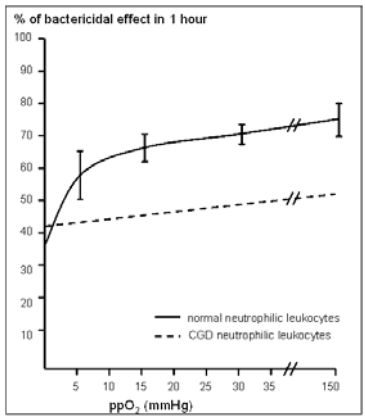

Figure 1.6-1. Effects of different pressures of oxygen on PMN's in normal subjects and subjects suffering chronic granulomatous disease (CGD) (bacteria : *Staphylococcus aureus*) [40]

3.4 Effects of HBO on the host defence mechanisms

Hamblen[47] carried out the first experimental study of the effects of HBO on osteomyelitis in rats. In 1980, in a rabbit model for osteomyelitis, Mader showed how HBO (100 % O_2 at 2 ata) improved the bactericidal activity of the PMN's against *Staphylococci* and how intramedullary PO_2 increased from 20 mmHg in normoxia to 104 mmHg at 2 ata[48]. In an *in vitro* study carried out at the same time, after increasing pressure of oxygen from 45 to 150 mmHg for two hours, the bactericidal activity of PMN's against *Staphylococcus aureus* increased from 44 to 71%. The partial pressures of oxygen obtained in the osteomyelitic bone and *in vitro* before administration

of HBO would have inhibited the bactericidal effects of PMN's to a greater extent than they would have inhibited the development of *Staphylococcus aureus*, which clearly illustrates the impact of HBO on the defence mechanisms of the host. We can therefore conclude that the bactericidal effect of HBO is due to the restoring of the pressure of oxygen required for the oxidative burst to occur.

In a model of subcutaneous infection in rabbits, Hunt (Figure 1.6-2) showed by counting the number of bacteria in the wound exudate that bactericidal activity was greater in animals placed in hyperoxic environments (40 to 45 % O_2) than in animals in hypoxia (12 to 14 % O_2)[38,49,50]. Likewise, Knighton showed in a model of skin infection in guinea pigs placed in various oxygen concentrations (hyperoxia : 45 % O_2, normoxia : 21 % O_2, hypoxia : 12 % O_2) that after 24 and 48 hours the diameter of the area of infective necrosis had decreased in the animals placed in hyperoxia as compared to those in hypoxia[51].

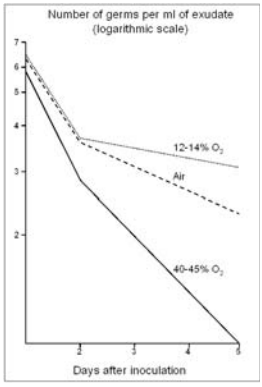

Figure 1.6-2. Effects of oxygen on the amount of bacteria in the exudate of experimental wounds on rabbits[19]

In contrast with these studies proving the usefulness of HBO for fighting infection in hypoxic tissues, prolonged exposure to high pressures of oxygen may also have deleterious effects on the functions of PMN's and macrophages. In guinea pigs, prolonged exposure to hyperoxia (85 % O_2, 90 hours) induced a decrease in the adhesion, chemotaxis, phagocytosis and bactericidal activity of the PMN's[52]. In a recent study on 10 healthy volunteers placed in HBO for 136 minutes at 1.8 ata, Labrouche observed an alteration in PMN's functions including a decrease in chemotaxis and in chemokinesis, combined with an increase in oxidative burst and phagocytosis[53].

3.5 Effects of oxygen on macrophage activity

Anaerobiosis does not reduce the phagocytic activity of peritoneal macrophages but prolonged *in vitro* exposure (over 24 hours) in hyperoxia or to HBO induces in macrophages a decrease in phagocytosis, bactericidal activity, cellular mobility and DNA synthesis[54]. These alterations could be due to the anomalies in oxidizing activity, since the NADPH oxidase activity and the production of $O_2^{\bullet}$ are decreased. However, short exposure (2 hours) to HBO (100 % O_2, 2 to 3 ata) does not alter phagocyte activity in the splenic macrophages of mice[17].

Phagocyte viability is not altered by a short exposure to HBO. *In vivo* studies have confirmed the deleterious effects of prolonged hyperoxia (85 % O_2, 90 hours) on alveolar macrophages with decreased chemotaxis, adhesion, phagocytosis and bactericidal activity. This partly accounts for the large number of respiratory infections in patients undergoing prolonged HBO[52].

3.6 Effects of oxygen on lymphocyte functions

Lymphocytes survive well in hypoxia and in hyperoxia. However, *in vitro*, in human lymphocytes stimulated by phytohemagglutinin, RNA synthesis undergoes a decrease after a 48-hour period of anoxia (3 to 9 % O_2) and stops after a 48-hour period of anoxia. Likewise, hyperoxia (70 to 100 % O_2 for more than 48 hours) inhibits DNA synthesis in lymphocytes. Hyperoxia inhibits the development of B and T lymphocytes (dosage- and duration-dependent effects)[55]. This effect is reversible after a latency period. A number of studies have demonstrated *in vivo* that hyperoxia and HBO induced a decrease in DNA synthesis in B and T lymphocytes. In most cases, the *in vivo* immunosuppressant activity of HBO is combined with a decrease in delayed hypersensitivity reactions and lymphocyte proliferation and numeration[56,57].

4. ANTIBIOTIC ACTIVITY ENHANCEMENT

In vitro studies on Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of various antibiotics and oxygen pressure have clearly demonstrated that antibiotic activity decreased in anaerobiosis. In anaerobiosis, the MIC of aminoglycosides (amikacin, gentamycin, kanamycin, tobramycin) are significantly greater for *E. coli*, *Enterobacter*, *Klebsiella*, *Salmonella*, *Staphylococcus* and *Streptococcus sp*[16,17]. The decrease of aminoglycosides activity in hypoxic conditions is

combined with a decrease of the oxygen-dependent penetration of the antibiotic through the cytoplasmic membrane. This is why anaerobes are not susceptible to aminoglycosides since they do not have the aerobic metabolism required for oxygen transport through the cytoplasmic membrane. Some facultative anaerobes are susceptible to aminoglycosides in normal pressures of oxygen but their susceptibility decreases in hypoxia, anoxia and acidosis[16,17]. The enhancement of aminoglycosides activity in hyperoxia seems to depend on the type of antibiotic and the strain of bacteria. However, the decrease of aminoglycosides activity in anaerobiosis and its recovery to normal in normoxic conditions are a universal phenomenon[58].

The activity of a number of other antibiotic classes decreases in anaerobiosis, although the mechanisms involved are not yet understood. The bacteriostatic activity of sulfamethoxazole and trimethoprime against *E. coli*, *Klebsiella sp*, *Proteus sp* and *Staphylococcus sp* is greatly reduced in anaerobiosis[59]. The MIC and MBC of vancomycin against *Staphylococcus aureus* is 4 times greater in anaerobiosis than in normoxia[60]. The bactericidal activity of fluoroquinolones such as ciprofloxacin, ofloxacin and norfloxacin against *E. coli* decreases in anaerobiosis. However ciprofloxacin does retain a bacteriostatic effect.

In contrast, the MIC of cefazolin, cefalotin, chloramphenicol, clindamycin, moxalactam and piperacillin for various positive and negative Gram-stain bacteria are not altered in anaerobic environments[16].

Metronidazole activity is at its best in anaerobiosis and stops in aerobiosis. It is enhanced by the decrease in redox potential.

A series of studies have proven that pressures of oxygen had an influence on post-antibiotic effects. Bayer observed that for a PO_2 of 80mmHg instead of 40mm Hg, amikacin had a greater bactericidal effect on *Pseudonomas aeruginosa* and double the post-antibiotic effect[61]. Park also showed how hyperoxia increased the post-antibiotic effect of tobramycin on *Pseudonomas aeruginosa*[62]. HBO increases the bacteriostatic activity of sulfisoxazole against *Pseudonomas aeruginosa* and increases the bacteriostatic effect of sulfisoxazole and trimethoprime on *Corynebacterium diphteriae*. HBO also enhances the activity of nitrofurantoin on *E. coli*[16].

These *in vitro* data have been confirmed in experimental models *in vivo*. On a model of experimental osteomyelitis in rabbits, HBO (100 % 2 ata 2 hour sessions) was found as effective in eliminating *Staphylococcus aureus* as cefalotin[63]. Knighton came to similar conclusions : after intradermal injection of *E. coli*, infectious necrosis in guinea pigs decreased when oxygen concentrations rose from 12 to 45 %; they also observed that oxygen and ampicillin had a greater effect when combined than oxygen or ampicillin alone[51] (Figure 1.6-3).

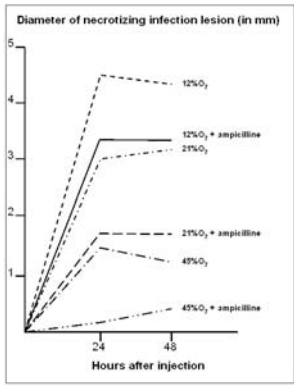

Figure 1.6-3. Effects of oxygen provided alone or combined with ampicillin on the diameter of necrotizing infection lesions after intradermal infection of *Escherichia coli* in guinea pigs[51]

In another study, Mader showed that HBO (100 %, 2.5 ata, 1.6 hours, twice daily) combined with tobramycin provided a greater effect than HBO or tobramycin on their own[64]. The enhancement of the activity of tobramycin in HBO has been explained by the recovery of oxygen levels in the infected bone which enables both aminoglycoside activity to resume and PMN's bactericidal activity to increase. In a model of polymicrobial infection in rats, Marzella studied on the additive effects of HBO and some antibiotics[58]. They confirmed that in terms of reduced mortality, HBO enhanced the activity of piperacillin, clindamycin and vancomycin;, this was not the case for metronidazole. Finally, as far as improved survival time was concerned, they observed that the effects of HBO were additive when it was combined with vancomycin or clindamycin.

At least three mechanisms can account for the role HBO plays in antibiotic activity[17] :

- increase of pressure of oxygen in ischemic tissues improving the activity of antibiotics such as aminoglycosides, some sulfonamides; fluoroquinolones, vancomycin and trimethoprime,
- inhibition of some of the reactions involved in bacterial biosynthesis such as the enhancement of sulfonamide activity and increased duration of the post-antibiotic effect of aminoglycosides in *Pseudomonas* induced infections,
- altered redox potential of the bacteria, combined with an increase in reactive intermediates such as nitrofurantoin and decreased activity of antimicrobial agents such as metronidazole, which require a low redox potential.

5. CONCLUSION

Through its direct activity on bacteria, improvement of cellular defence mechanisms of the body and synergistic effect on antibiotic activity, HBO when combined with antibiotics and surgery, is extremely useful as adjunctive therapy for treating tissue infections involving both anaerobic and aerobic bacteria in hypoxic wounds and tissues. Its usefulness has been clearly proven by a large amount of *in vitro* and *in vivo* experimental research and further confirmed by extensive clinical series. The benefit HBO provides in the field of infectious disease medicine is mostly due to the restoring of adequate, normal or above-normal pressures of oxygen in hypoxic infected tissues.

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Chapter 1.7

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON ISCHEMIA-REPERFUSION PHENOMENON

Rachmaninov's Third Piano Concerto in Hyperbaric Physiology

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Abstract: Reperfusion injury is a complex but clinically well-defined entity although its complete mechanism is not entirely elucidated yet. The re-oxygenation phase is characterized by vasoconstriction, platelet and polymorphonuclear leukocytes activation, and release of mediators and the production of free radicals. The goals of the available therapeutic approaches are to oppose directly the consequences of re-oxygenation following the ischemic phase. Clinical and research evidence demonstrated that hyperbaric oxygen could be effective to reduce or stop ischemia-reperfusion related injury. Although many unanswered questions remain and the effects of hyperbaric oxygen seem paradoxical at first glance, the supportive literature is growing

Keywords: hyperbaric oxygen; ischemia-reperfusion; free radicals; hypoxia; no-reflow; oxygen paradox

1. INTRODUCTION

The third piano concerto of Rachmaninov rightfully retains the reputation as being the most daunting of all piano concertos making tremendous demands on the pianist...Similarly, the maintenance of adequate tissue oxygenation permitting a normal metabolism and essential for the physiologic functioning within different organs and tissues is equally challenging. It necessitates a preserved micro- and macro-vascular architecture. An ischemic accident develops when blood supply (and oxygen delivery), is insufficient or stopped. Consequently, the hypoxic tissue aggression may be

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 121–134.

responsible for dramatic (cacophonous) consequences and irreversible tissue injury. Several organs are involved in this process (brain, heart, muscles, kidneys, intestinal tract) and the causes of the aggression are multiple (e.g., embolism; toxicity[1,2]; thrombosis ; surgical interventions and others[3, 4]). Recent studies indicate that an important mechanism by which cells adapt to changes in oxygenation involves modifications in endogenous nitric oxide (NO) and carbon monoxide (CO) signalling[5-7]. The moment the ischemic obstacle disappears and the perfusion and the tissue oxygenation are restored, there is a paradoxical aggravation of the initial state with a micro-circulatory ischemia and tissue necrosis is observed immediately on re-oxygenation. This paradoxical, harmful effect in which re-oxygenation induces tissue injury is called reperfusion injury or the oxygen paradox. The term ischemia-reperfusion reminds us of the fact that the tissue injury with an interruption or reduction of blood flow is the result of two phenomena: a direct effect of ischemic hypoxia and an indirect effect following reperfusion, i.e. re-oxygenation. In this context, and frequently observed in medicine, reperfusion syndromes may become the limiting factor in our clinical or surgical interventions or treatments. For example: cardiologists are confronted by ischemia-reperfusion with every successful balloon angioplasty or thrombolysis. Transplant surgeons face it with every successful organ replacement[8]. Plastic surgeons are challenged by ischemia-reperfusion with every flap. Orthopedic surgeons address it by decompression fasciotomies and reattachment of severed extremities. Finally, all physicians who have successfully resuscitated critically ill patients know the frustrating consequences of subsequent multi-organ failure syndrome.

Hyperbaric oxygen (HBO) is frequently associated with the nefarious production of free radicals[9-13] but in certain conditions, perhaps within a narrow time frame[14], hyperbaric oxygenation can be valuable in the treatment of ischemia-reperfusion, a condition also related with the production of free radicals. At the first glance it would seem that providing HBO would further fan the flames of oxygen mediated reperfusion injury. This chapter endeavours to navigate the extremely complex “concerto” of damage and defense, stability and derangement. This is indeed the tip of the iceberg. So what is under it?

2. MECHANISMS OF ISCHEMIA-REPERFUSION

The initial hypoxic phase is characterized by a depletion of the cellular energy reserves followed by a loss of cellular functions. The loss of the intra-/extra-cellular ion balance precedes eventual necrosis.

Recent papers using different research models, illuminate distinct pathophysiological mechanisms.

2.1 Calcium and ischemia-reperfusion

Calcium metabolism is affected by ischemia-reperfusion syndromes but the entire mechanism of this perturbation needs to be clarified[15]. Almost the entire intra-cellular calcium concentration is bound to phospholipids or proteins, or sequestered into the endoplasmatic reticulum, to calciosomes and mitochondria. In physiologic conditions, a very large electrochemical driving force tends to translocate calcium into cells. This force has two components: (1) a chemical gradient – intra-cellular calcium concentration being 10^4 lower than the extra-cellular concentration - and (2) an electrical gradient - the electrical potential across plasma membranes (the inside being 60-90 mV negative to the outside). It is clear that a coupling exists between influx of calcium into the cells and their production of reactive oxygen species. Mitochondrial calcium accumulation and oxidative stress can trigger the assembly of a high-conductance pore (i.e., MPT or mitochondrial permeability transition) in the inner mitochondrial membrane. This leads to a collapse of the electrochemical potential for H^+, thereby arresting ATP production and triggering the generation of reactive oxygen species. During the hypoxic ischemia phase, calcium homeostasis is greatly affected, it starts activating phospholipases, endonucleases and proteases and it affects protein phosphorylation by altering the activity of protein kinases and phosphatases. Moreover, it activates enzymes that give rise to the production of reactive oxygen species and NO. For instance, the intracellular calcium concentration activates proteases permitting the conversion of xanthine dehydrogenase (d-form) to xanthine oxydase (o-form) with the formation of free radicals during reperfusion and re-oxygenation.

2.2 Production of free radicals in ischemia-reperfusion

Free radicals are atomic or molecular structures with one or more unpaired electron in the outermost orbital. Such unpaired electrons make these species very unstable and therefore quite reactive: free radicals tend to react with other molecules to pair this electron and thereby generate a more stable species. Ground state molecular oxygen is a bioradical with its two outermost valance electrons occupying separate orbitals with parallel spins. Pairs of electrons typically have opposite spins, and thus fortunately impose a restriction on the reaction of molecular oxygen with most organic molecules. However, ground state oxygen may be converted to the much

more reactive ROS (reactive oxygen species) forms by energy transfer (-> singlet oxygen) or by electron transfer reactions (superoxide, hydrogen peroxide and hydroxyl radical). The equilibrium between production and scavenging of ROS may be perturbed by a number of factors and disease states[16,17]. ROS recently have been related to signalling, and gene expression[18]. Free radical production is increased in ischemia-reperfusion syndromes (xanthine oxidase pathway and NADPH oxidase system), even though one would expect a reduced free radical production during times of hypoxia[18,19]. Reactive oxygen species generated during the reperfusion phase overwhelm the scavenging capacities of antioxidant enzymes, and result in oxidative damage.

2.3 Role of leukocytes during ischemia-reperfusion

Ischemic hypoxia induces an inflammatory reaction and activates polymorphonuclear leukocytes (PMN's) by pro-inflammatory mediators. PMN's then adhere to the micro-vascular endothelium by means of adhesion molecules, a process mediated largely via CD11a/CD18 and CD11b/CD18 interactions with intercellular adhesion molecule-1. PMN's are required for necrotic debris removal after severe ischemia. The cascade of diapedesis is orchestered by these adhesion molecules (selectins, integrins), cytokines and NO. The ensuing tissue damage is no longer limited to free radicals but also by proteolytic enzymes released by PMN's (elastases, collagenases, gelatinases) activated by HOCl. Importantly, proteolytic enzymes demonstrate a much longer activity than free radicals, partially explained by the neutralization effect of free radicals on the anti-proteases shield.

2.4 Alterations in the microcirculation during ischemia-reperfusion

A compensatory hyperemia with vasodilatation can be observed following a relatively short duration of ischemic hypoxia. However, after a longer ischemic period, micro-vascular alterations develop and a reduction or complete cessation of the capillary perfusion is observed (no-reflow phenomenon). The point in time during the course of ischemia and reperfusion where tissue injury becomes irreversible is unknown.[20] Microscopic studies demonstrate formation of edematous endothelial cells, rouleaux formation of erythrocytes, reduction of red blood cell deformability, arterial vasospasm and the formation of microthrombi.[21, 22] During an experimental compartment syndrome, vasodilatation was followed by an intense vasoconstriction within the first hour.[23] Moreover, over three hours following reperfusion, neutrophils were sequestered in the

muscle circulation due to adhesion of neutrophils to the endothelium within post-capillary venules – a process that started within minutes.

2.5 Edema formation in ischemia-reperfusion syndromes

Edema formation as a consequence of ischemia-reperfusion has been extensively studied in experimental compartment syndromes and flap surgery.[21] Initially, ischemia induces a functional alteration of endothelial cells by the loss of their intercellular connection and energy homeostasis. Consequently, an increase in permeability of the capillary vessel wall and an increase in plasmatic filtration is observed causing interstitial edema responsible for compartment syndrome. The increase in compartmental pressure again causes ischemia as compression of blood vessels aggravates the problem of tissue hypoxia – a vicious circle.

3. CLINICAL CONSEQUENCES OF ISCHEMIA-REPERFUSION

The first clinical manifestations of ischemia-reperfusion syndromes are observed within the tissue or organ where the initial ischemia started. The ischemic insult, ensuing reperfusion and the secondary ischemia then aggravates the first lesion. This secondary ischemia is the result of different phenomena: the development of a compartment syndrome following edema formation; a reduction in blood flow due to arteriolar vasoconstriction; and capillary occlusion explained by endothelial cell alterations and intravascular thrombosis (platelet activation and release of proteases).

If the severity of the lesions provoked by the ischemia-reperfusion syndrome exceeds the metabolic capacity to deal with ischemia-reperfusion consequences (e.g. free radical scavenging potential), systemic manifestations develop that may ultimely be fatal. This is represented by hemodynamic shock, hyperkalemia, hypocalcemia, renal failure and ARDS.

4. THERAPEUTIC APPROACHES FOR ISCHEMIA-REPERFUSION SYNDROMES: THE USE OF HYPERBARIC OXYGEN

4.1 Introduction

The majority of the treatment options available in clinical practice are based on animal experiments and these should be extrapolated to human pathophysiology with due caution. In animal undergoing reconstructive vascular surgery, the use of calcium channel blockers, anticoagulants, vasodilating drugs, free radical scavengers, etc. have been tested with success. Similarly, experimental and clinical research demonstrates that the administration of hyperbaric oxygen[24], in certain situations, can attenuate some of the nefarious consequences of reperfusion.

4.2 Hyperbaric oxygen (HBO)

4.2.1 HBO and leukocyte adhesion

Several studies in brain and muscles or flaps demonstrate the decrease of leukocyte adhesion when hyperbaric oxygen is administered[23, 25-29], by temporarily (or not[30,31]) inhibiting neutrophil beta$_2$-integrin function[32-34], via endothelial intercellular adhesion molecule-1 (ICAM-1) modulation[15,30,35,36] and from peroxynitrite-related inhibition of P-selectin expression[37] on the endothelial cells.

4.2.2 HBO and lipid peroxidation

Increased oxygen tensions in ischemia-reperfusion syndromes have been associated with an increase[38], no increase[39] or a reduction in lipid peroxidation, the latter particularly when HBO is used[33, 40, 41]. Hyperbaric oxygen appears to play a crucial role in protecting against neuronal death induced by brain ischemia[42, 43].

4.2.3 HBO and ischemia-reperfusion in CNS models

Ischemic neurological diseases are an important cause of death and a leading cause of long-term disability.[44] In experimental and clinical settings hyperbaric oxygen has been demonstrated to have ameliorating and protective effects[45], within a narrow time frame[46,47] and at certain

pressures[48,49]; with an ensuing reduction in neuronal apoptosis following ischemic damage of the brain and spinal cord [14,50-56]. This might seem paradoxical given the nature of hyperoxic vasoconstriction (see chapter 1.5) and indeed the literature is divided on this mechanism[48,57-59]. However, changes in NO levels may explain the differential and sometimes variably detrimental or positive effects of HBO[58, 60].

The clinical efficacy of HBO for the treatment of stroke remains controversial[31] and is still in need of being validated[61,62]. Experimentally, ischemic tolerance can be induced using hyperbaric oxygen pretreatment in ischemia-reperfusion models[63,64]. It also appears as though hyperbaric oxygen is able to regulate brain metabolites that explain its protective effects in a rat microdialysis middle cerebral artery occlusion model.[65] Hyperbaric oxygen certainly demonstrates a superior protective effect than normobaric oxygen.[66]

Acute carbon monoxide intoxication gives rise to hypoxemic, ischemic and histotoxic hypoxia and shares many pathological similarities with ischemia-reperfusion syndrome. Different oxygen pressures seem to have different effects on lipid peroxidation[33] and as this is related to increased free radical production, it may be paradoxically counteracted by HBO.

4.2.4 HBO and ischemia-reperfusion in myocardial models

Ischemia-reperfusion is a common element of coronary bypass surgery, thrombolysis, PTCA, and transplant surgery. Even with a successful reperfusion procedure, myocardial dysfunction is often observed. HBO has been shown to exert (or not[67,68]) favorable effects on the myocardium and myocardial functions in these conditions[8,69,70]. Routinely treating patients with acute myocardial infarction in hyperbaric chambers seems impractical and difficult[71], therefore aqueous oxygen in solution with a high oxygen concentration has been tested[72]. In a porcine model of myocardial infarction, intracoronary reperfusion with aqueous oxygen revealed significant improvement in left ventricular ejection fraction, mean infarct size, post-mortem hemorrhage score and myocardial myeloperoxidase levels.[73] Similar results were obtained by infusion of a hyperbaric oxygen solution into the anterior interventricular vein at reperfusion, giving rise to a reduction the infarct size in swine.[74] Ischemic tolerance against ischemia-reperfusion appears to be related to catalase induction in an ischemic myocardium model in rat[75].

4.2.5 HBO and ischemia-reperfusion in intestinal models

The intestine is one of the most susceptible organs to ischemia. Intestinal cells but also hepatocytes, have the highest concentration of xanthine dehydrogenase of all tissues. Ischemia-reperfusion injury to the gut causes enterocyte apoptosis that may contribute to intestinal barrier failure[76]. In the rat model, evidence suggests that HBO before ischemia may ameliorate the ischemia-reperfusion injury of the liver[77,78]. Hyperbaric oxygen inhibits TNF-alpha production during intestinal ischemia-reperfusion which may be related to the beneficial effects of HBO[79-81]. Hyperbaric oxygen in circulatory shock induced by splanchnic artery occlusion and reperfusion in rats exhibited a significantly higher survival rate [82]. HBO also demonstrated a favourable effect on experimental colitis in rats[83].

4.2.6 HBO and ischemia-reperfusion in reconstructive surgery and urology

Skeletal muscles demonstrate an important resistance to ischemia. Hyperbaric oxygen has been shown to reduce (or not[84]) ischemia-induced skeletal muscle injury[55,85-88], skin grafts and flaps[36, 89-91] as demonstrated with videomicroscopy and laser Doppler studies. A rat testicular model suggests a potential benefit of HBO treatment in clinical situations of testicular torsion[92]. Hyperbaric oxygen even might increase the beneficial effect of fibrinolysis[93].

5. CONCLUSION

Ischemia-reperfusion syndromes are well defined clinical entities although the mechanism explaining the entire process still needs to be elucidated. The re-oxygenation phase is characterized by an arterial vasoconstriction, activation of platelets and leukocytes, a release of inflammation related mediators and increased free radical production. The therapeutic approaches aim to reduce the negative effects related to re-oxygenation. Both experimental models and clinical studies demonstrate a favorable effect by the administration of hyperbaric oxygen, even when it seems paradoxical. Given the variety of models used to study the individual components involved in ischemia-reperfusion, it is difficult to determine which factor is affected predominantly by hyperbaric oxygen and which generates the observed beneficial outcome. In the mean time, several questions remain unanswered. Significant differences on the effect of hyperbaric oxygen are observed between *in vivo* and *in vitro* models. Extrapolation from animal models to human clinical practice is inappropriate because of the

interspecies[94] and inter-strain differences in expression and distribution of enzymes and adhesion molecule, and immunologic reactions.

The favorable effect of hyperbaric oxygen is determined by the duration and the degree of ischemic hypoxia, the duration of secondary ischemia and the time and dose of administration of hyperbaric oxygen.

Defining research protocols remains difficult because of the lack of effective classification of the degrees or grades of ischemia. An interesting point, however, is the differential effect of hyperbaric oxygenation on normoxic tissues compared to hypoxic tissues.

In the future, clinical evidence should assist in identifying the window of opportunity for HBO administration during ischemia-reperfusion. It seems quite obvious as far as the inflammatory cascade is concerned, probably neither HBO nor any other drug alone will be sufficient to completely reverse all aspects of the inflammatory cascade during ischemia-reperfusion.

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Chapter 1.8

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON WOUND HEALING PROCESSES

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Abstract: The value of hyperbaric oxygenation has been well established in the treatment of hypoxic and ischemic wounds in which local oxygen tensions are below optimal for healing. The greatest benefit of hyperbaric oxygen therapy is achieved in situations where the nutritive flow and oxygen supply to the repair tissue are compromised by local injury or infection, but in which the regional vascular network, a prerequisite for oxygen to reach tissues is intact or only partly damaged. On the other hand, hyperbaric oxygen seems to possess significant angiogenic potential in tissues suffering from chronic lack of oxygen due to defective vasculature. During wound healing the presence of oxygen takes on additional importance because of the increased demand of reparative processes like cell proliferation and synthesis of collagen. In addition, superoxide generation by polymorphonuclear leukocytes, which is essential for bacterial killing, is critically dependent on tissue oxygen levels. Ischemic soft tissues also benefit from hyperoxygenation through improved preservation of energy metabolism and reduction of edema. It may be generally stated, that any treatment that augments the oxygen supply or avoids hypoperfusion of the wound tissue tends to increase the rate of healing and decrease the susceptibility to infection

Keywords: hyperbaric oxygen therapy; wound healing; tissue repair; wound contraction; wound epithelization; wound environment; tissue perfusion; growth factors; cytokines; lactate; wound energy metabolism; angiogenesis; cell proliferation; cell differentiation; nucleic acids; fibroblast; collagen synthesis; bacterial killing; oxidative burst; wound infection; wound ischemia; wound edema; tissue hypoxia; problem wounds; tissue oxygen tension; transcutaneous oxygen tension; oxygen tension measurements; rabbit ear chamber

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 135–145.

1. INTRODUCTION

Many clinical observations, strongly supported by experimental evidence in animals, have led to the conclusion that hyperbaric oxygen therapy (HBO) may be used as an effective tool in stimulating repair of hypoxic and ischemic wounds. The most important effects of added oxygenation are the stimulation of fibroblast proliferation and differentiation, increased collagen formation and crosslinking, augmented neovascularization as well as stimulation of microbial killing by leukocytes. Hypoxic wounds also benefit from increased oxygen supply through improved maintenance of energy metabolism and reduction of edema.[1]

Oxygen is a drug, with many pharmacological effects. The mechanism by which oxygen is supplied to the tissues is via respiration of oxygen and subsequent delivery by the blood circulation. Beyond the most superficial cell layers, there is no significant topical absorption of oxygen. Therefore, for additional oxygen to be delivered to hypoxic tissues, it might be administered systematically, i.e., it must be breathed. HBO is a treatment in which a subject breaths 100% oxygen while inside a treatment chamber at an atmospheric pressure higher than that at sea level.

2. WOUND ENVIRONMENT

During wound healing new capillaries are stimulated to migrate towards the hypoxic and acidotic area at the wound edge. Cells in the advancing wound edge produce lactate, growth factors and chemotactic stimuli that diffuse back toward the developing vasculature. Wound angiogenesis needs stromal support. On the other hand, fibroblasts which supply the stromal support require nutrients to make collagen, fibronectin, and proteoclycans. The wound architecture is partly controlled by the energy needs of the wound cells. In the wound environment a delicate interaction exists between the inflammatory cells, new capillaries and fibroblasts.[2-4]

Migration of reparative cells towards the wound edge occurs along steep concentration gradients. Gradients of oxygen, carbon dioxide, pH, lactate, and glucose have been measured. Measurements of oxygen tension gradients by means of ultramicro electrodes in a rabbit ear chamber model demonstrate that PO_2, which is of the order of 60-90 mmHg over the most distal capillary at the wound edge, decreases to near zero at the zone of macrophages, leukocytes and the central dead space. In the area of dividing fibroblasts, which is almost confined to the leading capillary zone, the PO_2 is in the region of 30-80 mmHg. Almost no cell division can be found where oxygen tension is consistently below 20 mmHg. Maximum synthetic and

crosslinking activity of collagen takes place in a zone in which the PO_2 is 20-60 mmHg and where the oxygen diffusion gradients are less steep than those at the wound edge.[2,5]

Growth-promoting substances are present in the wound environment. Transforming growth factor α (TGF-α), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), leukocyte-derived growth factor (LDGF) and insulin-like growth factor (IGF-1) as well as interleukins 1, 6, and 8 (IL-1,6,8) have been found there. The presence of these substances in the wound environment can be contributed by blood circulation, but it is generally agreed that most are synthesized or released locally.[1]

Several growth factors and interleukins are elicited by exposing wound cells to hypoxia. Thus, it is reasonable to hypothesize that low oxygen tensions could play a role as an early stimulus for tissue repair/angiogenesis. As a result of this observation, there has been interest in the impact of low oxygen tension on growth factor synthesis and gene activation in general.[6]

Another look at wound environment discloses that a surrogate or equivalent of hypoxia, high lactate concentrations, is also a constant feature. Lactate levels in the range of as high as 5-20 mmol/l are characteristic in human and animal wounds,[7-9] and these levels remain high even when the oxygen tension increases in the wound tissue. Further studies have shown that lactate is in fact one of the driving forces of repair, and that the effects of lactate in many ways duplicate those of hypoxia and are even more powerful.[1]

Conventional thought dictates that lactate must accumulate because of hypoxia, but in wounds this is only partially the case. In wounds the major portion of lactate load is contributed by leukocytes, which derive the great majority of their energy from glycolysis even in the presence of oxygen with the end product of their energy metabolism being lactate. Lactate accumulation is therefore relatively insensitive to changes in oxygen tension in wounds. Lactate, in common with oxygen, excites many cells to release growth factors and cytokines such as TGF-α, VEGF, and IL-1 and 8, and can excite their production in the presence of oxygen. Furthermore, lactate alone can stimulate and govern collagen synthesis and angiogenesis, two of the major components of wound healing.[10,11] Hypoxia does not share this property and in fact has the opposite effect.[1,6]

3. IMPACT OF HYPEROXIA ON WOUND HEALING

The discovery that oxygen is an essential nutritional ingredient of healing has stressed the importance of adequate oxygen supply to the repair tissue. Reports from several laboratories have indicated that in many types of wounds hyperoxia enhances healing and conversely, hypoxia inhibits repair.[12-15]

Measurements of local tissue oxygen tensions in a rabbit ear chamber model by means of polarographic ultramicro electrodes have shown that cell replication is hardly seen in portions of wounds where PO_2 falls below 20 mmHg. Fibroblasts and endothelial cells replicate best in the range of 30-80 mmHg.[2,5,16]

Collagen synthesis is crucially dependent on the availability of molecular oxygen. Oxygen is incorporated into the peptide chain to form hydroxyprolyl and hydroxylysyl residues. Hutton[17] found a close correlation between the rate proline hydroxylation and oxygen concentration over the range of 0.51-14.9 volumes per cent of oxygen by using a partially purified chick embryo hydroxylase. The Km value for oxygen was 2.6 volumes per cent, equaling a PO_2 of about 20 mmHg. These results were supported by Myllylä[18] and more recently challenged by De Jong and Kemp[19] who suggested a value closer to 100 mmHg. The former estimates suggest that collagen deposition will become maximal at about 200 mmHg, and the later estimate predicts that it will not become maximal until a PO_2 of 1000 mmHg is reached. Because hydroxylation of proline is one of the essential steps of collagen synthesis, its rate seems to limit the rate of collagen deposition. This means that the deposition of collagen is limited by the oxygen tension under normal circumstances, and even more so under hypoxic circumstances. By the rules of enzyme kinetics, this data gives a target PO_2 for hyperbaric oxygen given in pursuit of wound healing.

The rate of collagen accumulation in healing wounds is also a function of arterial PO_2 and of wound PO_2 over the entire physiologic range.[2,5] This agrees with observations made with ultramicro oxygen electrodes in rabbit ear chambers in which the minimal PO_2 in the area of newly formed collagen fibers is of the order of 20-30 mmHg.[2,4,16] The ear chamber studies have also shown, that oxygen tensions in healing tissues are heterogeneous. Areas of extremely low oxygen tensions, that are not optimal for healing, are found in wounds even in normal physiologic circumstances.

In addition to its effect upon collagen deposition, PO_2 also influences collagen crosslinking, an important factor in the development of wound strength. Chvapil[20] reported that the crosslinking of collagen in chick embryo skin slices increased almost linearly when oxygen concentration in

the incubating gas was elevated from 20 to 95 volumes per cent. Lysyl oxygenase, which catalyses an important extracellular step in formation of covalent bonds that crosslink collagen peptides also uses molecular oxygen as a substrate. The critical or limiting range of oxygen tensions is in the same range as in the case of prolyl hydroxylase. Thus, crosslinking of collagen, which determines its mechanical strength, is also a function of oxygen tension.[1]

Niinikoski[9] reported that the tensile strength of incisional skin wounds in rats increases as ambient oxygen concentration increases from 18 to 70 volumes per cent. When 70% oxygen was administered, the tensile strength was 35% above the control level in 10-day wounds. Systemic hypoxia suppressed the rate of gain of tensile strength and optimal conditions were passed when the oxygen treatment was extended to 100% oxygen at 1 ATA ambient pressure. At this level, however, evidence of lung oxygen toxicity was found, because the animals were exposed for a considerable period of time to this high oxygen concentration. Parallel observations in subcutaneous cellulose sponge implants demonstrated that the favourable effect of oxygen resulted from enhanced accumulation of collagen, augmented crosslinking of collagen and increased synthetic activity of wound cells as indicated by the rise in their RNA/DNA ratio. Studies of the synthesis of RNA and DNA as well as collagen by means of incorporation of specific radioactive isotopes into granulation tissue *in vitro* supported and further confirmed the beneficial action of oxygen.

Vihersaari[8] investigated enzyme activities in the limiting steps of glycolysis, citric acid cycle and pentose phosphate cycle in subcutaneously implanted hollow cylindrical cellulose sponge implants of rats chronically breathing 12% O_2, air or 55% O_2 in ambient pressure. Respiratory gas tensions and concentrations of puryvate and lactate were measured in wound fluid aspirated from the central dead space of the implants. Significant portions of repair tissue existed in conditions of extremely low oxygen tension. Probably because all added oxygen was readily consumed, the wound fluid PO_2 increased only slightly in hyperoxic environment. The wound PCO_2 increased in parallel with the inspired PO_2, probably due to enhanced production of carbon dioxide. Hyperoxia shifted the wound metabolism from anaerobic towards aerobic glycolysis. This occurred concurrently with activation of citric acid cycle. The activity of succinic dehydrogenase, a linking enzyme between citric acid cycle and electron transfer chain, also increased with increasing oxygen tension. It has to be stressed, however, that even in animals breathing 55% O_2 wound fluid lactate levels remained as high as at the level of 6 mmol/l as opposed to 1 mmol/l or less in blood.

In addition to oxygen, the supply of other substrates is of vital importance for healing. If the Pasteur effect pertains, it indicates that in hyperoxic environment lactic acid is oxidized to carbon dioxide and water and the energy yield per molecule of glucose is considerably increased. Hence, the energy needs of the cell can be met by consumption of considerably less glucose. In spite of this the granulation tissue consumes increased amounts of glucose if added oxygen is available.[8,21] It is possible that the cells in the vicinity of the capillary consume glucose so extensively that the supply to the most peripheral cells is limited. This imbalance could probably be corrected by increasing the mean capillary blood PO_2 which would decrease the glucose utilization of cells adjacent to capillaries. Relatively more glucose would then be available for the most peripheral cells at hypoxic areas. This could explain the elevated glucose consumption in the wound at increased oxygen supply. This hypothesis was later supported by the finding of Silver who reported with a use glucose electrodes that intercapillary glucose gradients in the rabbit ear chamber tissue partially level off under hyperoxic conditions (personal communication).

During wound healing new blood vessels grow rapidly from areas of high oxygen tension and low lactate concentration to areas of low oxygen tension and high lactate. Recent data indicate that several angiogenic factors, e.g. VEGF and IL-8 are preferentially expressed in areas of low oxygen tension. More recent measurements indicate that not only low oxygen tension, but also high lactate causes the same effect, and that secretion of these factors is even greater when both are present.[1,6] Interestingly, the angiogenic response from the intact venules in which blood is flowing freely at the wound edge is greatly enhanced by hyperoxia. No mechanism for this is known, but the strongest clinical evidence of it comes from reports on HBO of chronic wounds.[22]

Epithelization of open wounds is also clearly dependent on the oxygen tension. Medawar[23] noted that epithelial cells grow in culture at a rate that is proportional to their oxygen tension, and others have refined the observation.[24,25] Simple acceleration of epithelization is rarely an indication for HBO, but because epithelization does require vascularized base, there is a role for hyperbaric oxygen in preparing this base in certain ischemic, chronic wounds.[22,26]

4. OXYGEN AND WOUND INFECTION

Oxygen is essential to immune mechanisms in wounds, because oxygen radicals derived from molecular oxygen are important agents in bacterial

killing. Normal leukocytes contain a NADPH-linked oxygenase that is activated during phagocytosis by assembly of its components into the phagosome membrane. This enzyme is the first step in a cycle in which various oxidants are produced from ambient oxygen. After activation, a "respiratory" or "oxidative burst" follows during which molecular oxygen is reduced in large quantities to superoxide radicals. These radicals are then sequestered in the phagosomes where they and other oxidants derived from them are produced and kill bacteria by oxidizing cell membranes. Two molecules of superoxide are subsequently reduced to one molecule of oxygen and one of hydrogen peroxide by superoxide dismutase. Myeloperoxidase then combines hydrogen peroxide with chloride or iodide to form hypochlorite or hypoiodite. Excess hydrogen peroxide is reduced intracellulary to oxygen by catalase. If iron is present and the reaction occurs extracellulary, hydrogen peroxide can be reduced to OH^{-} which is a particularly harmful oxygen radical. While hydroxyl radicals kill bacteria quite effectively, they also injure surrounding cells.[1,27]

In wounds, the activity of the NADPH-linked enzyme can be a limiting factor and superoxide production is reduced. The Km for this reaction has been variously estimated as 15-12 mmHg and about 75 mmHg. If the latter estimate is accurate, full resistance to infection is reached only when intraleukocytic PO_2 rises as high as 750 mmHg. This is clearly possible only in hyperbaric circumstances. The kinetics curve, however, is hyperbolic, and the greatest portion of the effect is exerted within the first 200 mmHg. This also gives a target for HBO.[1,27]

In a study of patients having colorectal operations a direct correlation was found between the subcutaneous tissue PO_2 and postoperative wound infection.[28] If an increase in oxygen concentration in the inspired gas did not result in an increased subcutaneous PO_2, 45% of the patients developed a postoperative infection. If, however, the tissue perfusion was sufficient to result in an increase of PO_2 in subcutaneous tissue to 90 mmHg or more, no patient developed a wound infection.

5. HYPERBARIC OXYGEN THERAPY AND WOUND HEALING

In uncomplicated surgical incision wounds possessing adequate nutritive flow, the optimal oxygen tension for healing is probably passed when the oxygen treatment is extended to hyperbaric conditions. This is supported by the finding that the rate of gain in the tensile strength of healing skin incision wounds was significantly lower in rats treated intermittently for two hours twice daily with hyperbaric oxygen at 2 ATA than in rats breathing air.

Hyperbarically oxygenated normal wounds contained less collagen hydroxyproline as well as less DNA and RNA than control wounds.[12]

The healing of open wounds involves contraction and epithelization, processes of relatively little significance in the healing of incisional wounds. In a study of rats, long-term intermittent hyperbaric oxygenation for two hours twice daily at 2 ATA had no effect on the healing rate of open skin wounds in which the circulation was left intact. When wound edges were devascularized, however, hyperbaric oxygen enhanced the rate of wound closure in the final stages of healing, thus counteracting the delay caused by disturbed blood supply.[29]

HBO in wound healing has resulted in increased growth factor production, particularly VEGF, but also PDGF-receptor when combined with PDGF treatment.[6] The additional angiogenic effect of HBO is likely due in part to an enhancement of the normal VEGF response to wounding.[30] Combined treatment of ischemic rabbit ear ulcers with hyperbaric oxygen and recombinant PDGF-BB increased PDGF-α receptor content of the treated tissue.[31] This positive effect seemed to be due to the effect of oxygen as signal transducer via reactive oxygen species. Furthermore, recombinant growth factors (r-TGF-β1, r-PDGF-BB) enhanced wound healing in ischemic rabbit ear ulcers. When these growth factors were applied together with hyperbaric oxygen, the negative effect of ischemia on wound healing was completely reversed.[32]

In clinical patients with problem wounds HBO has been used as an adjuvant to surgical debridement, tissue grafting and antibiotics. The central question is whether there is an adequately perfused capillary bed in the wound area to allow oxygen delivery even at high arterial oxygen tensions possible with hyperbaric oxygen. Although hyperbaric oxygen can be a powerful adjuvant in the management of selected soft tissue wounds, it is only a part of co-ordinated medical-surgical approach to such patients. Careful attention to underlying diseases, effective treatment of infection, and meticulous wound care with necessary surgical debridement and grafting remain the cornerstones of treatment. Hyperbaric oxygen is used to improve results.[26]

A number of studies have shown the importance of enhancing tissue perfusion and oxygenation in obtaining healing in chronic wounds. Transcutaneous PO_2 in the skin adjacent to chronic wounds is remarkably predictive to whether wounds will heal or not with hyperbaric oxygenation.[26,33-35] The technique can be used in the evaluation of healing potential, selection of amputation level, and patient selection for HBO. Furthermore, the efficacy of HBO can be estimated by repeated, continuous recording of the response of the peri-wound $TcPO_2$ in the chamber during

hyperbaric oxygenation. Transcutaneous oxymetry has become a routine method in many hyperbaric centers. However, as with any measurement method, its application requires strict calibration and checking observations to provide clinicians with values reliable to be interpreted.[36]

With the exception of $TcPO_2$ measurements, none of the techniques for measuring perfusion and oxygenation have been fully applicable for routine use during HBO. Any technique must be safe and measurements inside the chamber must be possible without electrical equipment to avoid the risk of fire. From this viewpoint the implanted Silastic tube tonometer and capillary sampling technique give an excellent opportunity to monitor tissue oxygen and carbon dioxide tensions, even under hyperbaric oxygen.[37-39] Korhonen[40] used these techniques to measure the response of peri-wound subcutaneous PO_2 to HBO in patients with necrotizing fasciitis. For comparison, the rise of subcutaneous PO_2 levels were simultaneously measured in intact distant tissue in these patients as well as in healthy controls under hyperbaric oxygen. The response of subcutaneous tissue PO_2 to HBO seemed to be regularly higher in the vicinity of the debrided infected area than in healthy or distant tissues. It was suggested that hyperbaric oxygenation created a specific "superoxygenated" zone around the infected area thus forming an oxygen barrier against the spreading of infective organisms.

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Chapter 1.9

PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON DNA AND DNA REPAIR – GENOTOXICITY OF HYPERBARIC OXYGEN AND ITS PREVENTION

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Abstract: HBO has a DNA-damaging and possibly mutagenic potential. *In vitro* studies with mammalian cells suggest that HBO-induced oxidative DNA damage mainly leads to gross genetic alterations and chromosome aberrations. Under therapeutic exposure conditions, DNA damage is detected with the comet assay, but mutations and chromosome aberrations are not observed in peripheral blood cells.

A very simple and efficient way to avoid HBO-induced DNA damage is to start with a shortened treatment before the standard protocol is applied the following days. Therefore, the hyperbaric community should think about an adaptation of the commonly used treatment protocols

Keywords: oxygen free radical, mutagenicity, DNA damage, DNA repair, antioxidant

1. INTRODUCTION

Any physician who is active in the field of hyperbaric medicine is well aware of the beneficial effects of hyperbaric oxygen in a broad variety of

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injuries and pathophysiological states. On the other side it is well recognized that high oxygen levels may have deleterious effects on the lungs (*Lorrain-Smith*-effect) and the central nervous system (*Paul-Bert-effect*)[1], as outlined in another chapter of this book.

The detrimental effects of exposure to high concentrations of oxygen are due to the abundance of oxygen free radicals[1-3]. Free radicals are defined as chemical species that possess one or more unpaired electrons. The term 'Reactive Oxygen Species' (ROS) collectively describes free radicals such as $O_2^{\bullet-}$, $OH^{\bullet}$,and other non-radical oxygen derivatives such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl)[2,3]. Unstable free radical species attack cellular components, causing damage to lipids, proteins and DNA[1,2,4-7], which in turn can initiate a chain of events that may damage mammalian cells. Enhanced formation of oxygen free radical levels in the blood as a result of HBO exposure was demonstrated by electron spin resonance (ESR) spectroscopy[8,9]. Increased free radical formation in the body is likely to increase damage, in particular when antioxidant defences are insufficient, a situation generally termed "oxidative stress"[2,10,11]. Among other cellular targets the genome is particularly vulnerable[11].

Oxidative DNA damage may consist of strand breaks, abasic sites, "alkali-labile sites" and oxidized bases[6,7,11,12]. Furthermore, ROS-induced DNA damage can lead to mutations, if lesions are not adequately repaired. If these relate to critical genes such as oncogenes or tumor suppressor genes, initiation and/or progression of cancer may result[13,14]. There has been concern about a cancer-causing or cancer-promoting effect of HBO, but a review of the scientific literature showed that the vast majority of published studies failed to demonstrate such an effect[15-17]. One of the mechanisms of a putative carcinogenic effect of HBO is the above-mentioned induction of DNA damage as a consequence of oxidative stress. Scarce data was only available until very recently the DNA-damaging potential of HBO has been thoroughly characterised using sensitive genotoxicity tests.

2. THE DETECTION OF OXIDATIVE STRESS

Several parameters are used for the detection of oxidative stress, which measure lipid peroxidation as a measure for oxidative stress in general.

On this behalf, quantification of F2-isoprostanes from biologic fluids and tissues has an important role in the detection and measurement of lipid peroxidation in vivo[18]. F2-isoprostanes are prostanoids produced independently of cyclooxygenase by free radical-catalyzed peroxidation of arachidonic acid-containing lipids.

Another commonly used marker for oxidative stress is malondialdehyde (MDA)[18,19], a highly reactive three carbon dialdehyde produced as a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid metabolism.

Lipid peroxides are the products of chemical damage done by oxygen free radicals to the polyunsaturated fatty acids of cell membranes, which can be measured with an assay of total thiobarbituric acid-reactive substances (TBARS) in serum using HPLC[18,20]. The HPLC separation step isolates the TBARS from potential interfering compounds that can give false elevations in a simple colorimetric assay. The results provide a measure of total serum lipid peroxidation, an indicator of whole body free radical activity.

3. THE DETECTION OF DNA-DAMAGE

DNA-damage can be evaluated with the so called "Comet-assay", which is a well-established, highly sensitive genotoxicity test that detects DNA damage on the single cell level[21-23]. In this microgel electrophoresis technique, a small number of cells suspended in a thin agarose gel on a microscope slide is lysed, electrophoresed and stained with a fluorescent DNA binding dye. Cells with increased DNA damage display increased migration of chromosomal DNA from the nucleus towards the anode, which resembles the shape of a comet. In its alkaline version (pH >13) DNA strand breaks, alkaline labile sites and incisions during DNA repair become apparent, and the amount of DNA migration[22,24], expressed by characteristic differences in the DNA migration. Using image analysis, various parameters can be measured for determining the length and/or the amount of DNA migration. The so called "tail-moment" is frequently used because it represents a product of both length and intensity and sensitively indicates the amount of DNA damage in the cell.

A genotoxic effect in the comet assay is not directly related to mutagenesis and carcinogenesis. DNA effects in the comet assay can be based on various types of DNA damage with different mutagenic potential. Neither the shape of the comet nor the extent of DNA migration directly reflects the mutagenic risk. The DNA lesions leading to DNA migration can represent repairable DNA single strand breaks (which even can be produced during the process of excision repair itself) but might also include highly toxic and mutagenic lesions (e.g. DNA double strand breaks). Furthermore, the comet assay is very sensitive but not specific, so different types of genotoxic effects can lead to increased DNA migration, and, hence,

additional information is needed to definitely evaluate the biological significance of the results.

Such additional information on the presence of a specific class of DNA damage can be obtained using the comet assay in combination with lesion-specific endonucleases[26]. Such tools are for instance formamido-pyrimidin-glycosylase (FPG) and endonuclease III (Endo III), which specifically detect oxidized DNA bases. Both proteins remove oxidized purines and pyrimidines, respectively, with the resulting abasic sites being converted into DNA single strand breaks by the associated endonuclease activity. This additional induced DNA damage leads to additional DNA migration in the comet assay and therefore provides an indirect measure for the presence of oxidative DNA damage.

Using this technique, Speit and co-workers[26] showed that a DNA-damaging effect in the comet assay was seen in healthy young male volunteers who had been exposed according to a therapeutically used HBO treatment protocol, i.e. 100% oxygen exposure at a hyperbaric pressure of 2.5 bar abs in a hyperbaric chamber for a total of 3x20 min periods, interspersed with 5 min of air breathing. The presence of oxidative base damage after HBO therapy assay suggested that at least some of the HBO-induced DNA modifications might have some relevance for mutagenicity and carcinogenicity.

4. DNA REPAIR

Besides its ability to detect DNA damage, the comet assay also allows to assess DNA repair following induced DNA effects. DNA repair can be determined by monitoring the time-dependent removal of induced lesions, i.e. the decrease in DNA migration. Follow-up experiments using the comet assay showed that HBO-induced DNA effects are rapidly repaired[27], leading to a reduction in induced DNA migration of >50% during the first hour after exposure. Using a modified comet assay protocol in conjunction with the FPG protein, a similar repair kinetic for the induced oxidative damage was observed. Furthermore, blood taken 6 or 24 h after HBO did not show any effect, indicating complete repair of the induced DNA damage[27].

It has to be mentioned, however, that the comet assay only measures the kinetic of strand break rejoining but not the accuracy of DNA repair. Incorrectly rejoined DNA breaks do no longer contribute to DNA migration in the comet assay, but nevertheless may lead to a disruption of genetic information with potentially functional consequences.

To further evaluate the biological significance of the comet assay effects in humans, the micronucleus test (MNT) with human lymphocytes was

performed, which is a well established and sensitive test for the detection of chromosome breakage in humans exposed to mutagens. The same blood samples that exhibited a significant increase in DNA migration in the comet assay did not show increased micronucleus frequencies[27]. Although an effect in the MNT is confined to proliferating lymphocytes, the comet assay results clearly demonstrated that genotoxic effects occur in the whole population of white blood cells, so it can be assumed that under therapeutical exposure conditions the primary DNA damage is repaired before the cells enter the mitotic S-phase and chromosome aberrations can be produced. In lymphocytes of healthy human volunteers, no induction of chromosome mutations was found after a single HBO. Therefore, it can be assumed that under therapeutical exposure conditions the primary DNA damage is repaired before they can lead to chromosome aberrations in mitotic cells.

Further studies gave additional evidence that HBO does not induce gene mutations in healthy volunteers either. No increase in mutant frequencies was observed at the *HPRT* locus in peripheral lymphocytes after a single HBO[28]. The *in vivo HPRT* test is a unique system for studies on spontaneous and induced mutant frequencies in humans and the mechanisms of mutagenesis. The assay detects a broad spectrum of gene mutations from single base substitutions to larger deletions and should detect mutations caused by oxidatively damaged DNA bases. The negative result in combination with the comet assay experiments suggests that the induced DNA lesions are completely repaired before lymphocytes are stimulated to replicate. However, the detection of mutations with the *in vivo HPRT* gene mutation test is known to be rather insensitive, and *in vitro HPRT* tests with cultured mammalian cells indicated that HBO seems to have a low potential for the induction of gen mutations (see below). Taken together, the *in vivo* mutagenicity studies with healthy human subjects exposed to HBO indicated that neither induction of chromosome aberrations nor induction of gene mutations can be detected in peripheral blood lymphocytes despite the clear DNA-damaging effect in the comet assay.

In contrast to these negative results, increased frequencies of chromosome aberrations after HBO exposure were reported in an earlier study. However, this effect was found in patients with various diseases and drug treatments after repeated HBO exposures[29]. As the comet assay results suggest that repeated HBO does not lead to further DNA damage due to induced antioxidant protection, it is likely that the observed elevated chromosome aberration frequencies are not directly related to HBO exposure. However, it cannot be excluded that individuals with specific diseases or genetic susceptibility exhibit higher vulnerability.

lt seems that at least in healthy individuals, efficient antioxidant defences together with DNA repair maintain a steady-state level of damage with minimal risk to the cell or the organism[30]. However, under conditions where antioxidant defense is deficient or overcharged, a significant mutational burden cannot be excluded[29]. *In vitro* experiments with cultured mammalian and human cells enable to increase HBO exposure and to study a possible mutagenic potential of HBO-induced DNA damage under conditions where antioxidant capacities are overwhelmed[30]. The main difference in these studies in comparison to *in vivo* exposure of human subjects was a permanent oxygen exposure, i.e. the absence of interspersed normal air exposures. Using the comet assay, a genotoxic effect of HBO could be demonstrated in various cell types[30].

Increased HBO exposures (3bar) clearly caused mutagenic effects in cultured mammalian cells. A dose-related induction of chromosome damage was measured in V79 cells (a permanent Chinese hamster cell line) with the micronucleus test (MNT) after treatment with HBO with increasing exposure time (0.5 to 3 hr)[31, 32]. The clastogenic (chromosome-breaking) effect of HBO in V79 cells correlated very well with the increase in DNA damage obtained with the comet assay in the same cell population. The same exposure conditions also increased mutant frequencies in a mammalian cell gene mutation assay at the tk-locus of mouse lymphoma cells (the so called mouse lymphoma assay, MLA), but failed to induce mutations in the *in vitro* HPRT test with V79 cells[31, 32]. The HPRT test predominantly detects point mutations and the negative result suggests that HBO does not significantly lead to point mutations even under high exposure conditions. In accordance with this finding there is increasing evidence that oxidative DNA modifications generated by oxygen radicals are not a significant cause of gene mutations due to efficient repair of these lesions. It is more likely that oxygen radicals are mutagenic through other kinds of DNA lesions (e. g. DNA strand breaks) leading to large rearrangements and gross deletions after high exposures. The mutagenic effect in the MLA was solely based on the induction of small colony mutants, which have in fact been shown to arise as a consequence of gross genomic alterations such as deletions and recombinations. Molecular analysis of HBO-induced mutations in the MLA revealed that all investigated mutants had deletions of the tk-gene. These results also demonstrate that the mutagenic effect of HBO is based on a clastogenic mechanism. Such a mutagenic mechanism has also been proposed for normobaric hyperoxia which induced a similar pattern of mutagenic effects *in vitro*. Taken together, the *in vitro* mutagenicity studies clearly demonstrate that HBO under high pressure conditions has the potential to induce mutations via a clastogenic mechanism. The negative

result in the *in vivo* MNT in HBO-exposed human subjects is obviously due to the lower exposure and/or a better protection of the peripheral blood cells.

5. PROTECTION AGAINST HBO-INDUCED DNA DAMAGE

Standard therapeutic regimens normally include repeated exposure to HBO over several days. It was assumed that repeated exposures may result in an accumulation of DNA damage, which could enhance a possible mutagenic risk. Surprisingly, when healthy human subjects were exposed to repeated HBO exposures, DNA damage was only found after the first treatment but not after or further HBO exposure[27, 33]. The extent of DNA damage after repeated HBO was even lower than in the control blood sample taken before the first HBO[27, 33]. Furthermore, the comet assay experiments revealed that a reduced first HBO of shorter exposure (for example 20 min at 1.5 bar) did not induce DNA damage but was sufficient to induce adaptive protection against further HBO-induced DNA damage[27, 33]. This adaptive effect was demonstrated to be a cellular response which cannot be explained by enhanced repair activity, but seems to be due to enhanced scavenging of oxygen species distant from nuclear DNA or increased sequestration of transition metals[27, 33].

The induction of heme oxygenase-1 (HO-1) seems to play a crucial role in the protection against HBO-induced DNA damage: Lymphocytes from healthy volunteers showed a markedly increased HO-1 protein concentration after HBO exposure both *in vivo*[34] and *in vitro*[35, 36]. Furthermore, in an *in vitro* study using cultured V79 - Chinese hamster cells, HO-1 overexpression significantly reduced the HBO-induced DNA damage[37], and inhibition of HO-1 with tin-mesoporphyrin aggravated the HBO-related genotoxicity and completely abrogated the adaptive protection against HBO-induced DNA damage, both *in vitro* and *in vivo*[35, 38, 39].

The role of another mediator, nitric oxide (NO), the release of which is tightly regulated by HO-1, for HBO-induced DNA damage is less clear: Increased formation of NO *per se* caused DNA strand breaks no matter whether NO release was a result of administration of NO donors[40, 41, 42] or due to cytokine stimulation[42, 43]. By contrast, increased DNA damage observed in other studies (with patients with hyperlipidemia[44] or type I diabetes mellitus[45]) was not related to the blood nitrate concentrations, e.g. endogenous NO production. Furthermore, NO has both anti- and prooxidant properties depending on the local milieu. In addition, the genotoxic potential

of NO is referred to the formation of peroxynitrite from NO and superoxide[46, 47] under conditions of increased release of these two molecules, but both increased[48] and decreased[49] NO production has been reported during HBO exposure. Finally, administration of NO donors leads to the activation of HO-1[50], which plays a crucial role for the defense against HBO-induced DNA damage as explained above.

Consequently, the effect of the interaction between HBO, NO, and HO-1 on DNA damage was investigated in rats exposed to hyperbaric oxygen[39]. Increased NO formation due to pretreatment with the NO-donor SIN-10 doubled the HBO-induced DNA single strand breaks. Furthermore, the increased DNA damage affiliated with HO-1 blockade seemed to be independent of endogenous NO production, since blood nitrite and nitrate concentrations, a surrogate for NO production, remained unchanged during HO-1 inhibition. The latter result suggests that the protective effect of HO-1 is related to the formation antioxidant molecules generated by HO-1, e.g. the heme degradation products bilirubin and iron, rather than the regulatory function of HO-1 with respect to NO production.

Interestingly, in contrast to these findings demonstrating that repeated HBO exposures may trigger adaptative mechanisms protecting against further DNA damage, the overall antioxidative capacity of the body decreased after repeated HBO-treatments, most likely due to increasing oxidative stress to the organism.

6. THE ROLE OF ANTIOXIDANTS FOR DNA PROTECTION

As the formation of ROS is inevitable in oxygen-consuming organisms, cells have evolved numerous mechanisms to decrease to level of oxidative stress. Therefore, a number of enzymes have strong antioxidative properties. Superoxide dismutase (SOD) for instance catalyses the dismutation reaction of the superoxide radical, which results in the production of hydrogen peroxide[2, 51] (H_2O_2). H_2O_2 is then in part catalytically converted into water and molecular oxygen by the enzyme catalase[2, 52]. The remaining part is removed by the glutathione peroxidase (GPx) which catalyses the reaction of of two molecules of reduced glutathione (GSH) and H_2O_2 to the oxidized form GSSG and two molecules H_2O[2, 10, 53].

Next to to enzymatic antioxidants some vitamins have an important antioxidative effect, e.g vitamin E and C[52, 53, 54]. Vitamin E is located in lipoproteins and membranes where it interrupts the radical-induced chain reaction of lipidperoxidation. Vitamin C has a double function. First, it is needed to restore Vitamin E, which is transferred from alpha-tocopherol

during the above-mentioned reaction to the tocopherol radical, and second, it has radical savaging properties as well. Exogenous antioxidants were also investigated with respect to their ability to blunt or even to completely prevent the oxidative damage to the DNA as described above, and at least with respect to clinical HBO therapy the question still remains unsettled whether antioxidant supplementation allows to prevent HBO-induced genotoxicity: both vitamin E and the synthetic antioxidant N-acetylcysteine failed to affect the HBO-induced DNA damage in healthy volunteers[55], but no data are available in patients with decreased antioxidant capacity. In fact, N-acetylcysteine attenuated the rise of blood lipidperoxidation markers in patients undergoing repetitive HBO treatment sessions[20]. Interestingly enough, in a prospective, double-blind randomised placebo-controlled study in healthy volunteers our group could recently demonstrate that a new orally effective nutritional formula (*Glisodin®*) containing a plant (*Cucumis melo L.C*) superoxide dismutase extract chemically combined with a wheat gliadin biopolymer effectively protected white-blood cell DNA from peroxidation, which coincided with reduced blood isoprostane levels[56]. These findings were confirmed in a subsequent *in vitro* study exposing isolated porcine lymphocytes to HBO-exposure resulting in a more pronounced oxidative stress than usually present during clinical HBO therapy. These findings suggest that long-term prophylactic antioxidant supplementation may indeed help to attenuate HBO-induced DNA damage.

7. CONCLUSION

HBO clearly has a DNA-damaging and possibly mutagenic potential. *In vitro* studies with mammalian cells suggest that HBO-induced oxidative DNA damage mainly leads to gross genetic alterations and chromosome aberrations. Under therapeutic exposure conditions, DNA damage is detected with the comet assay, but mutations and chromosome aberrations are not observed in peripheral blood cells. Although human blood cells do not seem to run a significant risk for producing (chromosome-) mutations, mutagenic effects in other target cells (e.g. lung cells) cannot be completely excluded. Nevertheless, genotoxicity of hyperbaric oxygen should be taken seriously, and, for this reason, induction of DNA damage by HBO should be avoided.

A very simple and efficient way to avoid HBO-induced DNA damage is to start with a shortened treatment before the standard protocol is applied the

following days. Therefore, the hyperbaric community should think about an adaptation of the commonly used treatment protocols.

The supplementation with antioxidants such as vitamin C, E or even N-acetylcysteine seems to be ineffective to prevent hyperbaric oxygen induced genotoxicity, at least in healthy volunteers. Their usefulness in patients with antioxidant depletion, however, is yet unknown. In contrast, the orally effective mixture of a vegetal SOD and wheat gliadin *Glisodin®* protects against HBO-induced DNA damage and may have a role in the prevention of oxidative DNA damage.

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PART II

INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

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Chapter 2.1

METHODOLOGY FOR ASSESSING HYPERBARIC OXYGEN THERAPY IN CLINICAL PRACTICE

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Abstract: HBOT has to compete for credibility and financial support with a number of medical therapies that have already established themselves according to modern evidence-based scientific standards. In order to compete and survive in a climate of cost-containment as well as finding general acceptance and appropriate use in the clinical setting, HBO has to be held to the same standards. This section reviews the methods in which this can be achieved

Keywords: Evidence Based Medicine, Consensus Conference, guidelines, review, cost-effectiveness

In the past Hyperbaric Oxygen Therapy (HBO) has been called a "therapy in search of disease". To change this reputation and define accepted indications, its effectiveness has to be proved as compared with that of alternative procedures and it must be found technically feasible and safe, with the least possible adverse effects. One way of doing this and helping clinicians in treating patients is to consider the best available evidence from experimental and clinical studies based on Evidence based Medicine (EBM), a recent approach for teaching medical practice involving the application of formal rules for assessing medical literature.

In the United States the Undersea and Hyperbaric Medical Society (UHMS) have set up a committee of university experts from a number of medical or surgical fields, all recognized as specialists in hyperbaric or underwater medicine whose task it is to analyze in depth the available literature and draw from this a report on accepted indications for HBO. For each pathology, the indication has to be justified and treatment protocols,

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 163–170.

assessment and cost-impact must be considered. The first list of HBO indications was published in 1977 by the UHMS in the form of a report to medical funders. Since then this report has been revised every 3 years – the length of time for which members are elected. The report summarises current scientific and medical progress and provides an analysis according to EBM criteria).

In Europe, the European Committee for Hyperbaric Medicine (ECHM) has chosen to hold international consensus conferences also following EBM methodology. The first took place in Lille, France in 1994. At that time, it was found that not many of the recommendations were supported by a high level of evidence according to the methodology of EBM, but as these recommendations were consensually agreed by a large number of experts, they were regarded as a good starting point for further research and experience. Since then a number of conferences have taken place (cf chapter 1), the last and 7th in Lille in December 2004.

1. EBM METHODOLOGY AND HYPERBARIC MEDICINE

EBM methodology has gained a widespread acceptance and is presently an integral part of modern medical practice. The approach and tools used in EBM involve using double-blind randomized prospective controlled clinical studies to provide answers to specific questions, grading rather than providing a general estimation of results to conclude clinical studies and finally collecting results into a meta-analysis to smooth variations between studies. It is typically based on 3 axes:

1- the level of evidence (i.e. quality of available data),

2- interpretation of the evidence (i.e. what the data suggest and how concordant these data are regarding a particular problem),

3- the type or strength of the recommended practice (i.e. the extent to which a physician is able to recommend a particular intervention on the basis of the first two considerations). This method may be used either by an individual physician or by a group of experts who could be expected to arrive at the same conclusion.

For clinical research the various levels of evidence are the following:

Level A: At least 2 concordant, large, double-blind, controlled randomized studies with no or little methodological bias

Level B: Double-blind controlled, randomized studies but with methodological flaws; studies with only small samples, or one study only

Level C: Consensus opinion of experts

Level D: Only uncontrolled studies with no consensus opinion of experts

Level E: No evidence of beneficial action, or methodological or interpretation bias precluding any conclusion

Level F: procedure not indicated by existing evidence

Unfortunately, this method only gives clinically useful recommendations when high quality randomized controlled clinical studies are available. When there is no such data, as in the HBO field no firm recommendation (level A or B) can be issued and the clinician in left without any guidelines. In those cases, the search of a consensus within experts is the method the most widely chosen. The expert consensus method is regarded as the best surrogate to EBM methods to assess procedures under the following circumstances:

1- where a particular procedure, unsupported by a high level of evidence, has become universally accepted to such an extent that it would be considered a violation of accepted standards of care to deny a patient the benefit of the therapy for the purpose of a study.

2- where the disease or condition of interest is so complex or where there are so many variables that it would be impossible to design a study sufficiently powerful to assess any single procedure.

3- where the application of the therapy is so logical that it would be grossly inappropriate to consider omitting it to establish proof of efficacy

4- where no current higher level of evidence exists, but experts are able to report, not only from their own experiences but also by producing comprehensive literature reviews from which consensus can provisionally be reached, pending the outcome of future studies.

Even if an enormous effort has been made by the hyperbaric medicine community in order to achieve high quality clinical studies, we are forced to recognize that in our field, many questions remain without sufficient evidence to give a definite answer. It is therefore hardly surprising to note that to this day, only a small proportion of therapy procedures conventionally used in hyperbaric medicine is supported by the highest level of evidence. Each therapy has its own imperatives. Physicians should remember that where therapy is concerned, clinical decision-making is usually based on the existence of evidence, rather than on the level of evidence required for establishing proof. No evidence of a benefit is not the same as evidence of no benefit. Finally, there is a hierarchy in levels of evidence : from the evidence which is strong enough to support clinical decision-making, through to the highest level where evidence is supported by many extensive clinical studies. A number of pathologies for which HBO is indicated have not undergone the stringent scrutiny of double-blind randomized prospective controlled clinical study but the considerable amount of available data in favour of the use of HBO for these pathologies justifies their choice as indications. Obviously the results of current or future

research can alter the current list of indications. Lastly the actual conception of clinical studies is essential to assess the effectiveness of a therapy such as HBO, all the more so when ethical considerations further complicate the issue. Here clostridial myonecrosis is a significant example. There are no double-blind randomized prospective controlled clinical studies with human subjects in this field but the scientific and medical community does agree, in view of the microbiology, animal experimentation and considerable clinical experience, that HBO has transformed the vital and functional prognosis of this terrible gangrene disease – so much so that such a study would now be considered pointless, dangerous and in contradiction with medical ethics.

2. METHODOLOGY OF CLINICAL TRIALS IN HYPERBARIC MEDICINE

The conventional methodology of randomized therapeutic trials can be applied to hyperbaric medicine as long as the following requirements are met:

- ethics / feasibility and legal requirements such as pertaining to emergency situations.
- choice of trial population. It must be precisely defined and trial results must be applied to this population only. Extrapolating is always dicey.
- modalities of random sampling, one of the essential elements of organizing therapeutic trials, since the whole point is to select comparable populations. So no bias must be allowed. Some predictable difficulties are specific to hyperbaric medicine: decisions must imperatively be made at a place and time where all forms of therapy are available. Lastly, the person performing the random sampling must not know results in advance.
- choice of judgement criteria and associated therapies, also an essential element of therapeutic trials. Since the pathophysiological justification is no longer considered sufficient, a clinical criterion must be selected (i.e., quality of healing at a given time, decrease in mortality, morbidity, etc.) In some situations double-blind studies can be considered, although they are more complicated. Obviously, hyperbaric chambers must already be provided with the necessary equipment for delivering various gas mixtures. In any controlled study, but particularly in multi-centre research, HBO therapy should be standardized to avoid centre-related effects. Variables in the way a therapy is provided may have significant impact on the results, not only whether or not it was given.

3. METHODOLOGY OF ECHM CONSENSUS CONFERENCES

Consensus Conferences aim to create an objective and complete review of current literature and solidify knowledge on a particular topic or field. This method has the advantage of involving a diverse group of experts, thus increasing objectivity. Participants in Consensus Conferences are selected from a broad range of relevant backgrounds to provide consideration of all aspects of the chosen topic and maximum objectivity. The opportunity to meet with other experts in the same field and share comments and information is also a valuable aspect of Consensus meetings.

In a Consensus Conference, experts present their review of the literature relating to a specific topic in front of a jury and an audience. Thereafter, the jury gathers in a secluded place to discuss the presentations, and presents its finding in a Consensus Statement that includes recommendations for clinical practice based on the evidence that was presented. These recommendations are then published in the medical literature.

The application of Evidence-Based Medicine methodology to the consensus conference process helps the jury members reach a consensus and strengthens the recommendation made. Thus, each jury member is expected to assess the literature and the evidence presented by the experts, and grades them according to their quality.

We recommend that jury members use the same grading scale, which has been extensively validated.

- *Basic studies* (tissue, cellular or sub-cellular levels)

1. Strong evidence of beneficial action
2. Evidence of beneficial action
3. Weak evidence of beneficial action
4. No evidence of beneficial action, or methodological or interpretation bias precluding any conclusion.

- *Animal studies with control groups*

1. Strong evidence of beneficial action
2. Evidence of beneficial action
3. Weak evidence of beneficial action
4. No evidence of beneficial action, or methodological or interpretation bias precluding any conclusion

- *Human studies*

1. Strong evidence of beneficial action based on at least two concordant, large, double-blind, controlled randomised studies with no or only weak methodological bias.

2. Evidence of beneficial action based on double-blind controlled, randomised studies but with methodological bias, or concerning only small samples, or only a single study.

3. Weak evidence of beneficial action based only on expert consensus or uncontrolled studies (historic control group, cohort study,...)

4. No evidence of beneficial action (case report only), or methodological or interpretation bias precluding any conclusion.

ECHM Recommendations

The Jury issues its recommendations using a 3 grade scale according to the strength of each recommendation that has been evaluated.

Type 1 : Strongly Recommended. The Jury considers the implementation of the recommendation of critical importance for final outcome of the patient/quality of practice/future specific knowledge.

Type 2 : Recommended. The Jury considers the implementation of the recommendation as positively affecting final outcome of the patient/quality of practice/future specific knowledge.

Type 3 : Optional. The Jury considers the implementation of the recommendation as an option.

The Jury also reports the level of evidence which supports, in its view, the recommendation. During the last consensus conference (Lille, December 2004), for example, after having listened to the experts and with the assistance of literature reviewers, the jury graded the existing evidence using the scale we have defined here.

Conditions where the use of HBO was supported by level A, B or C evidence were considered accepted indications

In order to make the jury discussion and decision on conditions not considered accepted indications for HBO more transparent, these levels D, E, and F were also reported with the jury's evaluation of the existing evidence. The scale used in this table is an extension of that used for accepted indications.

4. CONCLUSION

In using this EBM methodology, we expect every physician reading the jury conclusions to be able to assess the strength of evidence supporting each statement and how this applies to his clinical practice.

It is good to note that using the same EBM methodology, the UHMS expert committee and the ECHM consensus conference juries have drawn up lists of indications which are very similar with only two exceptions : the use of HBO in treating sudden deafness is not accepted in the USA and the

treatment of acute blood loss anaemia is not accepted in Europe. Further randomised clinical study is needed to clear up these differences.

Table 2.1-1. List of potential and proposed indications for HBO (Lille, December 2004)

CONDITION	**ACCEPTED**			**NON ACCEPTED**		
	Level of Evidence			**Level of Evidence**		
	A	**B**	**C**	**D**	**E**	**F**
Type I						
CO poisoning		X				
Crush syndromes		X				
Prevention of osteoradionecrosis after dental extraction		X				
Osteoradionecrosis (mandible)		X				
Soft tissue radionecrosis (cystitis)		X				
Decompression accidents			X			
Gas embolism			X			
Anaerobic or mixed bacterial anaerobic infections			X			
Type II						
Diabetic foot lesions		X				
Compromised skin graft and musculocutaneous flap			X			
Osteoradionecrosis (other bones)			X			
Radio-induced proctitis / enteritis			X			
Radio-induced lesions of soft tissues			X			
Surgery and implant in irradiated tissue (preventative action)			X			
Sudden deafness			X			
Ischemic ulcers			X			
Refractory chronic Osteomyelitis			X			
Stage IV neuroblastoma			X			
Type III						
Post anoxic encephalopathy			X			
Larynx radionecrosis			X			
Radio-induced CNS lesion			X			
Post-vascular procedure reperfusion syndrome			X			
Limb replantation			X			
Burns >20 % of surface area and 2nd degree			X			
Acute ischemic ophthalmological disorders			X			
Selected non healing wounds secondary to inflammatory processes			X			
Pneumatosis cystoides intestinalis			X			

CONDITION	ACCEPTED			NON ACCEPTED		
	Level of Evidence			Level of Evidence		
	A	B	C	D	E	F
Others indications						
Post sternotomy mediastinitis				X		
Stroke				X		
Sickle cell disease				X		
Malignant otitis externa				X		
Acute myocardial infarction				X		
Femoral head necrosis				X		
Retinitis pigmentosa					X	
Tinnitus					X	
Interstitial cystitis					X	
Facial (Bell's) palsy					X	
Cerebral palsy						X
Multiple sclerosis						X
Foetoplacental insufficiency						X

2.2 Recommended Indications

Chapter 2.2.1

DYSBARIC ILLNESS

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Abstract: Dysbaric Illness (DI) is a term that covers a broad range of complex pathophysiological conditions associated with decompression. Much of the actual etiology of DI remains unknown although the primary cause is believed to be the separation and/or the appearance of gas within the body, as result of decompression. Gas bubbles may originate from inert gas supersaturation or the traumatic injection of gas into the arterial circulation following pulmonary barotrauma. Their effects are multiple and manifestations of the condition are protean. This has led to the recommendation that any signs and symptoms, observed in individuals recently exposed to a reduction in environmental pressure, must be considered as being DI until proven otherwise. A high index of suspicion should be observed. Modern evidence-based medicine has offered mechanisms for the systematic evaluation of therapy and these have been applied to recompression and particularly adjunctive therapy for DI. This chapter provides an overview of the current state of understanding on DI and offers recommendations by the ECHM for the various methods of prevention and treatment

Keywords: caisson's disease; decompression sickness; decompression illness; decompression; dysbarism; arterial gas embolism; gas bubble illness; gas bubble injury; bends

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 173–216.

1. INTRODUCTION

Dysbaric Illness (DI)♠ is a term that covers a broad range of complex pathophysiological conditions associated with decompression. Although much of the actual etiology of DI remains undefined, the primary cause is believed to be separation and/or the appearance of gas within the body, whether stationary or migratory, as result of decompression.

Gas bubbles form due to inert gas supersaturation or the traumatic injection of gas into the arterial circulation following pulmonary barotrauma. Its manifestations are protean which has led to the recommendation that any signs and symptoms, observed in individuals recently exposed to a reduction in environmental pressure, must be considered as being DI until proven otherwise. This high index of suspicion should be extended to sub-acute and chronic changes and to sub-clinical or ambiguous symptoms that may affect the long bones, central nervous system and lungs.

Although primarily associated with compressed gas diving, DI also occurs in association with altitude exposure and other sub-atmospheric pressure reductions as well as in compressed air workers and health care providers attending to patients while receiving hyperbaric oxygen therapy. While the principles of management are similar, the environments in which they may be applied vary greatly. This chapter focuses almost exclusively on the consequences of compressed gas diving.

In understanding the study and classification of DI a technical distinction needs be made between disease and disorder: Although often used synonymously, the term *disorder* is usually assigned to physical derangements, frequently slight and transitory in nature. A *disease*, on the other hand, is usually a more serious, active, prolonged and deep-rooted condition[1]. Acute DI therefore begins as a *disorder* which, depending on its pathophysiology and treatment, may become a *disease* [2-4] .

♠ Although imperfect, the term Dysbaric Illness (DI) was chosen as the umbrella term for decompression-related disorders and diseases. Although Dysbarism and Decompression Illness have been proposed, these present linguistic challenges and their use is associated with one particular descriptive classification. Although DI conceivably also includes medical problems associated with compression its application in this chapter refers only to those conditions that may develop upon decompression after breathing from a compressed gas source.

2. HISTORIC BACKGROUND

2.1 Discovery of Dysbaric Illness

Already in 1670, Robert Boyle demonstrated that Dysbaric Illness (DI) could be produced in a reptile by the sudden lowering of atmospheric pressure. Nearly two hundred years later the first case of DI was recorded in compressed air workers: In 1845 Triger reported that two men had suffered "very sharp pain" in the left arm and another had "pain in the knees and left shoulder" thirty minutes after emerging from a seven hour exposure to a pressure of between 2.4 atmospheres and 4.25 atmospheres [5]. As technology advanced and supported longer exposures to greater pressures the incidence of DI gradually increased until it became recognized as an occupational illness in need of prevention and treatment.

2.2 Prevention and Treatment of DI

Prevention of DI could only follow an understanding of its cause. Accordingly, the first measures were aimed at merely alleviating the symptoms. Triger himself advocated "rubbing with spirits of wine" which, he reported, "soon relieved this pain in both men and they kept working on the following days". Two years later, Pol and Watelle wrote that they felt "justified in hoping that a sure and prompt means of relief would be to recompress immediately, then decompress very carefully" [6].

By the turn of the 19th century civil engineering had achieved proportions of depth and complexity that DI became more than a trivial concern: On 15th May 1896 the Journal of the Society of Art described the landmark work of E. W. Moir during the digging of the Hudson river tunnel in 1889 [7]. Facing a DI fatality rate of over 25% of the employed workers, Moir installed a recompression chamber at the worksite. The result was a dramatic reduction in mortality – only two deaths were recorded during the next 15 months out of a workforce of more than 120. Moir, who seemed almost apologetic about this empirical therapy, wrote: "*With a view to remedying the state of things an air compartment like a boiler was made in which the men could be treated homeopathically, or reimmersed in compressed air. It was erected near the top of the shaft, and when a man was overcome or paralyzed, as I have seen them often, completely unconscious and unable to use their limbs, they were carried into the compartment and the air pressure raised to about 1/2 or 2/3 of that in which they had been working, with immediate improvement. The pressure was then lowered at the very slow rate of one pound per minute or even less. The time allowed for equalization being from 25 to 30 minutes, and even in severe cases the men went away quite cured*".

Ironically Paul Bert in 1878 had already validated this concept [8]. He had demonstrated that the cause of DI was nitrogen going into gas phase in the tissues and that this bubble formation was responsible for symptoms. Bert understood that prompt recompression was the key to effective treatment. Remarkably, he already highlighted the existence of "silent bubbles" in the venous blood; used oxygen at one atmosphere following very rapid decompression; and observed that cardiopulmonary symptoms, but not spinal cord paralysis, were relieved by normobaric oxygen breathing.

Since that time, prompt recompression followed by slow decompression has been universally considered the standard of care in the treatment of DI. Further developments delineated the best combinations of pressure, time, gas composition and decompression rates as well as the addition of resuscitation and adjunctive therapy (Fig. 2.2.1-1).

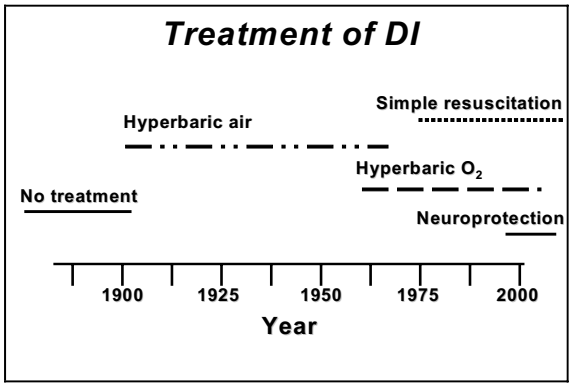

Figure 2.2.1-1. Developments in the Treatment for DI over the past century (Courtesy of Richard Moon, MD)

However, even though we are now gaining a better understanding of the tools of therapy, we remain challenged by inconsistency and confusion in terminology for DI and uncertainty of diagnosis. Clearly there is little uncertainty in the case of severe neurological DI. However, minor forms may manifest in very subtle ways. These are likely to be ignored or denied by the affected diver unless there is an appropriate level of awareness. Indeed, there is reason to believe that there is widespread underreporting of symptoms that may cause an unquantified amount of morbidity. On the other hand over-emphasis of risks and hazards may cause hypochondriacal responses or deter pursuit of the activity altogether. It remains, therefore, an ongoing challenge to achieve the correct balance between denial and hysteria in the face of untoward symptoms following diving.

As far as prevention is concerned, the definitive contribution in the context of diving was made by Boycott, Damant and Haldane in 1908 [9]. Their work, although based on speculative mechanisms, forever changed the fate of those facing decompression after breathing compressed gas. For the next 60 years refinements in modeling theory, mathematics and statistics have suggested a variety of depth-time combinations followed by various decompression stops strung together by empirical ascent rates. Unfortunately the fundamental principles on which all of these systems are based are empirical as are their progeny of tables and decompression algorithms. Their limitations have become particularly evident in recreational diving where one half of DI cases do not appear to be the consequence of overt dive profile violations. These observations have led to a search for unique physiological factors and other unique risk factors. Possibilities have included pulmonary-systemic shunts (e.g., patent foramen ovale, atrial septal defects, intra pulmonary shunts, etc.); endothelial morphological anomalies and reactivity; activation of complement; and many more. The search for these elusive risk factors continues, as does their ambiguity [2,10,11].

The introduction of precordial Doppler in the 1970's promised a solution to the mystery of DI [12]. Unfortunately the association between recordable bubbles and DI symptoms did not prove to be particularly strong: high grade bubbles correlated more closely with DI than lower grades, but DI has even been observed in the absence of any detectable bubbles. Nevertheless, this modality may again enjoy greater utility in the years to come: Recently there has been an increasing emphasis on paradoxical embolism of venous gas and a growing body of experimental and clinical evidence suggesting that large quantities of asymptomatic or "silent" venous bubbles may in fact be causing cellular and biological reactions and be releasing potentially damaging biochemical substances in the blood [13-16].

Current prevention theory for DI recommends that participants: (1) possess and maintain an appropriate level of dive medical fitness (including controlling daily physiological variables such as body temperature and hydration status); (2) avoid / prevent air trapping with gas expansion (e.g., not diving with respiratory infections and untreated reactive airway problems); and (3) observe appropriate decompression procedures for their exposure (i.e., following the recommended combination of pressure and time for their planned diving activities). Violation of one or more of these parameters increases the risk of DI [2,3].

In the future our improved ability to detect bubbles and – more recently – to detect the biochemical injuries they cause, may ultimately generate more physiological approaches to decompression. Accordingly, future decompression safety is likely to focus on three areas of intervention: (1) manipulating decompression (ascent) to reduce the appearance, quantities and size of venous gas emboli; (2) reducing the propensity of the body to

form bubbles; and (3) preconditioning the body biochemically and/or physically to reduce the pathophysiological impact of such bubbles [17-25].

3. TERMINOLOGY FOR AND CLASSIFICATION OF DYSBARIC ILLNESSES

DI has suffered from great inconsistency in terminology and classification. There are many reasons for this, including wide variations in latency, severity and diagnostic certainty. In addition, the boundaries between arterial gas embolization and decompression sickness are blurred due to possible arterialization of venous gas. These factors have confounded research and remain an ongoing challenge.

There are many ways to classify medical conditions in general, e.g., by diagnosis, prognosis, pathology, pathophysiology, clinical presentation, etc. The objective for classification is usually for the purpose of simplification. This may include improving communication between clinicians; determining treatment guidelines; establishing prognosis; or conducting research and analyzing epidemiological data.

Unlike most other diseases, there is no definitive test for DI. It is only the causality to decompression and the prevalence of neurological involvement that respectively provide epidemiological boundaries and clinical relevance to defining and classifying the condition. To date no single system has emerged that provides both clear pathological stratification and clinical utility.

3.1 Terminology

Various clinical terms have emerged in an ongoing effort to describe and classify DI. These have ranged from descriptions of a limited number of distinct clinical syndromes (e.g., the “bends”, “chokes” and “staggers”); a presumptive assignment of etiology and severity (e.g., type I decompression sickness and arterial gas embolism); and the systematic capture of descriptive clinical and causal factors associated with the condition (e.g., decompression illness or dysbarism, and gas bubble illness). Not only have these terms proven to be ambiguous, but they have been applied inconsistently and have introduced many linguistic challenges (e.g., the differentiation between illness and sickness).

3.2 The Classification Systems

To date, three enduring systems have appeared for the classification of DI:

- the traditional or Golding Classification [26]
- the descriptive or Francis / Smith Classification [27-29]
- the ICD-10 Classification

Each of these classification systems addresses different objectives and accordingly has inherent strengths and weaknesses.

3.2.1 The Traditional / Golding Classification

The Golding classification, developed during the building of the Dartford Tunnel, was based on the assumption that DI was bivariate [26]: It was either inert gas (decompression sickness or DCS) or embolic (arterial gas embolism or AGE) related. DCS was either mild (Type I) or severe (Type II) and each category had specific treatment recommendations. Then, in 1970 a combined form of DCS and AGE was described. It was called "Type III decompression sickness" in an effort to contain it within the existing classification system, but it demolished the previously clearly defined boundaries between DCS and AGE and illustrated the shortcomings of the classification system [30]. Also the Golding Classification made no provision for the dynamic nature of DI (i.e., its tendency to present in one way but evolve into another), nor could it account effectively for the wide range of clinical severity and variability in prognosis contained within the given category of 'Type II DCS'.

The main benefit of the Golding classification remains its simplicity. Unfortunately, while its application may indeed have been equally uncomplicated in the days when commercial and military diving predominated the sub aquatic realm, this is no longer applicable to the nebulous world of recreational diving and its injuries. Recent comparisons have also shown significant discordance in a retrospective application of the Golding classification to cases relevant to the spectrum of DI encountered today[31-33].

Table 2.2.1-1. Modified Golding Classification for Dysbaric Illness

• Arterial Gas Embolism
• Decompression Sickness
- Type I (Musculoskeletal Pain; Skin; Lymphatic; Extreme Fatigue; Peripheral Nervous Symptoms)
- Type II (Neurologic; Cardiorespiratory; Audiovestibular; Shock)
- Type III (Combined Decompression Sickness and Arterial Gas Embolism)

3.2.2 The Francis / Smith Classification

To solve the inherent problems of the Golding Classification, Francis and Smith proposed a new descriptive classification system that focused on clinical presentation rather than etiology of DI [27-29,33]. It contained descriptive categories that served a dual purpose of capturing actual clinical manifestations (e.g., the dynamic evolution and organ systems involved) as well as detailing factors relevant to etiological considerations (e.g., latency, inert gas burden and evidence of pulmonary barotrauma). This system offered flexibility, provided more relevant information and had a much higher degree of concordance between clinicians (see Table 2.2.1-2.).

The greatest utility of this classification system is its ability to describe and adapt to the evolving signs and symptoms of presumed DI in a diver. However, it does not establish a diagnosis, only factors relevant to the probability thereof within a descriptive matrix of an evolving clinical presentation [34]. However, a collection of these descriptions can be used for clinical comparison and to examine trends. The latter can then be analyzed in the pursuit of underlying pathophysiological mechanisms and – based on they probability of diagnosis generated by the various determinants – a specific diagnosis may be assigned with appropriate nomenclature or descriptions of symptom-clusters. Kelleher has shown that useful predictions regarding outcome can be made using such data [35].

Table 2.2.1-2. The Francis & Smith Classification for Dysbaric Illness

- Evolution
  - Spontaneously Recovery (Clinical improvement is evident)
  - Static (No change in clinical condition)
  - Relapsing (Relapsing symptoms after initial recovery)
- Progressive (Increasing number or severity of signs)
- Organ System:
  - Neurological
  - Cardiopulmonary
  - Limb pain exclusively
  - Skin
  - Lymphatic
  - Vestibular
- Time of onset:
  - Time before surfacing
  - Time after surfacing (or estimate)
- Gas Burden
  - Low (e.g., within NDL)
  - Medium (e.g., Decompression Dive)
  - High (e.g., Violation of Dive Table)

- Evidence of Barotrauma
    - Pulmonary (Yes / No)
    - Ears
    - Sinuses
- Other Comments

Unfortunately, although the Francis / Smith system has received increasing acceptance, its strength has also remained its fundamental deficiency – the inability to assign a specific diagnosis. Clinicians and statisticians ultimately need to work with diagnoses or case definitions. These have remained elusive. Nevertheless, the current recommendation of the European Committee for Hyperbaric Medicine (Type 1 recommendation) is to provisionally accept the Francis and Smith classification until a superior system emerges [28,29,36].

3.2.3 The ICD-10 Classification

In the International Classification of Diseases, 10th edition, there are various codes related to decompression illness. These are broad categories and do not serve the purpose of differentiating the clinical and etiological subtleties of the conditions: There is no sub-classification for caisson's disease, although certain forms of barotrauma are sub-classified.

The ICD-10 codes most frequently used are:

- T70 (Effects of air pressure and water pressure)
- T70.0 (Otitic barotrauma)
- T70.1 (Sinus barotrauma)
- T70.3 (Caisson's disease)
- T70.4 (Effects of high-pressure fluids)
- T70.8 (Other effects of air pressure and water pressure)
- T79.0 (Traumatic air embolism)
- T79.7 (Traumatic subcutaneous emphysema)
- M90.3 (Osteonecrosis in caisson disease – T70.3+)

While the ICD-10 has become the international standard for diagnostic classification of general epidemiological data, its primary application is for billing and national healthcare decision-making processes rather than unraveling the intricacies of a given medical condition. In short the ICD-10 has function and value but contributes little to the sub specialty of diving medicine.

3.2.4 Future classification systems

The present trend is towards developing clearly defined case definitions for DCS, AGE and combined forms. The dilemma in developing these is that

there is disparity between epidemiological and clinical objectives. The former requires specificity in favor of reliable diagnosis, the later sensitivity in favor of avoiding under-treatment. It is likely that a scoring system will ultimately be accepted which records risk-factors relevant to the exposure and clinical features consistent with a diagnosis. Then, depending on the objective the relative weighting of these factors will be adjusted respectively for greater specificity or sensitivity. The ECHM has recommended the development and acceptance of such an epidemiological classification system which will allow multi-centre, multinational, retrospective analyses derived from broad-based classifications that include the type of diving, chronological data, clinical manifestations and outcome of a two-year follow up for prognostic purposes.

4. PATHOPHYSIOLOGY

Although DI is causally related to bubbles, there are a multitude of pathophysiological mysteries between the physical appearance of bubbles and the onset of biological injury or clinical illness. Various unknown individual physical and physiological factors may contribute towards individual variability in the production of, and response to, bubbles [37,38]. Venous bubbles are commonly observed following routine and even relatively shallow dives and appear to be largely asymptomatic. On the other hand, the appearance of left ventricular or arterial bubbles are thought to be of greater clinical importance; however these have rarely been observed, even in a laboratory setting. Recently, ocular tear film bubbles have generated some interest, but their persistence following decompression has limited their reliability as a predictor of decompression stress [3,39].

When it comes to actually diagnosing DI, we presently rely almost exclusively on the diver's history and an estimation of clinical probability from an enormously divergent spectrum of signs and symptoms following decompression. As yet, there are no specific biochemical markers for bubble related injury [40-42]. Also, the sensitivity of radiological and nuclear medical examinations does not exceed that of clinical observation and, in the absence of diagnostic uncertainty, these rarely affect management. We must therefore accept that the best scientific case definition we have for DI at present is one of exclusion, i.e. the appearance of unexplained pain, cutaneous, cardiovascular or neurological abnormalities – chronologically associated with compressed gas diving – upon the exclusion of other etiologies. In a clinical setting, our index of suspicion should be high to avoid under-treatment. Fortunately, the risk of injury remains relatively

small: in recreational diving, for example, DI occurs with an incidence of one to three per 10,000 dives [43].

4.1 The origin and destination of bubbles

With decreasing pressure, a threshold is eventually reached where bubbles start to form in the body; this depends on the amount of inert gas and the extent of decompression. At extreme altitudes, DI cannot be avoided, even after prolonged oxygen pre-breathing [44].

Although decompression bubbles are traditionally classified as intra- or extravascular, this division may be misleading as it does not describe the origin of bubbles but rather where they have been observed. In fact, there is no proof that bubbles form directly in blood vessels. Rather, it is believed that they may be admitted through endothelial gaps as they develop within surrounding perivascular tissues [45]. Another mechanism for the intravascular appearance of bubbles is by traumatic introduction during pulmonary barotrauma [46]. As little as 10% overexpansion of the lungs is enough to cause gas embolism [47,48]. This would occur with an intratracheal pressure of 76-80 mm Hg (or 99.2-108 cm H2O), or during a breath-hold ascent (after breathing compressed gas) from only 3 feet (~1 meter) of seawater to the surface [48]. Although traumatic injection of gas vs. bubbles released by inert gas supersaturation represent two completely different etiological mechanisms, they are often difficult to differentiate clinically: physical or radiological evidence of pulmonary injury is often absent in AGE [49], whereas arterialization of inert venous gas emboli may result in arterial gas embolization with clinically indistinguishable results.

Although the origin of bubbles may be ambiguous, their effects are more distinct. Intravascular bubbles embolize tissue causing ischemia [50]; they also traverse the microvasculature (so-called "transbolism") and injure endothelium [51]; they cause reperfusion injury and vasospasm [18]. Bubbles can cause venous stasis, hemorrhage and precipitate plasma protein interactions [52]. Extravascular or tissue bubbles disrupt and tear delicate tissues and blood vessels; they can also increase tissue compartment pressures i.e., cause regional compartment syndromes [53].

4.2 Effects of Bubbles on various Tissues and Organ Systems

To consolidate the various mechanisms involved in DI into meaningful clinical entities, it is useful to observe their effects on known target organs: (1) blood and blood vessels; (2) the lungs; (3) the central and peripheral

nervous systems; (4) the inner ear; (5) the skin and lymphatics, and (6) bones and joints.

4.2.1 Blood and blood vessels

Bubbles are biologically active. They interact with the cellular elements in blood as well as plasma protein cascades – coagulation, complement, kinin and plasmin. In addition, bubbles denature lipoproteins, liberating blood lipids [54-57]. Blood vessels, on the other hand, sustain damage through physical contact. This may range from minimal damage to bleeding [51,58].

Blood:

Upon appearance of a bubble in blood, the catalyzing event appears to be the formation of a plasma-protein coat around the bubble. This bubble "skin" is made up of plasma glycoproteins, fibrinogen and gamma globulins [59,60]. It is a biologically active interface that allows thrombocytes and white blood cells to become attached [61].

In time, activation of platelets leads to aggregation and coalescence around bubbles with entrapment of other blood constituents. Cellular blood elements – such as red blood cells – may become entangled in the growing fibrin web. This thickening of the bubble "skin" may reduce diffusion producing a mechanism for bubble stabilization and survival [62]. General platelet adhesiveness also increases in response to bubbles. Some studies have reported platelet depletion following decompression, even in the absence of symptoms [63]. However, thrombocytopenia or anti-platelet therapies do not appear to protect against DI. Also aggressive anticoagulation runs the risk of precipitating hemorrhage in DI affecting the spinal cord and inner ear [61,62,64,65]. On the other hand, DI does induce a hypercoagulable state with a high risk of thromboembolism aggravated by paralysis. This should be actively prevented.

The activation of platelets and Hageman Factor also leads to activation of inflammatory cascades. Leukotrienes are released while the presence of gammaglobulin on the bubble skin, combined with the products of complement activation, attract white blood cells to the area [66]. Leukocytes may interact directly with the bubble or with damaged endothelium. The relevance of inflammation in DI underlies the recommended use of anti-inflammatory agents and, more recently, of lidocaine [67]. Lidocaine also has leukocyte anti-adherent properties [68,69].

DI has also been shown to result in elevations of blood lipid levels with as yet undefined clinical implications [70].

While the role of various elements in blood in DI has become downplayed in recent literature, the significance has not disappeared: The search continues to find safe and effective drugs or interventions that may

attenuate the various pathophysiological events following exposure to bubbles. Recently research on nitric oxide donors and exercise have suggested that they may have a modifying role in vivo [17].

Blood vessels

The injection of 10-20μm bubbles into the carotid artery of a guinea pig has been shown to cause visible damage to the luminal surface surfactant layers of endothelial cells [71]. This form of injury may result in alterations in vasomotor tone, precipitate platelet or leukocyte adhesion, and cause failure of the blood-brain barrier. In more extreme cases endothelial cells may actually be stripped, exposing the basement membrane to plasma proteins and platelets as well as adding bioactive cell remnants to the blood [61].

4.2.2 The Lungs

Unlike pulmonary barotrauma, pulmonary DI is an intravascular occlusive bubble disease. It results from the passage of venous gas emboli through pulmonary capillaries. The peri-alveolar network of capillaries serves as a trap for venous gas emboli. However, if the amount of gas is excessive, it may cause cardiac air locking and pulmonary outflow obstruction or microvascular obstruction with vasoconstriction, endothelial damage, inflammation, capillary leak and pulmonary edema – "the chokes". The pulmonary "bubble trap" may also be overcome by massive embolization or be bypassed via broncho-pulmonary shunts, arterio-venous fistulae, or intra-cardiac shunts. A reduction in the diameter of circulating bubbles – such as by repetitive diving or "yoyo" diving – may allow bubble passage through the pulmonary capillary beds. All of these mechanisms may lead to arterialization of bubbles – so-called paradoxical gas embolism. The latter provides an attractive theoretical explanation for the poorly understood associations between "chokes", patent foramen ovale, and DI of the central nervous system and skin [11,43].

4.2.3 Nervous System

Approximately two thirds of DI affects the nervous system. Although clinical features may be ambiguous a distinction is made between three potential locations of injury: (1) the spinal cord, (2) cerebrum and (3) peripheral nerves. In each case, the primary mechanism may be vascular (embolic) or extra-vascular.

In a review of 1070 cases of neurological decompression sickness, Francis et al discovered that 56% occurred within 10 minutes – some even prior to surfacing [72]. Even when considering the 768 cases of obvious spinal cord injury in this series the majority still presented within 10 minutes of

surfacing. Therefore any mechanistic theory for DI would have to account for this short latency. Conversely, there were 44% of cases that developed clinical manifestations as long as 48 hours after surfacing. This supports the probability of multiple mechanisms with varying latencies.

4.2.3.1 Spinal Cord

Four etiological theories have evolved to reconcile the varying observations of onset time, severity, response to therapy, and histopathology. They are (1) gas embolism; (2) venous infarction; (3) autochthonous ("in situ") bubbles; and (4) hemorrhage or inflammation.

Gas Embolism:

The first theory for DI of the spinal cord was developed by Boycott and Damant. Lesions in the spinal cord of goats were found to consist, almost entirely, of white matter lesions [9]. Indeed human pathology, although rarely observed in this mostly non-fatal condition, has also shown similar punctate, white matter lesions and hemorrhage. However, embolic injury to the spinal cord is, generally speaking, very rare. This is believed to be due to the relative difference in blood flow favoring embolization of the brain. Experimental spinal cord embolism has also been shown to produce ischemic grey matter pathology rather than white matter lesions [73]. To confuse the matter further a type of DI was identified that began as rapid onset cerebral arterial gas embolism but then evolved into a particularly resistant form of spinal injury. This has been called "combined", "concurrent" or "Type III decompression sickness" [30,74-76]. Although the exact mechanism is still unknown, the predominant theory is related to growth of arterial gas emboli in tissues saturated with inert gas.

Venous Infarction:

In 1975, based on Batson's experiments on tumor embolization via epidural veins [77], Hallenbeck et al postulated that DI of the spinal cord was due to bubble accumulation in the epidural venous plexus with subsequent venous infarction of the spinal cord. Although confirmed in extreme decompression [78-80], loss of function only occurred after several minutes and therefore did not offer an explanation for ultra-short-latency disease. In addition, the pattern of dysbaric injury was different to that observed in other causes of venous infarction of the spinal cord that typically affects the central grey matter [81].

Autochthonous Bubbles:

Francis proposed that rapid-onset spinal cord damage may be related to spontaneous bubble formation in the spinal cord white matter. He felt that this was the only mechanism that could explain both the rapid onset and the distribution of lesions observed in the spinal cord. In his classic experiment, the spinal cord of decompressed dogs was rapidly perfusion-fixed at the

moment of maximal disruption of somatosensory evoked potentials. He consistently found extravascular, white matter lesions – called autochthonous bubbles [82,83]. The puzzling piece is how these small, scattered and isolated space occupying lesions (making up no more than 0.5% of the spinal cord and being no more than 20-200um in diameter) are able to produce such catastrophic clinical effects [84]. It has been postulated that autochthonous bubbles could account for loss of function if more than 30% of the axons became dysfunctional due to direct injury, stretching or compression, inflammation, biochemical injury or hemorrhage. In support of this, Hills et al has also shown that small lesions (able to increase the spinal cord volume by 14-31%) can cause an increase in tissue pressures with a resulting spinal compartment syndrome [85].

Hemorrhage and Inflammation:

In his studies on autochthonous bubbles, Francis made three important additional observations [86]: (1) animals that only developed abnormalities after 30 minutes had no demonstrable space occupying lesions suggesting another mechanisms for the dysfunction; (2) animals sacrificed some time after the development of rapid-onset dysfunction no longer had bubbles suggesting that they are temporary; and (3) the histological appearance of spinal cords from dogs with late-onset spinal symptoms was similar to that of spinal embolism or ischemic lesions [73]. Interestingly in the animals harvested some time after rapid onset illness, hemorrhage and inflammation were observed in the same areas where autochthonous bubble injuries were seen in those harvested early. This could explain why some cases of rapid onset spinal cord DI appear resistant to recompression and would suggest caution in the use of anti-coagulants in DI of the spinal cord.

Intriguingly, all of the mechanisms appear to converge within a particular area: a c-shaped area around the spinal cord grey matter. This area represents a watershed zone between the anterior and posterior spinal cord circulation and would therefore be susceptible to both inert gas accumulation as well as subsequent bubble-related ischemia. The cervical and lumbar enlargements are particularly vulnerable and also correspond to the areas of greatest clinical importance in DI.

It is unlikely that one single mechanism can account for the wide variety of latencies and presentations of DI of the spinal cord and the decompression schedules leading to them. Rather it is probably the result of several interacting, compressive-ischemic mechanisms. DI of the spinal cord should be thought of as a spectrum of cause-and-effect over a 48-hour time-continuum. It is an interplay between a variety of distinct, yet synergistic pathophysiological processes - some of which are amenable to recompression and adjunctive medical therapy and some which, unfortunately, are not.

Finally, in spite of the disturbing vulnerability of the spinal cord, it has a remarkable capacity of recovery. Many divers with residual deficits after recompression therapy continue to improve for years afterwards. However, this does not indicate that the injury has been reversed, only that the body has compensated for it [87,88].

4.2.3.2 Cerebrum

Cerebral decompression disorders differ from those of the spinal cord in that there is no experimental evidence suggesting autochthonous or venous stasis mechanisms. Accordingly, greater emphasis is placed on embolic and inflammatory mechanisms.

Cerebral DI has a very short latency. In the review by Francis, 75% of the 311 cerebral DI cases became symptomatic within 10 minutes (even with all cases of overt pulmonary barotrauma specifically excluded) [72]. This leaves paradoxical gas embolization as an attractive alternative possibility.

Clinical Features Systemic Gas Embolism (SGE):

Gas embolism is by its nature a systemic disease although clinically it primarily affects the myocardium and the brain. While coronary embolism may account for some diving fatalities, it is not associated with long term morbidity. Cerebral events, on the other hand, are associated with both short term mortality and long term morbidity.

SGE gain access to the cerebral circulation via the carotid and vertebral arteries that converge at the base of the brain forming the circle of Willis. Depending on the volume of gas and region of the brain involved the clinical outcome of gas embolism ranges from instant death to spontaneous uneventful recovery. Relapses have been reported in up to 30% of patients with arterial gas embolism following submarine escape, irrespective of preceding or concurrent recompression [89-91]. A subset of patients may also suffer subclinical damage only visualized by medical imaging [74].

Irrespective of the cause, the ultimate outcome of cerebral gas embolization appears to depend on the anatomical location, gas volume, delivery rate, pre-embolic gas saturation as well as co-morbid factors such as hypotension or dysfunction of vital centers.

4.2.3.3 Peripheral Nervous System

The peripheral nervous system may be affected by decompression injuries anywhere from the posterior horn of the spinal cord, to the mixed nerves, brachial or lumbar plexus, and cutaneous or muscular innervations. The most important considerations are differential diagnosis and prognosis. This area probably represents one of the areas of greatest clinical ambiguity. However, even though the underlying pathophysiology remains obscure, the prognosis is usually good.

4.2.4 Inner Ear

There are four dominant theories for the clinical and pathological findings associated with DI of the inner ear. They are: (1) explosive / hemorrhagic injuries; (2) counter diffusion; (3) gas induced osmosis; and (4) vascular emboli [92,93].

Explosive / hemorrhagic injuries

In 1980, Landolt et al found hemorrhage in the inner ear of squirrel monkeys subjected to rapid decompression from saturation [94]. Three years later Venter was able to show an implosive injury of the semicircular canals as the cause for the hemorrhage [95]. The mechanism, they proposed, was one of gas accumulation in temporal bone osteoclast pockets that then explosively ruptured into the inner ear during decompression. Money subsequently found evidence of the same type of injury in a diver who died 56 days after left inner ear DI [96]. This mechanism is plausible for deep mixed gas diving, but less convincing for inner ear DI following shallower dives.

Embolism

Blood supply to the inner ear is endarterial and consequently prone to embolic or vascular injury. Embolic disturbance has been shown in cardiac bypass surgery, but how this relates to diving remains uncertain [97].

Counterdiffusion

This theory entertains the possibility that counterdiffusion can occur under conditions where the inert gas in the middle ear differs from that in the breathing mixture. Diffusion through the round or oval window could result in accumulation of inert gas with bubbling, resulting in deafness or vertigo. This theory has developed due to a high prevalence of inner ear DI in helium-oxygen and mixed gas divers [27]. Counterdiffusion may also occur within the partitions of the inner ear itself. The vascularity of the inner ear is not uniform: the stria vascularis supplies the endolymph directly and from there inert gas would diffuse to the perilymph. Therefore, with gas switching, it is possible that the endolymph could rapidly take up a new inert gas, e.g. helium, before the perilymph has had time to eliminate the former inert gas. Bubbles could then form within the endolymph with disruption of function and even rupture [27].

Gas-induced Osmosis

Finally, by a similar mechanism, inert gas accumulation in the endolymph could result in gas-induced osmosis: an osmotic fluid shift towards the endolymph resulting in a form of hydrops endolymphaticus analogous to Meniere's disease.

4.3 Skin

Skin bends or DI of the skin may present in a variety of ways with varying etiologies and clinical significance.

Diver's Lice

This erythematous rash usually presents in association with dry chamber dives or the use of dry suits. The hypothesis is that inert gas enters the skin directly and causes dermal bubbles with histamine release upon decompression. The condition can be avoided by not having gas skin contact, or by heating the skin during decompression. It is not considered serious in the absence of other findings, and does not require recompression.

Cutis Marmorata

A more significant form of DI of the skin is called cutis marmorata or skin marbling. Although the condition itself is benign, its association with pulmonary and neurological DI requires careful consideration. Experimental work in pigs has shown that this pattern of illness is associated with venous congestion, inflammation, leukocyte adherence and endothelial damage [98]. No bubbles have been visualized, but the manifestations usually resolve promptly with recompression.

Counterdiffusion

A rare type of DI may result from exposure to different inert gases, such as helium and nitrogen. Diffusion-related gas accumulation may occur when one gas is in contact with the skin, while another is breathed [99,100].

4.4 Musculoskeletal

Some of the first descriptions of DI or "the bends" involved painful joints [101]. Even today, musculoskeletal pain it is the most common presenting complaint [102].

There are two bone and joint conditions associated with decompression: acute muskuloskeletal DI and dysbaric osteonecrosis.

4.4.1 Acute Musculoskeletal DI

Although they have similar blood supply, joints, and musculo-tendinous attachments, it is noteworthy that 'bends' pain only appears to affect long bones of the appendicular skeleton – not the axial skeleton. Adult long bones contain a fatty marrow cavity that could be a reservoir for inert gas and predispose to DI. Axial bones largely contain haemopoietic tissue which appears to be unaffected by decompression.

Another interesting feature of 'bends' pain is that it is influenced by pre-morbid hyperbaric activity. In a review of more than 19,000 cases, Sowden

found that bounce divers and pilots primarily developed shoulder pain, whereas saturation divers and caisson workers developed knee pain [103]. There are many theories but little evidence to explain this phenomenon.

There are four theories for bubble-related pain in bones and joints. They involve stretching of nerve endings or inflammation occurring (1) within joints; (2) around the joints, such as within tendons and muscle; (3) within bone, due to gas expansion within fatty marrow, the medullary cavity and bone sinusoids (a phenomenon also associated with cancer-pain), and; (4) as a result of referred pain, either due to an injury to the nerves or nerve roots associated with the joint, or due to a generalized release of inflammatory modulators with flu-like symptoms and poliarthralgia.

Intra- and periarticular pain associated with decompression can usually be localized and is of a non serious nature. There is a trend towards treating these conservatively although they respond well and promptly to recompression. Referred pain is part of the neurological spectrum of DI that has been considered elsewhere. What remains, is medullary pain.

The discovery of sinusoid innervation has led to the concept of a venous congestive mechanism for cancer and osteoarthritic bone pain [104,105]. This sinusoid congestion pain theory is also attractive as an explanation for 'bends' pain as it addresses several clinical phenomena: (1) the deep, poorly localized, boring pain; (2) relief achieved by the local application of pressure (e.g., a BP cuff); and (3) a gravity-related distribution of manifestations in the various patient subgroups.

Although there is no scientific association between medullary pain and dysbaric osteonecrosis, it is usually viewed as a more serious form of musculoskeletal DI and recompression is recommended.

4.4.2 Dysbaric Osteonecrosis

Dysbaric osteonecrosis appears to affect predominantly saturation divers and caisson workers. Again it appears to be the appendicular skeleton that is at risk, particularly the humoral head, femoral head and juxta articular area of the distal femur and proximal tibia. Lesions in proximity to the femoral and humeral head may be symptomatic and may eventually become disabling whereas femoral and tibial shaft lesions remain asymptomatic. The question remains why it is only certain types of diving that predispose to this disease, and why these areas are so uniquely vulnerable [106].

4.5 Concluding Remarks on DI Mechanisms

The confusion and controversy regarding the pathophysiology of DI is exemplified by the division that still exists in the use of two classification systems: one pathological [107], and the other clinical [28,29].

While we do not always know the cause of DI, we must not ignore mechanisms altogether, thereby being unable to appreciate risk, determine probability of injury and prescribe effective and rational treatment. Astute clinical observation and focused research must remain the vital tools for unraveling the mysteries of DI.

5. EPIDEMIOLOGY

There are five important epidemiological observations that have been made regarding DI [2-4,14,21-24,108-123]:

- The incidence is very low in general – in the order of 0.01-0.05 % (1 to 5 per 10,000 dives).
- There is no demonstrable gender-specific predisposition to DI.
- Novice and experienced divers are at greatest risk for developing DI.
- Dives in excess of 24 meters (80 feet) have a significantly greater incidence of DI.
- Neurological involvement is by far the most common manifestation in recreational divers.

5.1 Risk Factors

A variety of risk factors have been identified over the past century in an effort to explain the variations in susceptibility to DI [2-4,14,21-24,108-123]. These include:

- Altitude Exposure: either diving at altitude or subsequent exposure
- Exercise: before, after or during the bottom phase of a dive
- Injury: previous DI or other acute injuries
- Omitted decompression: missed stops / errors of depth monitoring
- Uncontrolled ascents
- Personal traits (gender; physiognomy; level of fitness)
- Profiles: (variables of depth, multiple ascents, ascent rates and the depth prior to final ascent to the surface within the same ‘square-profile’ or depth-time envelope)
- Previous dives: residual nitrogen
- Hypoventilation: CO_2 build-up

- Hypothermia: gas retention-release due to solubility changes
- Hypovolemia: dehydration and hemoconcentration

Although the relevance of individual factors is understood and – in some cases – obvious, there is surprisingly little evidence on the relative contributions of these factors towards the overall risk [38]. The following are discussed in more detail below:

5.1.1 Exercise: before, after or during the bottom phase of a dive

Exercise during exposure to increased ambient pressure (during the bottom phase of the dive) appears to increase the incidence of DI. The probable explanation of this is that the increased perfusion during exercise leads to an increased uptake of inert gas that must be subsequently eliminated during decompression. Conversely Vann *et al* have shown that exercise during decompression stops may reduce the incidence of DI by an opposite mechanism [25]. Exercise prior to or following diving are risk factors however and there are at least three reasons for this:

- Rapidly flowing blood, especially in the area of bifurcation of vessels, may create foci of relative negative pressure through a Venturi effect. Small numbers of molecules of gas from the surrounding supersaturated blood may then diffuse into these foci down a partial pressure gradient. The resulting localized collections of small numbers of gas molecules are known as gas micronuclei and are thought to act as a 'nidus' for bubble formation.
- Distraction between articulating joint surfaces causes extreme reductions in ambient pressure and gradients of up to 270 atm. This process – called tribonucleation – is thought to offer some explanation for the variable incidence between different forms of diving and compressed air activities vs. the ultra-low incidence of DI during extravehicular activity in space. In the latter case it is thought that the absence of gravity reduces articular shearing forces and in the absence of ongoing production these micronuclei seem to disappear.
- Increased local CO_2 production in exercising muscle may play a role since CO_2 is a highly diffusible gas and might contribute to the formation of gas micronuclei.

5.1.2 Injury: previous DI or other acute injuries

Recent local injury seems to lead to an increased incidence of DI manifested by pain at or near the site of the injury. The mechanism responsible for this phenomenon is unclear. Changes in local perfusion and

increased gas micronuclei formation in injured tissue are postulated mechanisms.

5.1.3 Personal traits (gender; physiognomy; level of fitness)

There is no convincing evidence that gender affects DI risk in recreational divers. Indirect measures of fitness and body mass have yet to yield definitive answers on relative risk for DI. Advancing age is thought to increase the incidence of DI for reasons that are not yet clearly known.

5.1.4 Hypoventilation: CO_2 build-up

Even small increases in $FiCO_2$ seem to increase the incidence of DI. The mechanism of this effect is not clearly understood, although increased availability of this highly diffusible gas for diffusion into gas micronuclei; vasodilatation with increased inert gas uptake; and reduction in the 'oxygen window' are all relevant factors.

5.1.5 Hypothermia: gas retention-release due to solubility changes

Diving in cold water tends to increase the incidence of DI. Inert gas uptake is generally not affected since the exercising diver is usually warm and has increased tissue perfusion because of exercise. However, when the diver leaves the bottom and reaches his decompression stop where he remains at rest he is likely to become cold. The resulting peripheral vasoconstriction may then impair inert gas elimination.

5.1.6 Hypovolemia: dehydration and hemoconcentration

Dehydration was reported as a factor that increases the risk of DI during studies on aviators during World War II, and it is still considered a significant risk factor by the international diving and diving medical communities. The mechanism is however again unclear and reliable scientific evidence is missing. Changes in the surface tension in serum favoring bubble formation has been postulated as a possible mechanism. Alcohol ingestion prior to diving, also seems to be a risk factor – possibly due to dehydration.

6. CLINICAL MANIFESTATIONS [2,3,14]

DI presents at various intervals following hyperbaric exposure [14]: 50% occur within 30 minutes of surfacing; 85% occur within one hour of surfacing; 95% occur within 3 hours of surfacing; 1% delayed more than 12 hours. However, symptoms have been reported to appear as late as 24 hours and more after surfacing and even longer if exposure to altitude follows the hyperbaric excursion.

As far as manifestations are concerned, the clinical presentation of DI has been divided into two broad categories based on severity of symptoms prior to recompression. ♣

MILD DI

This category includes the following:

- Limb pain
- Lymphatic manifestations, or
- Cutaneous manifestations,

in the absence of any other systemic manifestations

MODERATE TO SEVERE DI

This includes the following:

- Pulmonary DI
- Central Nervous System DI (Brain; Spinal Cord; Inner Ear)
- Shock
- Girdle Pain (Abdominal; Thoracic; or Lumbar)
- Extreme fatigue

6.1 Mild DI

Mild DI includes those categories traditionally assigned to Type I in the Golding Classification [26]. Mild DI forms do not display any features of moderate to severe DI and this should be confirmed by a competent health care professional.

Pain

The upper extremities are involved 3 times more often than the lower limbs in recreational and compressed air commercial diving. The situation is reversed in caisson workers and in commercial saturation (Heliox) diving.

The pain can range from slight transient discomfort (‘niggle’) to a dull, deep, boring and unbearable pain. It is usually not affected by movement and

♣ As iterated in the preceding sections, DI does not present in watertight clinical compartments, nor can the etiology always be confirmed. It should therefore be understood that the clinical entities presented here may coincide or overlap with others across the arbitrarily assigned boundaries of mild, moderate and severe DI.

there can occasionally be some degree of overlying local pitting edema and subjective numbness (refer section 4.4.1).

Lymphatic Manifestations

The lymphatic manifestations of DI presumably result from obstruction of lymphatic vessels by bubbles. The manifestations can include pain and swelling of regional lymph nodes, with lymph edema of those tissues drained by the obstructed lymph nodes.

Cutaneous Manifestations

Itching is commonly reported during decompression from dry chamber dives where the skin is surrounded by chamber atmosphere rather than water. It is thought to be the result of diffusion of gas from the chamber atmosphere directly into the skin, followed by expansion during decompression and a consequent itching sensation. This is not considered a systemic form of DI and therefore need not be treated with recompression. Itching with or without discoloration, signs of urticaria and/or blotchiness occurring *after* in-water diving is considered to be systemic cutaneous DI ♦.

Cutis Marmorata or marbling is thought to result from bubble-related cutaneous venous obstruction. It usually presents as an area of erythema, frequently affecting the upper back and chest. Lesions may migrate spontaneously or with palpation and prominent linear purple markings are frequently observed. These manifestations are considered to be an overt manifestation of DI and should be promptly treated ♥. Recompression often, although not always, leads to prompt resolution.

6.2 Moderate to severe DI

Moderate to severe DI includes those categories traditionally assigned to Type II (and III) in the Golding Classification [26]. The criteria for moderate to severe DI are met if *at any stage* DI presents with more than simple limb pain and cutaneous features:

Pulmonary DI

This relatively uncommon syndrome usually presents with a pathognomonic triad of:

♦ If a wet dive took place in a dry suit, then there may be direct absorption of gas into the skin as for a chamber dive. This should be distinguished from dives resulting in cutaneous lesions where no skin-gas contact occurred.

♥ Cutis marmorata is associated with systemic decompensation, paradoxical embolism (e.g., via a PFO, ASD or intra-pulmonary shunt) and high spinal, cerebral and audiovestibular forms of DI. Therefore while the condition itself is not particularly serious, its associations prompt attention to the other systems of greater vulnerability and justify urgent recompression.

- Substernal pain: usually burning and progressively increasing. Initially the pain may be noted only when coughing. Over time the pain may become constant.
- Cough: initially intermittent and easily provoked by cigarette smoking (Behnke's sign). Paroxysms of coughing may become uncontrollable.
- Progressive respiratory distress and dyspnea.

The manifestations of pulmonary DI are believed to result from the combined effects of gas emboli in the pulmonary artery and obstruction of the vascular supply to the bronchial mucosa. Untreated Pulmonary DI may be fatal.

Neurological DI

The neurological manifestations of Dysbaric Illness are unpredictable: They range from minor sensory abnormalities to loss of consciousness and death. Clinically they may resemble acute stroke or an acute exacerbation of multiple sclerosis. Although an increasing number of mild sensory changes are being assigned to peripheral nerve and nerve root lesions (some of which may not necessarily be related to DI), the clinical prerogative is to assume a central origin until proven otherwise and to manage these presentations promptly.

Cerebral DI: Brain involvement in DI appears to be especially common in aviators. However it is not known if this is due to paradoxical embolization of large volumes of venous gas; the release vasoactive mediators; hypoxemia due to a disruption of pulmonary circulation in conditions of marginal oxygenation at extreme altitude or something else entirely. In this group a migraine like headache often accompanies visual disturbances. When there is brain involvement in divers a common presentation is hemiparesis which is different to the clinical presentation in aviators. Collapse with unconsciousness are rare presentations of DI and more likely to be due to injected gas than bubble evolution from supersaturated tissues.

Spinal Cord DI: Paraplegia is a 'classic' symptom of DI in divers and almost invariably represents spinal cord involvement [8]. Bladder paralysis with urinary retention and fecal incontinence frequently accompany paraplegia. In the last few years, cases of serious paralysis in recreational divers dropped from 13.4 percent in 1987 to only 2.9 percent in 1997, and the number of cases of divers losing consciousness dropped from 7.4 percent to 3.9 percent of total injuries during the same period. The incidence of loss of bladder function, another sign of neurological DI, dropped from 2.2 percent to 0.4 percent during this period (DAN Diving Accident Reports) [119].

[8] A notable exception is embolization of the anterior cerebral arteries which can also present with bilateral lower extremity paralysis and loss of bladder function.

However this change in incidence has not been balanced by an equivalent rise in the frequency of pain only or skin DI. On the contrary, there seems to be a trend towards an increased incidence of milder neurological manifestations. Paresthesias, some with well and other with less clearly defined presentations (including ubiquitous numbness and/or tingling) as well as vague, ambiguous and ill-defined symptoms now predominate recreational DI. The diagnostic ambiguity is compounded by the fact that many of these manifestations appear to respond to normobaric oxygen and recompression. However, while suggestive, response to recompression cannot be considered diagnostic in these conditions. Certain non-diving related nerve damage also appears to respond to hyperoxygenation so that one of the greatest clinical challenges in DI lies in unraveling true diving injuries from a myriad of other transient peripheral neuropathies [124].

Inner Ear DI

Cochlear and/or vestibular DI was previously almost exclusively associated with saturation and experimental diving and – accordingly – quite rare. In recent times the incidence has been increasing due to an escalation in deep recreational technical diving involving mixed gas and gas switching on decompression. Either or both cochlear and vestibular apparatus may be involved presenting with tinnitus, deafness, vertigo, nausea, and vomiting. Nystagmus may be present on physical examination. The mechanisms remain unclear (refer section 4.2.4.). Inner ear DI is a serious medical emergency and must be treated immediately to avoid permanent damage. Since the nutrient arteries of the inner ear are very small, rapid reduction in bubble diameter, with immediate 100% oxygen administration and prompt recompression are essential.

Shock

Shock occasionally occurs in DI and is usually associated with serious pulmonary and cardiovascular manifestations. Fatalities are usually the result of shock or pulmonary forms of DI and resuscitation and immediate recompression are of paramount importance.

Girdle Pain: Back, Abdominal, or Chest Pain

Unlike limb pain, pain in these areas should be considered carefully as it is frequently associated with progressive spinal cord DI.

Extreme Fatigue

Fatigue disproportionate to the amount of preceding activity has long been regarded as an evolving serious manifestation of DI. The biochemical and pathophysiological mechanisms are unknown although there is increasing evidence that it may be the result of vasoactive mediators and cytokines released due to venous gas embolization.

7. THE TREATMENT OF DI

Until Yarborough and Behnke's preliminary experiments in 1939, pressurized air was used in the treatment of DI [125-127]. Gradually oxygen was introduced, both in normobaric and hyperbaric treatment. Today the treatment of DI is performed on two levels: recompression and adjunctive therapy (including first aid).

7.1 Recompression

Modern recompression therapy includes several therapeutic options employed differentially based on the capabilities of the treating facility; the severity and delay of the presenting case; and the effectiveness of, complications experienced during, recompression therapy. They are:

- 2.8 ata oxygen tables (USN Treatment Tables [USN TT] 5 and 6 or Royal Navy [RN] Tables 61 and 62)
- 4 ata mixed gas tables (e.g., Comex 30)
- 6 ata mixed gas / air tables (e.g., USN TT 4 [or RN 54 or 55] and USN TT6A)
- 2.8-6 ata saturation tables (e.g., USN TT7).

In spite of the relatively wide range of pressure-gas-time choices and the paucity of research and outcome comparisons to other recompression procedures, USN TT 6 remains the most popular first-line treatment in use today. Available evidence suggests that this table is adequate in the majority of cases if treatment is initiated immediately [10]. Unfortunately there is often considerable delay in initiating treatment meaning that the secondary effects of the bubbles become more significant. Under these circumstances Kelleher has shown that initial treatment is curative in only 66% of the cases [36]. Even so, none of the alternative proposed protocols, including saturation decompression, have clearly distinguished themselves as being superior to USN TT 6 [128-130]. There may however be certain conditions where Heliox or greater pressure are definitely indicated. These include blow-ups from saturation and commercial Heliox diving as well as immediate recompression treatment for DI following recreational Trimix dives. In this conditions, extreme bubble formation and differences in partition coefficients of helium and nitrogen in the tissues may favor the use of greater pressure and mixed gas [2].

The use of gas mixes, particularly Heliox, for the treatment of DI following compressed air diving, remains controversial. A practical approach to the various therapeutic choices is to commence with recompression on oxygen at 2.8 ata and only in the presence of deteriorating

or severe refractory DI (and even then only if experience and available infrastructure permits this) to consider 4 ata and 6 ata mixed gas regimens.

7.1.1 Summary and currently ECHM Guidelines for recompression treatment [10,131,132]

One should be careful in extrapolating interventions successfully employed in the military and occupational diving setting to recreational diving. For instance, the occupational nature and operational risk for DI in professional diving mandate the availability of on-site recompression; the outcomes of treatment are therefore proportionally good. However, this level of medical support is neither practical nor necessary for typical recreational diving. Importantly, however, a lack of expedient recompression changes the nature of the disorder in need of treatment. With delay to recompression comes a multitude of additional pathophysiological mechanisms that may require more than pressure alone. The importance of oxygen above increased pressure, may therefore be a relevant consideration in these cases. Ultimately answering the various complex questions on appropriate therapy will only be possible after further studies specifically relevant to recreational diving.

Hyperbaric treatment, commenced as soon as possible, using 100% oxygen at pressures not exceeding 2.8 atmospheres absolute (ata), achieves very good results in more than 80% of recreational DI cases. There is no convincing evidence that higher pressures or other breathing mixtures achieve better clinical outcomes in such surface-oriented diving. The administration of adjunctive fluid therapy is usually recommended by diving/hyperbaric medicine specialists in Europe whereas the role of other drugs, such as steroids and anti-coagulants remains controversial.

In 1994, the European Committee for Hyperbaric Medicine (ECHM) organized its first European Consensus Conference, where DI was one of the topics [131]. In 1996 a second, more specific Consensus Conference was organized [132], the theme of which was "The Treatment of Decompression Accidents in Recreational Diving". Their recommendations regarding recompression were as follows:

Decompression accidents are true medical emergencies that should receive the benefit of dedicated treatment in *specialized centers* as soon as possible. A *specialized centre* is considered a hospital-based recompression facility with permanent and adequately trained medical and paramedical staff.

After immediate stabilization and medical evaluation, the victims of a decompression accident should be immediately directed to the closest

specialized centre – (*ECHM Type 1 recommendation: strongly recommended*).

In water recompression should never be performed as the initial recompression - (*ECHM Type 1 recommendation: strongly recommended*).

Minor decompression accidents (pain only) can be treated with oxygen recompression tables at 18 meters depth maximum. (Note: this is based on the experience and the good results observed in commercial diving) - (*ECHM Type 1 recommendation: strongly recommended*).

For more serious decompression accidents (e.g., neurological and vestibular accidents), there are presently two acceptable protocols:

- Oxygen recompression tables at 2.8 ata (with or without extensions)
- Hyperoxygenated breathing mixtures at 4.0 ata (50:50 Heliox or Nitrox as per Comex 30 Table or derivatives)

As for pressures exceeding 4 ata: In lieu of scientific evidence, no specific recommendations can be made at this stage regarding the optimal PiO_2 (i.e., the range of 1.26 ata [i.e., Air] to 3.0 ata [i.e., 50:50 Nitrox] at 6 ata) nor on the preferred choice of diluent inert gas. Familiarity, availability and experience may affect decisions, but under no circumstances should the lack of availability of gas mixtures preclude or delay treatment by means of "low pressure oxygen tables" - (*ECHM Type 1 recommendation: strongly recommended*).

Compression to 6 ata in case of Cerebral Arterial Gas Embolism is optional, with the proviso that this be performed using mixed gas (50:50 or 60:40 Nitrox) and not compressed air and only if the delay to recompression is no more than a few hours - (*ECHM Type 3 recommendation: optional*). Again there are no data guiding the maximum piO_2 nor the maximum delay within which this therapy is still considered appropriate.

In case of severe, persistent clinical signs, during the initial recompression, the continuation of treatment with a therapeutic saturation table may be useful – (*ECHM Type 3 recommendation: optional*).

All decompression accidents should recorded in a standardized way for the purpose of compiling an epidemiological database.

7.2 Adjunctive therapy (including first aid)

Adjunctive pharmacological treatment to recompression began to be emphasized in the late 60's and 1970's.

In 1979 the Undersea Medical Society organized a workshop on the management of severe and complicated cases of DI, where the importance of hydration, steroids, heparin, aspirin and other agents were discussed [133].

Over the years, many attempts have been made to improve the treatment of DI with other drugs – with limited success.

Some of these agents have not been sufficiently studied and may be deserving of additional attention: an example is the use of fluorocarbons. The latter has a higher solubility for nitrogen than plasma and may attenuate gas phase separation in extreme decompression scenarios like submarine escape. Lutz and Herrmann were able to substantially reduce the mortality of rats undergoing rapid decompression from 8 ata when fluorocarbon was infused after decompression [134].

Another area which deserves ongoing attention and study is complement activation and its effect on leukocyte-endothelium adhesion, which appears to be important in DI and possibly responsive to intervention with drugs.

7.2.1 ECHM Consensus Recommendations of Adjunctive Therapy and First Aid [131,132]

Following both ECHM Consensus Conferences, and after extensive presentations by leading international experts, the two International Juries formulated Recommendations that have since been adopted in Europe as the current standards for the treatment of DI in Europe. These are:

- On-site 100% oxygen first aid treatment
- On-site fluid administration
- Therapeutic recompression must be initiated as soon as possible
- "Low pressure (2.8 ata) oxygen treatment tables" are recommended as the treatment tables of choice, with
- High pressure oxygen/inert gas mixture tables used in selected and/or refractory cases. Deep, mixed gas or saturation diving require special treatment protocols.

Adjunctive pharmacological treatment remain controversial but:

- I.V. fluid therapy is recommended
- The use of steroids and anticoagulants is considered optional
- Recompression and rehabilitation is recommended until no further significant improvement is observed.

Other relevant recommendations which emerged from the ECHM Consensus Conferences included the following:

General

- Implementing diving medical / fitness standards respectively for recreational and commercial diving
- Implementing a appropriate classification system for Decompression Accidents
- Implementing a coordinated network for the collection and the retrospective analysis of data concerning decompression accidents.

- Improving recreational diving safety standards towards achieving the same safety record attained in commercial diving, with special regard to:
- availability of oxygen on every dive site
- availability of a recompression chamber within 4 hours
- preparation of an emergency plan before any dive
- training in the recognition of signs and symptoms of decompression accidents.

First Aid

One hundred percent oxygen should be administered immediately to all diving casualties; it is the single most important first aid treatment for surface-oriented diving. Appropriate rehydration is an important adjunctive first aid measure. First aid measures should not delay or defer definitive treatment.

Fluid Replacement / Resuscitation

Diving activity usually results in some level of dehydration due to immersion diuresis, increased respiratory fluid loss, perspiration and reduced fluid intake. In addition, DI causes hemoconcentration due to capillary leakage and inflammation. Identifying and treating dehydration is an important component in the treatment of DI. The degree of dehydration should be evaluated *on site* (from history, dive conditions, thirst, clinical evaluation of neurological conditions, hemodynamics, temperature, vasoconstriction, dryness of mucosa, urinary output) and *at the hospital* (from urinary output – beware of urinary retention with spinal DI, hemodynamics including CVP, hematocrit, plasma proteins and electrolytes). Recommended Hydration Protocols are:

<u>On Site</u>:

- Oral hydration: recommended only if the patient is fully conscious. Absolute contra-indications to oral re-hydration are:
    - depressed level of consciousness or loss of airway control
    - nausea and vomiting
    - suspected illness or injury of the gastro-intestinal tract

  This should be done with non-carbonated, non-caffeinated, isotonic fluids or drinking water if this is all that is available. If the patient is hyperthermic, the liquid should be cooled. High glucose content is not recommended. The amount of fluid should be adapted to the patient's thirst and willingness to take them.
- Intravenous rehydration: preferred if a trained healthcare professional is available. Access should preferably be via 18 gauge catheter with Ringer's Lactate or Saline as the infusion fluid. Glucose containing solutions are not recommended. Colloids can be considered if large quantities of fluids are needed. Recommended colloids, in order of

preference, are starch-containing solutions, gelatines, and haptene added dextranes.

In Hospital:

- intravenous rehydration is recommended
- urinary output, hemodynamics, CVP, standard laboratory tests should be performed.

Drug treatment

Normobaric Oxygen (Strongly recommended):

- The administration of normobaric oxygen allows for the treatment of hypoxemia and favors the elimination of inert gas bubbles.
- Oxygen should be administered with an oro-nasal mask with reservoir bag, at a minimal flow rate of 15 L.p.m., or CPAP mask and circuit, using either a free flow regulator or a demand valve, in such a way as to obtain a FiO_2 close to 1.
- In case of respiratory distress, severe shock or coma, the patient should be intubated and ventilated with a $FiO_2 = 1$ with settings to prevent pulmonary barotrauma. Normobaric oxygen should be continued until hyperbaric recompression is started (with a maximum of 6 hours when the FiO_2 is 1).

Resuscitation Drugs and DVT Prophylaxis (Recommended).

Optional

- On site:
    - Prevention of hyperthermia
    - Aspirin: 500 mg orally in the adult patient (contra-indications similar to oral re-hydration)
- At the Hospital: (only drugs with minimal side-effects should be used, such as:
    - Aspirin 500 mg if not already administered an not contraindicated
    - Lidocaine for severe neurological DI
    - low dose heparin (other than for DVT prophylaxis) -- avoid complete anticoagulation
    - steroids, calcium channel blockers, antioxidants

7.2.2 Recommendations on Adjunctive Therapy by the Undersea and Hyperbaric Medical Society (UHMS) [135]

The UHMS has recently published guidelines for the use of adjunctive therapy for DI. These describe specific aspects related to drug therapy in greater detail [135]. The following is an extract of the UHMS Document "Adjunctive Therapy for Dysbaric Illness (DI): Summary of Undersea and Hyperbaric Medical Society Guidelines December 2002":

Oxygen

100% O_2 administration can be safely administered for 12 hours with air breaks; thereafter, at the discretion of the receiving physician.

Fluids

For intravenous administration, lactated Ringer's solution or other glucose-free isotonic crystalloids are suggested, unless otherwise indicated. Patients who have been immersed for prolonged periods may require additional fluid because of immersion-induced diuresis.

NSAIDs.

NSAIDs are not currently recommended for use in the field. The only evidence thus far applies to the use of tenoxicam, a nonselective inhibitor of cyclo-oxygenase (COX) for pain-only DI [136].

Anti-coagulants.

Routine therapeutic anticoagulation or use of thrombolytics or IIB/IIIA anti-platelet agents in patients with neurological DI is not recommended, due to concern about worsening hemorrhage in spinal cord or inner ear DI. Low molecular weight heparin (LMWH) is suggested for all DI patients with an inability to walk. Enoxaparin 30 mg, or its equivalent, subcutaneously every 12 hours, should be started as soon as possible after injury. These guidelines are extrapolated from observations in patients with traumatic spinal cord injury. Neither the efficacy nor the safety of these guidelines in neurological DI has been specifically confirmed in patients with DI. However, deaths have occurred in divers due to documented pulmonary thromboembolism. Furthermore, there is a recognized need for prophylaxis in traumatic spinal cord injury. Thus specific prophylaxis against DVT in spinal cord DCS has been assigned a 1A guideline.

Corticosteroids

Corticosteroids are not recommended for the treatment of DI.

Lidocaine / Lignocaine

There is insufficient evidence to support the routine use of Lidocaine / Lignocaine for DI, and it is not considered standard of care. However, if it is to be used, evidence suggests that an appropriate end-point is attainment of a serum concentration suitable for an anti-arrhythmic effect (26 mg/L or ug/mL). Intravenous dosing of 1 mg/kg then subsequent boluses of 0.5 mg/kg every 10 minutes to a total of 3 mg/kg, while infusing continuously at 2-4 mg/minute, will typically produce therapeutic serum concentrations. Use of more than 400 mg within the first hour may be associated with major side effects unless the patient is continuously monitored in a medical unit with the appropriate facilities and personnel. In the field, intramuscular administration of 4-5 mg/kg will typically produce a therapeutic plasma concentration 15 minutes after dosing, lasting for around 90 minutes.

SUMMARY: ECHM & UHMS RECOMMENDATIONS FOR TREATMENT OF DI

Table 2.2.1-3.

ON SITE MANAGEMENT				
First Aid	***ECHM***		***UHMS EBM***	
On Site First Aid – Oxygen 100%	1	C	1	C
On Site First Aid – Fluids (oral)	2	C	-	-
On Site First Aid – Fluids (IV)	3	C	-	-
No In-Water Recompression	1	C	-	-
HOSPITAL-BASED THERAPY				
HBO	***ECHM***		***UHMS EBM***	
Hyperbaric Tx Hyperoxygenated Tables	1	C	1	C
Recompression (Other: e.g., USN TT6A/7 for AGE or recalcitrant DI cases)	3	C	-	-
Fluids	***ECHM***		***UHMS EBM***	
Fluid Therapy in General (Hospital Based)	2	C	-	-
Fluid Therapy (IV – Hospital based)	2	C	-	-
No Fluid Therapy D5W	1	C	1*	C
Fluid Therapy LR/crystalloids (Pain only/mild)	2	C	1	C
Fluid Therapy LR/crystalloids (Chokes)	2	C	2B	C
Fluid Therapy LR/crystalloids (Neuro DI)	2	C	1	C
Fluid Therapy LR/crystalloids (AGE)	2	C	2B	C
Fluid Therapy Colloids (Pain/Chokes/Neuro/AGE)	2	C	1/ 2B/1/2B	C
Drug Therapy	***ECHM***		***UHMS EBM***	
Life Support Drug Therapy	2	C	-	-
Drug Therapy in General	3	C	-	-
Aspirin	3	C	2B	C
NSAIDs (AGE and Chokes)	3	C	2B	C
NSAIDs (pain only & neurological)	3	C	2B	B
Anti-coagulants (AGE, Neurological, Chokes)	3	C	2B	C
Anticoagulants (pain only)	3	C	3 γ	C
Anticoagulants (leg immobility – DVT prev.)	-	-	1	A
Corticosteroids	3	C	3 γ	C
Lidocaine (AGE)	3	C	2A	B
Lidocaine (neuro DCS)	3	C	2B	C
Lidocaine (pain only, chokes)	3	C	3 γ	C

* UHMS recommendations are classified inversely, i.e., D5W: Class 3 (harmful). However for the sake of uniformity it has been changed to the negative: No D5W: Class 1

γ UHMS Class 3 suggests an agent is harmful, whereas ECHM type 3 indicates optional use. This is an area in need of more careful delineation

Experience with the use of Lidocaine / Lignocaine in other settings indicates that ataxia and perioral paresthesias are common. More serious toxic effects such as seizures can also occur.

Although the respective ECHM and UHMS recommendations were developed independently and were separated by significant time intervals, they reflect a remarkable degree of consensus. Additional study and harmonization is required in those areas where information is lacking and where differences exist between ECHM Type 3 (optional) and UHMS Class 3 (harmful) classifications.

8. PHYSICAL THERAPY & REHABILITATION

There are no scientifically valid data on which to base firm recommendations for the treatment of persistent or residual DI. Further research is required using standardized disability recording systems. Concerning spinal cord injuries, a validated scoring system (e.g., the ASIA scale) is generally recommended for pre- and post-treatment evaluation and during the two-year follow up. Randomized prospective studies are needed to better evaluate the effectiveness of hyperbaric oxygen therapy and rehabilitation. At this time a maximum of 10 additional hyperbaric treatment sessions are recommended, based on clinical response, after the initial recompression in combination with rehabilitation therapy. If a clinical plateau has not been achieved by 10 treatments, and there is objective evidence of ongoing improvement, HBO_2 may be continued – (ECHM Type 3 recommendation: optional). However, as with any neurological injury, conventional rehabilitation should be started as soon as possible (ECHM Type 1 recommendation: strongly recommended) [131,132].

9. CONCLUSIONS

Dysbaric Illness is generally considered a benign condition. If adequate treatment is started promptly, the success rate is in excess of 80 - 90%.

There is universal consensus that 100% oxygen should be administered immediately as the single most important first aid treatment of any DI case related to surface-oriented diving, and that rehydration is a very valuable first aid measure. Hyperbaric treatment should be started within the shortest possible delay from the onset of the first DI signs and symptoms. Hyperbaric Treatment tables using 100% Oxygen at environmental pressures not exceeding 2.8 ata ensure very good results in the vast majority of cases. There is no evidence that other more complex therapeutic schemes achieve better results in surface-oriented and particularly air diving. For other forms

of diving there are guidelines on the use of higher pressures and breathing gases other than 100% oxygen, but experience and appropriate infrastructure is required to perform this safely and effectively.

Although conclusive scientific evidence is lacking for many adjunctive modalities, the administration of fluid therapy is considered very important and generally recommended by diving and hyperbaric medicine specialists. The role of other drugs, such as steroids and anticoagulants, although widely used without any apparent adverse effects, is still controversial.

For neurological DI cases with significant residual deficits, continuation of hyperbaric oxygen therapy in combination with a dedicated rehabilitation protocol is considered important; there is growing scientific evidence that it can contribute significantly to achieving a better functional recovery [117,122,137].

The Consensus Conference System of the ECHM, over the last 10 years, has produced literature that are consistent with international evidence-based medical approaches on matters concerning diving medicine and the treatment of DI. These have now been adopted by the European Union Countries as the common standard of practice.

There are several important areas in need of research, namely: the relationship between gas separation and DI; the relationship between clinical symptoms and the severity of the disease; the relationship between initial clinical onset, treatment results and permanent sequelae; the reason for the large variation in individual susceptibility to DI; the life time of gas bubbles; and the actual incidence of DI. These questions will remain unanswered unless a focused, coordinated and concerted effort is made to solve them. It is hoped that Consensus Conferences and Workshops will continue to pave the way towards uniformity of practice and collaborative research efforts.

10. APPENDIX: EVIDENCE-BASED MEDICAL PRINCIPLES RELEVANT TO THE SUDY OF DI

Scientific consensus is an integral part of modern evidence based practice and is typically based on three axes: (1) the level of evidence (i.e., quality of available data), (2) interpretation of the evidence (i.e., what the data suggest and how concordant the evidence is regarding a particular intervention), and (3) the type or strength of the recommendation issued by the expert panel or jury (i.e., the extent to which the reviewers are able to recommend a particular intervention on the basis of the first two considerations). Various systems have evolved to report and interpret evidence. What follows are the ones used in the evaluation of therapeutic interventions in the treatment of DI.

10.1 ECHM Method: European Consensus Conferences (1994-2004)

10.1.1 Levels of Evidence

- *ECHM Level A*: At least 2 concordant, large, double-blind, controlled randomized studies with no or little methodological bias
- *ECHM Level B*: Double-blind controlled, randomized studies but with methodological flaws; studies with only small samples, or only on a single study
- *ECHM Level C*: Only uncontrolled studies or consensus opinion of experts

10.1.2 Recommendations

ECHM Type 1: the implementation of the recommendation is of critical importance for future specific knowledge / final outcome of the patient

ECHM Type 2: the implementation of the recommendation can positively affect future specific knowledge / final outcome of the patient

ECHM Type 3: the implementation of the recommendation is optional

10.2 American Heart Association Guidelines for Clinical Efficacy (EBM) 1996

10.2.1 AHA Levels of Evidence

- *Level A*: Data derived from multiple randomized clinical trials
- *Level B*: Data derived from a single randomized trial or non-randomized studies
- *Level C*: Consensus opinion of experts

10.2.2 AHA Recommendations

- *AHA Class 1*: *Definitely Recommended/Useful*: Conditions for which there is excellent evidence and/or general agreement that a given procedure or treatment is useful and effective
- *AHA Class 2*: Conditions for which there is fair to good, but conflicting, evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
- *AHA Class 2A*: *Probably Useful*: Weight of evidence/opinion is in favor of usefulness/efficacy

- *AHA Class 2B*: *Possibly Useful*: Usefulness/efficacy is less well established by evidence/opinion
- *AHA Class 3*: *Possibly Harmfu*l: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful
- *AHA Class Indeterminate:*
  Preliminary evidence good but insufficient to allow recommendation

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Chapter 2.2.2

GAS EMBOLISM

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Abstract: Gas embolism (GE) refers to all pathological events related to the entry or the occurrence of gas bubbles in the vascular system. Nowadays, GE is largely an iatrogenic problem that can result in serious morbidity and even death. It can be caused by procedures performed in almost all clinical specialties: heart and neurosurgery, coelioscopy, endoscopy, haemodialysis, central venous catheterization, etc. Upon entering the vascular system, gas bubbles follow the blood stream until they obstruct small vessels. Depending on the access route, gas embolism may be classified as venous or arterial gas embolism. Clinical manifestations depend on the site and extent of vascular obstruction and the subsequent intensity of the systemic inflammatory reactions. Diagnosis is based on the sudden occurrence of neurological and/or cardiac manifestations in clinical situations where there is a risk for GE. Once suspected, treatment for GE must be begun at once, the source identified and eliminated, life support be instituted as required and Hyperbaric Oxygen provided as quickly as possible. All clinicians should be aware of the risks of GE and appropriate preventative measures should be observed whenever there is a risk of occurence

Keywords: gas embolism, arterial gas embolism, venous gas embolism, pulmonary arterial hypertension, blood-gas interface, heart surgery, neurosurgery, coelioscopy, haemodialysis, central venous catheterization

Gas Embolism (GE) refers to all pathological events related to the entry or appearance of bubbles of air or any other gas in the bloodstream.

It is an infrequent accidental pathology, which nowadays is mostly of iatrogenic origin. It may occur during several medical or surgical procedures in which this risk should be realized in order to implement effective preventative strategies. GE is an emergency – outcome depends on the expediency with which hyperbaric oxygen (HBO) is provided.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 217–238.

1. PATHOPHYSIOLOGY

1.1 Origin and path of gas emboli

GE is usually caused by the injection or penetration of gas through a vascular wall. An exception to this mechanism is decompression sickness, where gas bubbles may develop spontaneously within the circulation.
The access route serves to distinguish GE into two types with very different specific manifestations:

- **Arterial Gas Embolism** where gas enters the vascular system beyond the pulmonary filter (i.e, at the point of the pulmonary veins, left heart or systemic arteries).

Even a small volume of gas can cause significant clinical manifestations, the degree of severity depending on the respective areas that may be obstructed (e.g., cerebral arteries or coronary arteries). Bubbles can also migrate up-stream following the laws of buoyancy: In an experimental study in dogs involving 41 injections of air into the left ventricle, gas was later found in the mesenteric arteries in 17 animals; the cortical cerebral arteries of 16; the femoral arteries of 2; and the coronary arteries of one animal[1].
Although clinical manifestations can be immediately apparent, clinicians must be aware that bubble migration can stop temporarily and start up again with patient movements or coughing.

- **Venous Gas Embolism** where the gas enters the vascular system before the pulmonary filter.

When gas entry is sudden (bolus effect), the bubble is trapped in the ejection chamber of the right ventricle and the root of the pulmonary artery. Because of the gas compressibility, the bubble absorbs the mechanical energy produced by ventricular contraction and obstructs the pulmonary artery tract. This leads to a circulatory arrest[2].

If gas enters more gradually, the gas entering the right ventricle is blended with the blood into a foamy mixture, which is propelled into the pulmonary bloodstream, obstructing it partially or completely. If the volume of gas is small, the obstruction is of no clinical consequence; the intra-vascular gas is eliminated by diffusion into the pulmonary alveoli[3]. However, if the volume is greater, the pulmonary arterial resistance is increased both because the pulmonary arterial tree is obstructed by the bubbles and because pulmonary artery vasoconstriction occurs due to the release of vasoconstrictive mediators (serotonin, histamine, thromboxane A_2 and endotheline-1)[4-6]. This results in pulmonary arterial hypertension[7-9], mismatch between ventilation and perfusion and subsequent hypoxemia[10,11]. The resulting clinical picture is an acute right ventricular failure [2].

Importantly, the increase of pulmonary arterial pressure may cause gas bubbles to pass through pulmonary capillaries into the venous pulmonary circulation and from there into the arterial circulation resulting in *paradoxical embolism*. Other mechanisms for this phenomenon include:

- bubbles passing through a patent foramen ovale (PFO) as a result of an elevation in right atrial pressure due to pulmonary hypertension[12]. Clinicians must remember that at least 20 to 25% of the population carries a patent foramen ovale[13].

- the bubbles passing through arteriovenous shunts within the lungs that are not functional in normal conditions but are also recruited as a result of the increase of pulmonary arterial pressure[14].

In a study on dogs, Butler et al. showed that quantities of air under 0.15 ml/kg/min do not cause an increase in Pulmonary Arterial Pressure (PAP) over 20 mmHg; quantities over 0.3 ml/kg/min increase PAP over 34 mmHg and leading to a passage of bubbles into arterial circulation[15-17].

1.2 Consequences of the embolus

1.2.1 Vascular obstruction

The embolus makes its way either in the form of a single bubble; a string of bubbles; or even as a foamy mixture if it has been mixed by cardiac action. As the size of the blood vessel decreases, the resistance to flow increases and the embolus is slowed, deformed into a cylinder shape, and eventually stopped as the increase in friction ultimately overcomes perfusion pressure – causing downstream ischemia[18]. Only certain bubbles get through capillaries towards veins. This depends on their volume, the vascular diameter and perfusion pressure overcoming the resistance[19].

The severity of the ischemia caused in the downstream depends to a large extent on whether the circulation is endarterial or if there is collateral supply[20].

1.2.2 Secondary manifestations induced by the gas-blood interface

The embolus acts like a foreign body[21]. Platelets, leukocytes, fibrinogen and thrombin adhere to the surface of the bubble[22]. Leukocytes and platelets as well plasma proteins are activated, triggering the activation of complement, coagulation, fibrinolysis and kinine cascades[23-27]. These phenomena reinforce the forces of adhesion between the bubble and the vascular wall and resist further embolus migration[28].

Over time, the embolic obstruction changes to a thrombotic one. Hyperbaric Oxygen is ineffective for the latter which emphasizes the importance of expediency in management.

The vascular wall is also injured[29]. It becomes increasingly permeable, causing oedema in the tissue, which in turn worsens the ischemia[30]. In the lungs, this can lead to ARDS due to non-cardiogenic pulmonary oedema[31] or severe bronchospasm due to bronchial hyper-reactivity[32]. In the brain, the oedema effects intra-cranial pressure and impairs brain metabolism[33].

1.3 Severity factors

The severity of GE depends on a number of elements:

- Gas type

The more soluble the gas is in blood, the more forgiving the insult will be and visa versa. The possible culprits, in order of decreasing solubility, are: CO_2, O_2, air, nitrous oxide, nitrogen protoxide, helium and argon. Thus for a given complication due to a hypothetical one-unit volume of air, 3 volumes of oxygen and 6 volumes of carbon dioxide would be required. Less soluble gases also lead to prolonged ischemia as they will linger for longer[34-36].

- Embolus volume

Where embolism affects arteries, even a small bubble can cause severe disorders depending on the affected area (cerebral arteries, coronary arteries).

But when embolism occurs in veins several milliliters of air may be asymptomatic due to the ability of the lungs to act as a filter and the significant vascular reserves within the lungs able to maintain ventilation-perfusion,. However, 10 to 15 ml are already enough to cause fatal GE and volumes of 100 to 300 ml are frequently fatal[37].

- Rate of injection

Injection rate is much more important than volume: the lethal volume is inversely proportional to the rate of injection[38]. For example in dogs, 5 to 8 ml / kg / minute of air or a single bolus injection of 3 ml/kg injected into a vein can cause death. However, if the rate of injection is low, 1400 ml of air can be injected over a period of 460 minutes into the central venous system before the death would occur[39].

In man, the lethal rate of injection is estimated around 70 to 100 ml / sec. For perspective, it has been shown that 100 ml / sec of air can enter a central vein catheterised by a 14 gauge needle when a negative pressure of 5 cm of water exists (i.e., as occurs during normal breathing)[40].

- Patient position

It was long been thought that emboli are buoyant and therefore would move in an anti-gravity direction. Therefore sitting or lying with raised head

would potentially encourage migration into the brain which is why the head-down position has been advised as a good precaution[38]. However, the buoyancy of gas bubbles is not sufficient to counteract advancement by blood flow, so placing the patient head-down is not very helpful. Moreover, the head-down position may aggravate the cerebral oedema that develops in these patients. So, the current recommendation is to place these patients in a flat supine position[41].

In the same way, the left lateral position has an effect of trapping venous bubbles in the tip of the right ventricle, removing the obstruction of the ejection chamber[42,43].

- Hemodynamic condition of patient

A decrease in arterial blood pressure would compound the blocking and pro-ischemic effects of bubbles; hypotension is an additional risk factor for injury[44].

Similarly, hypovolemia increases the relative proportion of the volume of embolized gas.

2. CIRCUMSTANCES OF OCCURENCE

Whenever there is a vascular lesion or gas is introduced artificially into the body, there is a risk of GE. Many circumstances are reported in the literature. They can however be classified according to the location and method of entry of the gas[37,45-48].

2.1 Venous embolisms by gas aspiration

Normally, for patients in supine position, a central venous pressure of 4 to 6 cm of water is enough to prevent air or gas at atmospheric pressure to enter the returning venous bloodstream. However certain circumstances can reduce the venous pressure under the atmospheric pressure: Examples include, surgery performed in partially seated position for veins located above the superior vena cava; Trendelenburg position for veins located under the inferior vena cava[49]; hypovolemia; and variations in central venous pressure during controlled ventilation. The risk of gas entering is proportional to venous diameter: trivial for small peripheral veins vs. life threatening for the dural venous sinuses, diploic bone veins that cannot collapse, and the large venous stems located within or in the vicinity of the thorax.

2.1.1 Surgical causes

- Surgery performed in a sitting position[44,50]

This concerns neurosurgery and particularly surgery of the posterior cranial fossae. GE can cause severe neurological sequelae that are hard to discriminate from the consequences of the initial disorder. The incidence appears to be decreasing as the upright positioning is falling into disfavour, but is reported to be between 8%[51] and 40%[52] depending on the method of detection.

- Other surgical causes

GE has been described during surgery of the large venous stems above the diaphragm (jugular, subclavicular, superior cava, azygos veins) or under the diaphragm (inferior cava, hepatic, renal, uterine veins), hepatic or pulmonary surgery, and surgical procedures on the right heart and the pulmonary arterial system[53].

These forms of GE can be classified in combination with other traumatic vascular injuries, particularly those related to the thorax[54].

- Abortions and surgical procedures on the uterus

Previously criminal abortions have a very frequent cause of GE[55]. Nowadays this aetiology has nearly completely disappeared[56], but the risk of GE during abortions by aspiration methods does exist. A few cases have also been described after caesarean operations[57].

A risk of GE also exists during orogenital sex with vaginal insufflation in pregnant women (10 deaths out of 11 cases reported in the literature)[58].

2.1.2 Medical causes

Nowadays they are the most frequent because of the frequency of medical procedures.

- Puncture of the central venous stems (subclavicular, jugular veins) and intravenous infusions are currently the major causes.

The literature estimates the risk between 1 per750 to 1 per 3000 central line placements[59-61]. GE can occur during either puncture or catheterization[62], particularly if the patient is hypovolemic and/or the precaution of placing the patient in a slightly lowered position has not been taken. It can also occur during infusions e.g., if the tubing is not airtight or becomes disconnected as reported by Boussuges with an incidence of 80%, particularly with pressure-driven perfusion pumps[59], or upon catheter removal.

2.2 Venous embolism by insufflation of gas under pressure

Venous gas emboli (VGE) are the result of gas entering the venous system under pressure, either because it is insufflated either by accident straight into the vessel, or because it accumulates in the vicinity of a vascular breach.

2.2.1 Surgical causes

Coelioscopy procedures are currently the major cause of VGE. Although CO_2 is used, there is a risk of GE, which is estimated at around 1 to 2 per 1000[63].

Gas can enter either by direct accidental injection into a parietal vessel or into a highly vascularized organ (liver, spleen, uterus), or by venous laceration caused by the surgical dissection or the parietal distension due to the pneumoperitoneum. Although authors agree that the abdominal distension caused by the pneumoperitoneum leads to collapse of adjacent veins, resolution stops this protective effect of mechanical compression and accounts for the occurrence of post-surgical GE. Gas can also accumulate in the entrance site and migrate later with patient movement, which accounts for delayed post-surgical occurrences[64].

Lastly, abdominal distension can be caused by other gases than the one causing the pneumoperitoneum: electrosurgical knives using an argon flow; gas-cooled lasers; haemostasis equipment spraying biological glue with air as a carrier gas[65] may all cause GE by allowing the abdominal pressure to rise temporarily above the safety level.

2.2.2 Medical causes

GE is a risk:

- **in pulmonology**, during pleural or transparietal pulmonary[66] or transbronchial[67] puncture, lavage and biopsy; pleuroscopy and mediastinoscopy. The use of Yag-laser for treating certain bronchial tumours can be associated with GE because a high flow of gas (1 to 2 Lpm) used to cool the sapphire[68].
- **during catheterisation of the right cardiac chambers**,
- **during mechanical ventilation** where the use of high pressures of insufflation can cause alveolar rupture with air passing into the interstitial tissue, the pleura, or the mediastinum and later into the vascular system. GE can be a complication of mechanical ventilation in status asthmaticus and acute respiratory distress syndromes in adults[69] or children[70]. It frequently

occurs at the beginning of the mechanical ventilation in trauma patients in case of lung trauma with intrathoracic vein injury[54].

- **during Extra-Corporeal Circulation (ECC) procedures** using arteriovenous or venous-venous circuits such as haemodialysis, haemofiltration, or plasma exchange which cause GE, often in large volumes, because of the pumps in use on the circuit.
- **other causes** have also been reported: pacemaker insertion; digestive endoscopy[71]; peritoneal irrigation and lavage; foaming antiseptic solutions (particularly hydrogen peroxide which should never be used for lavage[72]).

2.3 Arterial Gas Embolism

2.3.1 Surgical causes

- Heart surgery using ECC is the main cause of AGE. This affects mainly the carotids, particularly the right carotid artery. Although the incidence was traditionally estimated at around 0.1 to 0.3%, endovascular bubble migration appears to be much more frequent now that more precise methods of detection are used. It approaches 50 to 60% by Doppler velocimetry[73]. Valve replacement surgery involves greater risk than coronary surgery. Three causal situations have been identified: a de-airing or gas leak in the ECC circuit; air entering an open and badly flushed cavity and – during systolic contraction – being suddenly ejected into the arterial system; and lastly oxygen gas bubble formation in blood during too rapid warming up procedures[74,75].
- Vascular surgery, particularly on the thoracic aorta or on the carotid.

2.3.2 Medical causes

- Diagnosis procedures: left ventricle catheterisation, coronary -, aortic -, carotid - and vertebral artery angiography involve a risk estimated around 1 to 4 %[76].
- Treatment procedures: e.g., rupture of an aortic balloon pump

2.4 GAS EMBOLISM IN DIVING ACCIDENTS

Two principle mechanisms are involved when neurological manifestations occur in direct relation to diving activities[77] :
- Lung barotrauma is relatively rare but a very serious cause. It is observed during the expansion of voluntary or pathological air trapping during decompression (ascent). Following Boyle-Mariotte's law, the air in the lungs

increases in volume as pressure decreases, enlarges the alveoli and breaks into the pulmonary circulation.

These accidents are not related to the duration or depth of the diving activities and are observed mainly in inexperienced divers or in the case of "blow up" (i.e, very rapid) ascents.

- Decompression sickness is caused by the formation of inert gas bubbles within the body – usually nitrogen or helium contained in the breathing gas mixture, depending on the mixture inhaled). The bubbles may form within tissues but frequently access the venous circulation and are detectible with via ultrasonography (i.e., Doppler or echocardiography). VGE caused by decompression are not always symptomatic, but if the volumes exceed a certain threshold biological injury occurs as detailed in the preceding sections. Usually decompression sickeness is the result of violations of decompression tables that control the duration and depth of diving activities.

In summary, the most common causes of GE are (Table 1):

- - vascular access and perfusion in the central veins,
- - coelioscopy surgery,
- - pleural or pulmonary exploration procedures,
- - vascular catheterisation with injection,
- - cardiac bypass (ECC), and
- - heart and brain surgery.

These are therefore predominantly iatrogenic and could be reduced by effective preventative measures.

Table 2.2.2-1. Personal series of 95 cases of GE collected in a 20 year period

Origin of bubble	Nb	%
Central venous access	38	40
Coelioscopy	14	15
Pleural puncture	10	11
Haemodialysis	9	10
Angiography (coronary / cerebral)	7	7
Trans-thoracic and trans-bronchial biopsy	6	6
Heart surgery	5	5
Neuro-surgery	3	3
Swan Ganz catheterisation	3	3

3. DIAGNOSIS

The diagnosis of GE is made in two very different situations: in some the GE risk and onset of GE symptoms are obvious allowing for immediate treatment (e.g., arteriography of a conscious patient); in others the risk is

unrealized and the clinical signs are hidden or related to another pathology, delaying diagnosis and producing a deleterious effect on prognosis (e.g., central line placement of an unconscious patient or anesthesia case).

3.1 Clinical signs

The clinical symptomatology induced by GE is due to the vascular obstruction. Thus it depends on the areas affected. However, in situations where there is a risk of GE, the sudden occurrence of a combination of neurological and cardiovascular signs is highly indicative. Although its occurrence is always sudden and is generally immediate, it can be delayed by a few minutes to even several hours. Delayed manifestations are associated with patient movement or changes in position dislodging bubbles.

3.1.1 Neurological signs

Initial clinical presentation may be the sudden occurrence of an isolated loss of consciousness, convulsive movement or a motor deficiency.

When fully evolved the clinical presentation may include (table 2.2.2-2) :

- coma of a varying degree but usually stage I,
- convulsions, either generalized or focal
- hypertonia often marked and interspersed with exacerbations (opistothonos or extensor limb posturing)
- pyramidal signs : bilateral extensor plantar response, exaggerated tendon reflexes,
- motor deficit (hemiplegia, monoplegia, facial paralysis, etc.),
- neuro-vegetative disorders, which immediately make the condition severe.

The above neurological manifestations frequently show variability in intensity and location – highly suggestive of the diagnosis.

Table 2.2.2-2. Neurological signs observed in a personal series of 54 cases of GE[78]

- Altered Consciousness	: 82 %
. Confusion / obtundation	: 20 %
. light coma (GCS > 10)	: 11 %
. moderate coma (GCS 6-10)	: 25 %
. deep coma (GCS <6)	: 26 %
- Motor deficit	: 47 %
- Pyramidal signs	: 32 %
- Seizures	: 16 %
- Hypertonia	: 11 %
- Neuro-vegetative signs	: 10 %

Once consciousness is regained, a complex clinical picture can be observed including motor deficits, sensory or cognitive disorders, ataxia, very frequently visual disorders (amaurosis, hemianopia, scotomata, or cortical blindness).

So the usual picture is one of cortical cerebral insult, frequently affecting the areas within the posterior circulation of the brain.

3.1.2 Cardiorespiratory signs

These are caused by the passage of the embolus into or through the heart chambers, and into the pulmonary or coronary circulation. They may present as:

- cardiac arrest (which adds further diagnostic confusion to possible GE due to the associated cerebral anoxia),
- transient cardiovascular collapse,
- pulmonary oedema,
- cardiac arrhythmias (various),
- sudden dyspnoea with anxiety and signs of acute cor pulmonale,
- a usually loud and continuous millwheel murmur with systolic reinforcement that is only heard in 10% of cases on precordial auscultation. An oesophageal stethoscope is thought to be more sensitive.

3.1.3 Other clinical presentations

- Sudden death

GE is one of the causes of sudden death that must always be considered. A careful post-mortem examination where bubbles are observed in the lumen of the arterial vessels of the brain, can assist in making the diagnosis

- Systemic Inflammatory Response Syndrome

The interaction of gas bubbles with the vascular endothelium may sometimes trigger a major release of endothelium-derived cytokines resulting in the physiologic response of Systemic Inflammatory Response Syndrome associated with the other symptoms and signs of GE[79]

- Gas embolism in patients under general anaesthetic

Clinical signs are masked. A sudden onset of coughing, cyanosis, unexplained hypotension or cardiac arrest are hallmark signs, and their occurrence should be noted carefully, particularly when they are associated with a change in patient position. Instrument (e.g., transoesophageal) detection methods are particularly valuable.

Unfortunately, the diagnosis is often only made at the end of surgery:

- either because neurological signs occur suddenly after normal wakening, or

- because awakening is slow, the patient is confused or agitated, or remains semi comatose with neurological deficits or seizures (these are the most common presentations), or
- because anaesthetic sleep is followed by a deep coma. This indicates massive GE with a very poor prognosis.

- Gas embolism in divers

Pulmonary barotrauma contributes several additional manifestations to the clinical presentation of GE in divers: acute thoracic pain, haemoptysis, thoracic or cervical subcutaneous emphysema, pneumothorax, or pneumomediastinum being the most common.

Decompression sickness resulting in VGE is quickly identified by cardio-pulmonary collapse and/or neurological signs occurring shortly after surfacing from diving activities with violation of correct decompression procedures.

3.1.4 Special Investigations

Once GE has developed, specialized testing is of limited use. However, the following are justified:

-Chest X-ray, not so much to get a picture of the embolus in the heart chambers (i.e., rare) but to check for associated pathologies (lung oedema, aspiration pneumonia; barotrauma),

-Arterial blood gases – directs resuscitative efforts (e.g., metabolic acidosis secondary to the initial cardiovascular collapse and hypoxemia in 50% of cases),

-ECG – indicates cardiac involvement and risk for decompensation (arrythmias are observed in 33% of case).

Some tests have been suggested to support the diagnosis but these are mostly useful for detecting the embolus itself:

- **EEG**[44], when performed at an early stage, show three different phases: (1) depression at the same time as the embolus; (2) transient recovery, and (3) subsequent deterioration with irritatable asymmetrical elements of varying locations; and(4) recovery – gradual and always delayed relative to the clinical picture.
- **Catheterisation of the right atrium** using an ordinary[80] or a SWAN GANZ catheter[81] is useful for diagnosis and treatment as it may allow aspiration of the air in the right cavities.
- **Capnography** shows an obvious and fast drop in the peak value of the expired fraction of CO_2, indicating haemodynamic disorders in the lungs[52,82].
- **Doppler ultrasonography** either of the precordial area[51,83], or by a trans-oesophageal probe[84], is a sensitive method for detecting even small bubbles in circulation; it is of little use when GE has occurred.

- **CT scan of the brain** can provide direct images of bubbles obstructing the brain vessels and indirect images of oedema or ischemia[85]. However it rarely makes a contribution to diagnosis (under 5% of images of intravascular bubbles) and a normal picture does not mean GE can be excluded.
- **Echocardiography** can also show up bubbles in the heart cavities.

Although various tests have been proposed, GE diagnosis remains mainly clinical, and is based on a combination of a situation of GE risk and the appearance of compatible signs. In no way must a quest for special examinations delay HBO treatment.

3.1.5 Evolution & prognosis

Although the natural history of GE has a high mortality (ranging from 23%[61] and 78%[43] in different series), clinical evolution can be surprising and individual prognosis cannot be made on the initial signs.

Signs of global encephalopathy (coma, convulsions, tetraplegia) seem indicative of a worse prognosis than focal signs (hemianopsia, hemiparesia)[61].

The most important factor for prognosis is early HBO[78].

4. THERAPY

This includes immediate measures and HBO[46].

4.1 Emergency care

- Against the actual embolus[42]**,** the injured vessel should be compressed and obstructed immediately; the patient must be placed on the left side (if possible) to collect the gaseous mass in the tip of the right ventricle so as to free the pulmonary arterial tract. Ventilation with 100% oxygen must be provided as soon as possible to begin denitrogenation. In cases of general anaesthesia with nitrous oxide, the latter must be stopped immediately as it makes the embolus obstruction worse[34,86].

In cases where a catheter is inserted in the right atrium, fast aspiration can sometimes remove large quantities of air[52,79,87]. Other methods (right ventricle puncture, opening of the pulmonary infundibulum, aortic clamping, etc.) can only be considered during heart or thoracic surgery.

- Cardiac arrest requires immediate conventional resuscitation (chest compression, controlled ventilation)

- Cardiovascular collapse must be corrected quickly because hypotension enables embolus to become lodged. Vascular volume should be restored and perfusion pressure maintained – with vasopressive drugs if necessary.
- Convulsions or agitation require benzodiazepines or barbiturates, while avoiding circulatory depression.

4.2 Hyperbaric Oxygen

It is recommended by all authors[45,88-90] in patients with clinical symptoms because it reduces the volume of the embolus (effect of the high barometric pressure); it enables gas removal by denitrogenation (effect of the hyperoxygenation); it maintains oxygenation in the ischemic tissues; and it decreases intracranial pressure and cerebral oedema formation[78].

In an animal model, it has been shown to decrease the harmful consequences of GE on intra-cranial pressure and brain metabolism even when applied with a some delay after the air injection[91].

From a technical point of view, two HBO regimens are commonly employed, depending on the facilities available: (1) either a brief period of compression in air or mixed gas to six times atmospheric pressure (6ata) followed by several hours in pure oxygen at 2.8ata (e.g.: US Navy Treatment Table 6A), or (2) several hours compression in pure oxygen (e.g.: US Navy Treatment Table 6 or 9: at 2.8 or 2.5ata respectively). Both approaches seem clinically comparable[90,92].

While symptoms remain HBOT is continued using therapy protocols similar to those used against cerebral anoxia.

4.3 Adjunctive Treatment

The objective of adjuncts is to attenuate the secondary consequences of GE due to gas / blood contact (e.g., with anti-platelet therapy or heparin) or to avoid the occurrence of cerebral oedema (e.g., controlled hyperventilation; barbiturates; mannitol). Profound hypocapnia and corticosteroids are no longer recommended.

4.4 Results

The outcome of treatment is favourable in around 70% of cases. However, mortality is 15% to 30% in various series and morbidity (i.e., neurological sequelae) is significant in 10 to 20% of patients[45,59,85].

Early HBO is the most important variable in prognosis (Table 3). Results are excellent if it is provided within one hour (90% success); good if

treatment is delayed between 1 and 6 hours (75% success) whereafter the prognosis becomes increasingly poor with further delay.

Table 2.2.2-3. Evolution with HBO (54 patients)[78]

Number of patients	Time elapsed before HBO_2T	Recoveries without sequellae	Survivals with sequellae	Deaths
54		38 (70%)	7 (13 %)	9 (17 %)
12 (22 %)	1h	11 (92 %)	-	1 (8 %)
21 (39 %)	1 - 6h	16 (76 %)	2 (10 %)	3 (14 %)
14 (26 %)	6 - 12h	8 (57 %)	4 (29 %)	2 (14 %)
7 (13 %)	12h	3 (43 %)	1 (14 %)	3 (43 %)

The prognosis of GE during neurological or heart surgery is less favourable. Here diagnosis is often delayed until reversal of anesthesia and/or referral is delayed until the surgical procedure is completed.

Finally, in cases of cardiac arrest that prove refractory to HBO – even with rapid referral – the poor prognosis may be due to cerebral anoxia rather than the embolis per se.

5. PREVENTION

As GE is mainly of iatrogenic origin, prevention is of paramount importance.

5.1 Gas embolism caused by surgery

- During neurosurgery in a sitting position

A variety of techniques have been proposed to detect gas bubbles: oesophageal stethoscope[44]; capnography[44,52,81]; continuous monitoring of mixed venous oxygen saturation[93]; continuous monitoring of the partial pressure of expired nitrogen[94]; Doppler ultrasonography in the precordial area[51,82] or by oesophageal route[51]; trans-oesophageal echocardiography[93,95]; transcutaneous oxygen and CO_2 pressure monitoring[93,96]; and right atrial catheterisation[79,80,87]. Their relative sensitivities have been compared with ultrasounds (i.e., trans-oesophageal echocardiography; precordial Doppler ultrasonography) being the most sensitive, followed by capnography and transcutaneous oxygen pressure monitoring[96,97] (Table 2.2.2-4). Preventing GE involves maintaining a high venous blood pressure (vascular filling, jugular compression)[98], and providing controlled ventilation at continuous positive pressures[99].

Table 2.2.2-4. Sensitivity of the various methods for detecting age (from Glenski et al.)[93]

Sensitivity	Monitoring methods	Mean quantity of air (in ml/kg) required to reach detection threshold (± SD)
Greatest	Trans-oesophageal echocardiography	0.19 ± 0.25
	Precordial Doppler ultrasonography	0.24 ± 0.33
Intermediate	PAP	0.61 ± 0.37
	$P_{ET}CO_2$	0.63 ± 0.23
	P_aO_2	0.71 ± 0.54
	$P_{tc}O_2$	0.76 ± 0.58
Least	P_aCO_2	1.15 ± 0.76
	MAP	1.16 ± 0.76
	$P_{tc}CO_2$	1.54 ± 0.70

PAP : pulmonary artery pressure P_aCO_2 : arterial pressure of CO_2
$P_{ET}CO_2$: end Tidal expired pressure of CO_2 MAP : mean arterial pressure
P_aO_2 : arterial pressure of O_2 $P_{tc}CO_2$: transcutaneous pressure of CO_2
$P_{tc}O_2$: transcutaneous pressure of O_2

Nitrous oxide has a worsening effect on the consequences of GE and it must therefore be avoided in such situations. From a surgical point of view, all bone edges must be filled with wax and, in the case of vascular injuries, the operating area must be flooded with physiological saline solution. The sitting position should actually be avoided unless is it absolutely necessary for technical reasons.

- During heart surgery

Continuous EEG and monitoring by spectral analysis (for years considered to be the best method for detection) is now being replaced by transcranial Doppler[100].

Preventing GE caused by the ECC circuit involves careful de-airing of the circuit and heart chamber. However the passage of microbubbles cannot be completely avoided and have been associated with post-operative neurological injuries.

Preventing GE caused by opening the heart chambers involves a number of well-known methods: clamping the descending thoracic aorta; inducing cardiac arrest via electrical ventricular fibrillation or hypothermia; and mostly careful de-airing procedures that are essential and are to be carried out on the heart chambers, pulmonary veins, left atrium and auricle, left ventricle, aortic root, and the pulmonary infundibulum.

5.2 Gas embolism during diagnostic or therapeutic procedures

- During endoscopic procedures with insufflation

Poorly resorptive gases should be avoided (e.g., air, helium) and CO_2 is preferred. Punctures should be carried out away from vascular areas; insufflation performed slowly; and the patient kept under close surveillance in order to be able to interrupt the procedure if circulatory or respiratory problems occur.

- During venous puncture and perfusion

When puncturing the sub-clavicular or internal jugular vein, needle progression must be made while carefully maintaining the vacuum, and the lumen of the needle must be obstructed when disconnecting the syringe. The patient should be placed with the head lowered and, if controlled ventilation is provided, end expiratory positive pressure should be maintained. After insertion, catheters and tubing must be firmly affixed to avoid accidental disconnection, particularly during changes in position.

Infusion pumps require very close surveillance because there are no absolutely safe procedures[57]. They should include a safety device to detect bubbles in the tubing.

Central venous catheter removal should be done with the patient in a supine position and the head lowered. Dressings must be airtight to avoid air penetrating the fibrous channel created by longer term catheters.

- During haemodialysis and other ECC procedures

The ECC circuit must be carefully flushed and primed. A bubble trap on the venous return line is an essential precaution, as is a bubble detector coupled to a cut-off alarm and device.

5.3 Gas embolism during diving activities

The only real preventative measure is to follow good diving practices and to correctly follow decompression procedures during ascent. By acquiring adequate technical and physical training and following a few simple safety rules (“safety” stop of 3 minutes at 3 meters) most accidents can be avoided.

6. CONCLUSION

Nowadays GE is mostly iatrogenic in origin. An extensive understanding of the situations involving risk of GE, and the implementation of preventative measures, are the best ways to reduce its occurrence. Should

GE occur, immediate emergency procedures and early HBO are the most important factors assuring a favourable prognosis.

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Chapter 2.2.3

CARBON MONOXIDE POISONING

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Abstract: Carbon monoxide (CO) poisoning still remains a serious public health problem in Europe. Beyond the well-known effects of CO on hemoglobin, the role of CO binding to other hemoproteins like myoglobin and cytochrome a-a3 has been identified more recently. Moreover, in addition to the hypoxic injury, the reoxygenation phase may itself induce toxic effects by mechanisms closely related to the ischemia-reperfusion phenomenon.

Clinical manifestations include neurological disturbances, cardiac arrhythmias, and respiratory and circulatory failure which usually ceases when the patient is removed from the toxic atmosphere and given oxygen. However, long term neurological manifestations may occur and lead to severe functional impairment and disabilities.

Oxygen is the basis of the treatment and Hyperbaric oxygen therapy (HBO) has been proven more effective in preventing cognitive sequelae than normobaric oxygen. HBO is recommended for all patients remaining comatose on hospital admission; those who have lost consciousness during toxic exposure; those with persisting neurological disorders. It is also indicated for pregnant women after exposure to CO. Well designed prevention programs are urgently needed in our countries to decrease the incidence and consequences of CO poisoning

Keywords: Carbon monoxide, poisoning (carbon monoxide), carboxyhemoglobin, myoglobin cytochrome a-a_3, ischemia-reperfusion, re-oxygenation, apoptosis, neurologic sequelae (carbon monoxide)

Carbon monoxide (CO) poisoning is actually the primary cause of accidental poisoning in Europe[1] and North America[2]. Despite efforts in prevention and public and medical education, this intoxication remains frequent, severe, and too often overlooked.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 239–261.

It occurs *frequently:* in France alone, carbon monoxide accounts for nearly 5000-8000 poisonings. This number is likely to increase because devices able to produce CO are used more and more by the general public. In addition, the energy crisis is leading people to decrease air ventilation in their homes even more. Thus, these two factors join together to increase the risk of CO production.

It is *severe*: Carbon monoxide is responsible for hundreds of deaths annually in Europe. Death is not the only adverse outcome, however. Many poisonings result in permanent neurological sequelae.

It is *underdiagnosed* and thus inadequately managed: A French Poison Control Center study[3] showed that nearly 30 % of CO poisonings were overlooked or misdiagnosed during the first visit to the hospital or to a general practitioner.

Hyperbaric oxygen (HBO) therapy is actually well recognized as the treatment of choice, even if some controversy remains concerning the treatment of minor poisoning.

1. ORIGIN OF CARBON MONOXIDE

Incomplete combustion is the primary exogenous source of carbon monoxide. The actual source may vary with geography, climate and local industry. In Northern France (table 2.2.3-1) faulty charcoal stoves and gas water heaters are the most common sources. Actually, individual gas or kerosene space heaters are now rising in importance. In France at least, suicide with CO is uncommon. Not so in the United States, however, where up to 50 % of admissions are for near suicide – usually involving the use of car exhaust fumes.

An endogenous source of CO exists physiologically, because carbon monoxide is an end product of metabolism, formed during the conversion of heme into biliverdin. However, most of the CO present in the body comes from pollution of the air. In normal nonsmokers, carbon monoxide is approximately up to 0.85 % saturation of hemoglobin, and in normal smokers is about 4%.

Table 2.2.3-1. Origin of CO poisoning in northern France (4902 cases; 5 years)

Unintentional		**4828 (98,5 %)**
	Domestic pollution	**4365 (89 %)**
	Coal stove	1910 (39 %)
	Gas water heater	1088 (22 %)
	Gas furnace	1076 (22 %)
	Kerosene space heater	195 (4 %)
	Other	96 (2 %)
	Fire	**390 (8 %)**
	Occupational	**73 (1.5 %)**
	Non automobile gasoline powered	
	Engines	34 (0.7 %)
	Others (steel industry…)	39 (0.8 %)
Intentional		**74 (1.5 %)**
	Car exhaust	**56 (1.1 %)**
	Fire (immolation…)	**18 (0.4 %)**

2. PATHOPHYSIOLOGY

Carbon monoxide is an odourless, colourless, extremely diffusible gas. Its toxic effect relates to its ability to bind with hemoproteins thereby blocking their function. In many respects CO mimics oxygen and binds to the same sites although with different affinity depending on the surrounding protein structure of the binding site.

3. EFFECT ON OXYGEN TRANSPORT

The quantity of CO absorbed by the body depends on the inspired CO concentration, alveolar ventilation, and duration of exposure[4]. Exposure to high concentration for a short period appears less harmful than exposure at a lower concentration but over a longer period of time.

Once inhaled, carbon monoxide crosses the alveolar membrane and dissolves in the plasma. Very little CO is metabolized in the body (less than 1 % is oxidized in CO_2). It binds to hemoglobin to form carboxyhemoglobin (COHb), blocking heme binding sites for oxygen transport. Carbon monoxide has about 250 times greater affinity for hemoglobin than has oxygen[5,6]. Because of alterations in the structure of the carboxyhemoglobin, the dissociation curve is shifted to the left. Red cell 2,3-diphosphoglycerate reduction accentuates the effect further[7].

The proportion between the partial pressure of carbon monoxide and oxygen determines the quantity of COHb formed. Carbon monoxide uptake is inversely proportional to the partial pressure of oxygen. This explains why the confinement (i.e., environmental oxygen depletion) increases the severity of CO poisoning significantly.

The binding of CO to hemoglobin leads to a non-functional form of hemoglobin. Consequently, arterial blood oxygen content decreases. But because oxygen delivery in ambient air relies on hemoglobin transported oxygen, CO poisoning induces an hypoxemic peripheral hypoxia.

4. EFFECT ON TISSUE

Decrease in peripheral oxygen delivery is not the sole mechanism of CO toxicity. Extravascular uptake of CO has been estimated at 10-50% of the total body CO[8]. Goldbaum et al.[9] showed that with the same blood level of carboxyhemoglobin, dogs inhaling CO died, whereas dogs transfused only with CO incubated erythrocytes did not. He concluded that the decrease in oxygen delivery induced by the interaction of CO with hemoglobin was not the most important fact in CO toxicity, and that extravascular CO had a toxic action probably by interfering with oxygen utilization. In a experimental CO poisoning in rabbits, Ludbrook et al confirmed that abnormalities in organ function (i.e., brain function) occurred without any decrease in organ oxygen delivery[10].

Carbon monoxide reacts with a number of other heme moieties besides hemoglobin. These include myoglobin, hydroperoxidase, cytochrome oxidase (also called cytochrome a-a3), and cytochrome p-450[11-13]. Although its affinity for these heme-like compounds is lower than its affinity for hemoglobin, as the blood oxygen pressure falls, a tissue PO2 level can be reached at which CO avidly binds to myoglobin and cytochrome oxidase.

4.1 CO Binding to Myoglobin

Myogolobin is an O_2 carrier protein that facilitates oxygen diffusion in skeletal and cardiac muscle cells by serving as a reservoir and maintaining a steep gradient for diffusion. The binding of CO to myoglobin leads to a non-functional form of myoglobin - the carboxymyoglobin (COMb) - with a ratio COMb/COHb of approximately 1[13]. The decrease in facilitated oxygen diffusion in muscle cells combined with a decrease in muscular oxygen delivery may limit maximal oxygen consumption (VO2 max)[14,15] and cause a decrease in cardiac output as seen in patients with even a mild CO poisoning[16,17].

4.2 Effect on CO Binding to cytochrome a-a3

Cytochrome a-a3 is the terminal enzyme of intra-mitochondrial respiratory chain; it catalyzes the reduction of molecular diatomic oxygen into water in a four-step electron transfer. The enzyme complex accounts for around 90 % of the total O_2 uptake of the body. Inhibition of cytochrome a-a3 by CO blocks the flow of electrons from substrate to O_2 which normally provides cell energy (ATP) via oxidative phosphorylation[18,19].

Under usual conditions of cellular pO_2, CO binding to cytochrome a-a3 is opposed by the greater affinity of O_2 to the binding site. However, when COHb increases, jugular venous pO_2 has been shown to drop to a level where – given heterogeneous circulation, capillary density and metabolic demands – pO_2 may decrease sufficiently to allow CO to bind to cytochrome a-a3[20]. Moreover, failure to adapt microcirculatory O_2 delivery to local O_2 demand has also been reported to be a potential direct toxic effect of CO on vascular smooth muscle[21]. This could contribute to the regional differences in CO uptake as dysregulation of blood flow renders certain areas hypoxic.

Evidence of CO binding to cytochrome a-a3 has in fact been shown by Brown and Piantadosi[22] who demonstrated this using in vivo reflectance near-infrared spectrophotometry. As COHb levels rise, cytochrome a-a3 inhibition occurs. This is followed by a decrease in intracellular ATP and pH[23] leading to neuronal depolarization, cathecholamine and excitatory amino-acid (in particular glutamate) intrasynaptic release and a concomitant decrease in re-uptake. These processes are independent of the hypoxia. They may explain the observation of seizures in CO poisoned patients. They may also initiate a process of apoptosis contributing to neuronal degeneration, especially in vulnerable areas such as the hippocampus[24,25].

In summary, in addition to hypoxemic hypoxia, CO poisoning induces a histotoxic hypoxia, and this process is self-perpetuating. This is also consistent with the clinical experience.

5. EFFECT OF REOXYGENATION

5.1 Dissociation of CO hemoprotein complexes

Dissociation of CO from hemoprotein complexes follows the laws of gaseous diffusion and mass action. The dissociation rate depends on the proportions of O_2, CO, the respective heme moiety, and their relative affinities for O_2 vs CO. So, to (1) remove a patient from the toxic

atmosphere in order to remove pCO and (2) restore pO_2 represent two fundamental therapeutic measures.

Carboxyhemoglobin dissociation begins as soon as the patient is removed from the CO-rich environment. It follows exponential elimination with an half-life of 230-320 min in room air. The dissociation rate is much increased when oxygen pressure is raised: in pure normobaric oxygen, the half-life of COHb dissociation is 90 min; it is 35 min in 2 ata pure oxygen, and 22 min in 3 ata pure oxygen[26].

The dissociation rate of CO from other hemoprotein complexes is unknown but likely to be much slower as they depend on the quantity of oxygen delivered to the tissues, which is much lower than arterial values and subject to the effects of COHb levels as well. Miro et al. showed that the inhibition of mitochondrial cytochrome a-a3 peaked at 76 % during the acute phase of an even moderate CO poisoning (COHb between 0 and 25 %) and that it remained at a 48 % inhibition level until the 3rd day post exposure[27]. This persisting inhibition in the presence of normalization of COHb could account for the persistence of clinical manifestations.

5.2 Evidence of Reoxygenation Injury in CO Poisoning

The fact that cytochrome a-a3 may remain inhibited when a patient is reoxygenated prompts consideration of the formation of free oxygen radicals and the occurrence of reoxygenation injury.

It has long been recognized that there are many similarities between the pathology of brain lesions from CO poisoning and ischemia reperfusion injuries. This has led to a hypothesis that the injuries share a similar pathophysiology as well[28-30].

Thom[31] showed evidence of the occurrence of lipid peroxidation in brain of CO poisoned rats during reoxygenation. Increase in conjugated dienes and malonyldialdehyde concentrations only appears 90-mins after CO exposure while breathing normal air.

He was further able to demonstrate that blocking xanthine oxidase by allopurinol or depleting animals of this enzyme by feeding them with a tungsten-supplemented diet decreased the magnitude of brain lipid peroxidation[32]. This offers further evidence that at least in part a common mechanism exists between CO poisoning and reperfusion injury.

Brown and Piantadosi[33] reported further evidence for oxygen free radical generation during the reoxygenation phase after CO exposure; They discovered a decrease in brain catalase activity that suggested hydrogen peroxide production with a decrease in the ratio of reduced glutathione and an increase in salicylate hydroxylation products - indicating hydroxyl radical production. Moreover, they were able to demonstrate that this

overproduction of oxygen free radical was related to a decrease in intracellular pH and ATP levels.

Apart from these neuronal changes occurring during the reoxygenation phase, Thom showed CO poisoning also caused endothelial - suggesting increased oxidative stress[34]. These injuries were due to an increase in nitric oxide (NO) generating increased quantities of peroxynitrite with protein nitrotyrosyl formation[35] and activation of the caspase pathway leading to increased apoptosis[36].

To summarize, CO poisoning harms tissues due to:

- hypoxic hypoxia: a decreased oxygen delivery to tissues as blood oxygen content falls due to COHb formation. Also cardiac output drops due to COMb formation, and there is a leftward shift of the dissociation curve of oxyhemoglobin (HbO_2);
- histotoxic hypoxia: a direct toxic effect on the cells from binding to cytochrome a-a_3 resulting in a disruption in oxidative phosphorylation and a reduction in ATP production;
- reoxygenation injury similar to ischemia-reperfusion syndrome with the onset of cerebral lipid peroxidation due to the activation of the polymorphonuclear leukocytes; endothelial injury related to the production of peroxynitrites; and the production of other potentially harmful cellular compounds including an increase in the output and reduced uptake of neurotransmitters and excitatory amino-acids. Both these mechanisms can trigger apoptosis in vulnerable cells.

6. CLINICAL PRESENTATION

CO poisoning is still poorly understood as far as its presentation (30 % of mistakes in diagnosis[37]) and long-term consequences are concerned.

The usual clinical presentation begins with minor signs (generalised weakness, headache, nausea, vertigo), later followed by muscular weakness, collapse and loss of consciousness; eventually hypertonic coma with exaggerated tendon reflexes supervene with signs of pyramidal irritation. Death eventually occurs due to cardiorespiratory failure[38].

The clinical presentation may mimic a number of other common conditions which may take the precedence in the differential diagnosis (e.g., influenza; alcohol intoxication; migraine; angina; etc.) which delays appropriate treatment or, worse, results in the patient being sent home to rest in the contaminated environment that originally caused the problem. Thus, the diagnosis relies on a high index of suspicion, confirmation of exposure to

CO by COHb determination, followed by a concerted effort in determining the source of CO exposure and eliminating it.

Table 2.2.3-2. Clinical picture of CO poisoning in relation with levels of carboxyhaemoglobin

Symptoms	COHb (%)
Asymptomatic	0 – 10
Weakness, headache	10 – 20
Severe headaches, nausea, vertigo	20 – 30
Nausea, vomiting, blurred vision, muscle weakness	30 – 40
Loss of consciousness, tachypnoea, tachycardia	40 – 50
Coma, convulsions	50 – 60
Cardiovascular collapse, respiratory distress	> 60

Although there are former studies relating clinical severity to COHb levels (Table 2.2.3-2), it is very important to emphasise that this is at odds with clinical experience. The level of CO measured in the hospital setting is preceded by a variable delay, frequently also affected by the administration of oxygen, making the level highly variable and correlating poorly with the original exposure levels[39].

COHb levels can be measured in venous or capillary blood – arterial blood gas is not required unless required by the medical condition of the patient.

Measuring COHb is usually carried out by CO-oximetry using spectrophotometry. There is a physiological COHb level between 0.3 and 0.5%, and a 1 to 2% variation due to urban pollution. The main variable is exposure to tobacco with heavy smokers reaching levels of up to 10%. Hence CO poisoning can be presumed whenever the COHb level is above 10% in non-smokers or 15% in smokers[40]. Lower COHb levels do not exclude the possibility of CO poisoning but require consideration of smoking habits and any delays or oxygen administration between the CO poisoning and blood sampling. Importantly, it must be noted that current pulse oximetry equipment is unable to distinguish between HbO_2 and COHb. They are not useful for diagnosis and – more dangerously – they overestimated blood oxygen content.

In appropriate circumstances (mass casualties or doubtful CO poisoning) with conscious subjects able to control their breathing) exhaled CO may be measured in lieu of COHb. The former does not require venipuncture and the results are rapid. A level of 50 parts per million (ppm) or 0.005% CO in expired air is the equivalent of about 6% COHb while 80 ppm level or 0.0085 equates to about 10%[41,42].

Measuring CO concentration in the atmosphere may also be helpful. Normal levels for CO are under 10 ppm. A level of 50 ppm is abnormal, even though it would take some time for toxicity to develop depending on

the patient's level of activity and breathing rate. Exposure to 1000 ppm or higher can be rapidly incapacitating or fatal – as may be observed in rescue teams.

Severe complications in the acute phase of CO poisoning, largely affect the cardiovascular system with, collapse, arrythmias, coronary ischemia ; and acute pulmonary oedema. Rhabdomyolysis may also occur with a risk of subsequent acute renal failure (Table 2.2.3-3).

Short term mortality is not the biggest area of concern. It is the long-term complications that vex clinician and prompt the controversies regarding optimal treatment. These include (1) persistent neurological deficits, such as persistent coma or cerebral dysfunction and (2) persistent neurological manifestations (PNM) which may appear up to a month after the exposure – frequently following apparent recovery. They may include Parkinsonism, confusion, dementia and memory disorders.

Table 2.2.3-3. Immediate complications with relation to severity of CO poisoning

Group	0	I	II	III	IV	Total
Number of patients	96	273	213	169	23	774
Cardiovascular complications including	0	5 (2 %)	15 (7 %)	22 (13 %)	12 (52 %)	54 (7 %)
• Collapse		-	-	3	3	6
• Coronary ischemia		3 2	6 7	7 4	3 5	19 18
• Arrhythmia						
Respiratory complications	0	1 (0.4 %)	3 (1.5 %)	26 (15 %)	9 (39 %)	39 (5 %)
• Pulmonary oedema						
• Bronchial-super-infection		- -	2 -	7	2 6	11 21
• Bronchospasm		- 1	1	15 4	1	9
Other complications	0	0	1 (0.5 %)	1 (0.6 %)	1 (0.4 %)	3 (0.4 %)

Group 0 : Normal consciousness, no loss of consciousness, no neurological signs

Group I : Normal consciousness, no loss of consciousness, objectives sign(s) on neurological examination

Group II : Normal consciousness, initial loss of consciousness

Group III : Stage I or II coma

Group IV : Stage III or IV coma

A significant difference ($p<0.01$) was observed between groups 0 and I vs., groups II, III and IV, as far as immediate complications are concerned. Similarly, there was a great difference between group II and groups III and IV. Thus loss of consciousness or altered consciousness is associated with more immediate complications; coma even more frequently so.

In the early 1970's, SMITH et BRANDON[43] reported a follow-up study showing that after CO poisoning, after excluding those patients with immediate neurological involvement, 33% of the remaining patients suffered behavioural disorders and 43% suffered memory impairment despite an apparent recovery. In a review of literature at the time, GINSBERG & ROMANO[44] determined PNM to occur in 15 to 40% of seemingly recovered patients. These occurred within 3 to 240 days after CO poisoning. PNM has been investigated by medical imaging and several characteristic patterns of injury have been reported using CT, MRI and PET scanning. The most commonly affected areas are the globus pallidus and the white matter[38].

Unfortunately there are no clinical or biological markers for PNM. However, age (> 60 years) and loss or altered consciousness seem to be risk factors[45,46]. Psychometric tests may be more sensitive in detecting early neurological involvement and prompt more aggressive treatment regimens[47].

Fortunately PNM improve or disappear in 50 to 75% of cases within 1 year of the event. Many uncontrolled clinical studies have reported that HBO in the acute phase appears to decrease the frequency of PNM[39,48-50] when compared to historic or normobaric oxygen (NBO) controls[45,51].

The pathophysiological mechanisms for these lesions still remain to be clarified, but hypoxia alone cannot account for them. The appearance of ischemia-reperfusion injury with delayed neuronal apoptosis offers a more attractive alternative hypothesis at present.

6.1 On-site patient management

Immediate management of CO poisoning patients starts with the removal of the patient from the toxic atmosphere (without exposing the rescuers to CO in doing so). Vital signs must be determined with basic life support measures undertaken as needed.

Clinical evaluation must include a neurological examination: consciousness, motor function, reflexes and muscle tone should be assessed as well as a general physical examination checking for other injuries, intoxication, or underlying disease (e.g., diabetes and ischaemic heart disease).

On-site, oxygen delivery is crucial via a high concentration, airtight oronasal mask with either a demand valve or high delivery (i.e., 12 to 15 L/min for adult patients). Endotracheal intubation and assisted ventilation with an FiO_2 of 1 (100% O_2) are indicated whenever the airway or breathing are compromised. Oxygen administration should be continued during transfer to hospital and the rescue teams should search for other casualties and terminate the source of exposure with adequate ventilation of the area or premises.

Table 2.2.3-4. CO poisoning patient management

1-	Assessment	Vital signs : cardiorespiratory condition Neurological condition : • consciousness, • motor response to stimulation • reflectivity Clinical examination, check for : • complications (ECG, chest X-Ray…) • associated trauma or poisoning • pre-existing disease Laboratory tests : • COHb • arterial blood gases as required
2-	Diagnosis	Circumstances of CO poisoning Compatible clinical picture COHb > 10 % Optional : • CO measurement in expired air • CO measurement in atmosphere
3-	Treatment	Emergency measures : • immediate removal of the patient from toxic atmosphere • cardiopulmonary resuscitation as required • oxygen by facial mask or controlled ventilation • stop source of CO, aerate the place, seek out other casualties Supportive measures : • controlled ventilation with $FiO_2 = 1$ • fluid resuscitation guided by central venous pressure • inotropic drugs as required Oxygen therapy : • HBO in patients with - coma, - loss of consciousness during CO exposure, - or whenever objective neurological anomalies are observed on clinical examination - pregnancy • NBO therapy: using a high concentration airtight face mask with demand valve or high delivery flow rate (12 to 15 L/min for adult patients), minimum duration 12 hours
4-	Prevention	Patient and relatives should be education on risks of CO poisoning On-site technical inquiry as to the source to prevent reoccurrence

6.2 Hyperbaric oxygen therapy (HBO)

Since Haldane's original experiment[52,53], oxygen has been the primary therapy for CO poisoning. The fact that CO elimination is proportional to the quantity of oxygen delivered justifies to the use of the highest possible pO_2 – i.e., hyperbaric conditions. In 1960, SMITH & SHARP were the first to provide this form of therapy[54]. Since then, its use has become so widespread that it is now considered in many countries as the standard of care in CO poisoning.

6.2.1 Effects of HBO

Elimination of CO depends on its release from hemoproteins. The latter will occur in the absence of ongoing exposure as a function of recovering pO_2.

COHb dissociation begins as soon the exposure is terminated. However, given the higher affinity of CO to hemoglobin, the half-life for elimination is between 230 and 320 minutes breathing ambient air. COHb Dissociation is greatly increased by oxygen: its half-life is 90 minutes during NBO; 35 minutes during 2 ata HBO and 22 minutes in 3 ata HBO[55].

Even though the affinity for CO is less than for hemoglobin, dissociation of CO from other hemoproteins is slower due to the low tissue pO_2 levels compared to the arterial pO_2. This is exacerbated by the COHb-related reduced oxygen delivery. Accordingly, detoxification cannot begin until peripheral oxygen delivery is sufficient, i.e., once COHb dissociation is well on the way. This may also explain why detoxification of the other hemoproteins is delayed relative to haemoglobin.

HBO, by increasing the quantity of dissolved oxygen, immediately restores to normal peripheral oxygen delivery. As a consequence, the hypoxemic hypoxia ceases prompting the recovery of the histotoxic hypoxia. Cytochrome a-a3 reverts to its functional form which enables the mitochondrial respiratory chains to recover their ability to reduce oxygen. The production of oxygen free radicals decreases, promoting an improved recuperation of cellular functions. Brown & Piantadosi have reported an experimental confirmation of these mechanisms[56,57].

Finally, Thom reported HBO decreases the vascular lesions caused by the reoxygenation phase by decreasing lipid peroxidation[58]. The mechanism involved was a decrease in leukocyte adhesion to the vascular endothelium. The latter was due to a decrease in beta-2 integrin expressure by means of cyclic GMP reduction caused by the effects of HBO effect on membrane guanylate cyclase[59]. This favourable action of HBO has also been observed in other situations of ischemia-reperfusion[60].

In summary, there is a large body of experimental data showing the greater effectiveness of HBO as compared with NBO.

6.2.2 Clinical studies

Since HBO was first used as a treatment in CO poisoning in 1960[61], treatment guidelines have been developed on the basis of clinical experience. Numerous uncontrolled studies reported lower mortality and morbidity in patients treated by HBO[15-18]. In the late 1980s, HBO treatment came under criticism due to the lack of prospective controlled studies supporting its use in CO poisoning.

This last 15 years, 6 prospective randomised trials have been reported comparing HBO and NBO for CO poisoning[19-23,61]. Of the 6 trials, 4 demonstrated better clinical outcome among patients receiving HBO while 2 showed no effect.

The first randomized study by Raphael et al[19] included 343 patients without loss of consciousness, treated either by HBO (2 ata for 60 min) or NBO (1 ata for 6 hours). There were no significant differences in PNM at one month after poisoning. A negative conclusion was drawn from 286 patients with loss of consciousness treated with one or two HBO sessions. This study was criticized for using overly broad inclusion criteria; an inadequate HBO regimen; inappropriate time of assessment; and unsuitable outcome measures.

A second prospective trial was performed by Ducasse et al[20] and included 26 non-comatose patients treated by HBO or NBO. Evaluation was done by clinical examination, electroencephalogram and cerebral blood flow response to acetazolamide. A significant benefit at 3 weeks was found in the HBO treated group. Limitations of this study included its small sample size and the use of surrogate outcome measures.

A third study by Thom et al[21] included 60 patients with mild CO poisoning, specifically excluding those with a history of unconsciousness or cardiac disturbances. After randomization, patients were treated by HBO (2.8 ata for 30 minutes, followed by 2 ata for 90 minutes) or NBO (until symptom relief). Patients were followed with neurological testing. Persistent neurological manifestations were found in 7 of 30 (23 %) patients treated by NBO and in none of the patients treated by HBO ($p<0.05$). Neurological manifestations persisted for an average of 6 weeks and often interfered with normal daily activities. The trial was stopped early due to the obvious treatment effect but has consequent limitations of having a small sample size. In addition it was not double-blinded and a relatively large number of patients were lost to follow-up.

A fourth randomized trial performed by Scheinkestel et al[22] enrolled 191 CO poisoned patients of different severity. Patients were treated either by

HBO (1 session a day, 3 ata, 60 minutes with intervening NBO for 3 to 6 days) or NBO for 3 to 6 days. Outcome measures were clinical evaluation and neuropsychological testing after treatment and one month after. No beneficial effect was found. There were numerous flaws: firstly, most of the CO poisonings were suicide attempts with associated ingestion of alcohol and other drugs that may have interfered with the results of neuropsychological testing. Secondly, neither the HBO nor NBO protocols were consistent with current practice. The HBO group received only 7 % more oxygen than the NBO group. The small difference in oxygen dosing would be expected to disguise an HBO effect in favour of an unattainable long normobaric regimen requiring admission that would have been more costly than repetitive HBO therapy over a shorter period of time. Finally, less than half of the patients completed the one-month follow-up.

These conflicting results have fed the controversy. Recently, however, a randomized, prospective, double-blinded study by Weaver et al[61] has reported unequivocal beneficial results of HBO treated patients. One hundred and fifty two patients were included and randomized to receive either HBO (3 sessions in 24 hours) or NBO. An extensive neuropsychological test battery was performed at 6 weeks and one year. Cognitive sequelae were significantly lower at 6 weeks in the HBO treated patients than in NBO treated patients (25 % versus 46 %, $p<0.07$). The beneficial effect persisted at one year (4 vs. 15 %, $p<0.04$).

A post hoc analysis of the results of this study[26] showed the beneficial effect of HBO was present in the following patients: age over 50 years; an episode of loss of consciousness during exposure; COHb levels over 25 %; and metabolic acidosis (BE lower than –2mEq/l). HBO had no advantage to NBO in patients without these criteria.

Another prospective randomized trial has been published but only as an abstract[23]. It provided an interim analysis of a prospective multicenter study. Five hundred and seventy five non-comatose patients were randomized to receive either HBO (1 session, 2.5 ata, for 90 minutes) or NBO (12 hours). Follow-up was done at 1, 3, 6, 9 and 12 months. A significant difference in favour of HBO existed at 3 months (8.7 % vs 15.2 %, $p<0.016$). The difference lessened at 6 months and disappeared at 1 year. However the reduction in morbidity within the first six months is important to consider and would have great economic impact on the ability.

In summary, following the recent Cochrane's review[62] we conclude that HBO is probably not always required for CO poisoning but rather should be guided by severity: Certain sub-groups of patients seem to benefit more from HBO than NBO – particularly cases with neurological involvement (coma, loss of consciousness or objective neurological manifestations). Psychometric testing might be useful in identifying those

with minor neurological involvement who are nevertheless at risk for PNM, but may be overlooked in the absence of specific screening.

6.2.3 Indications

Treatment of CO poisoning with HBO is superior to NBO in its ability to reduce PNM. However, treatment by HBO is not required for all forms of CO poisoning unless there is a risk for long-term sequelae[28]. Under these conditions HBO should be used. The ongoing dilemma is to identify those who are at risk and this requires further study.

From the published studies[26,29] the following patient subgroups are at risk: comatose patients; those with loss of consciousness or neurological abnormality, especially cerebellar impairment; those with COHb levels greater than 25 %; and those with metabolic acidosis. Neuropsychological testing could perhaps be an important tool in the future. Pregnancy is an additional indication due to risks to the fetus.

There is no randomized study for CO poisoned children. However it would seem appropriate to extend the same clinical principles as are applicable to adults. Cognitive function, as indication for treatment, may be more difficult to assess in a young child than in an adult. Thus, HBO indicators may be broader for children.

In 2004, the European Consensus Conference on Indications for HBO recommended its use in cases of CO poisoning if there is / are:

(1) persisting coma
(2) history of loss of consciousness,
(3) neuropsychological impairment,
(4) abnormal neurological signs (e.g., exaggerated tendon reflexes, hypertonia, pyramidal signs, etc).

These criteria are very similar to those recommended in North America[63-65].

6.2.4 HBO protocol

HBO should be employed according to the clinical situation. Results of recent randomized studies strengthen the basis to use HBO in acute CO poisoning. However, a number of very important issues remain unanswered. This includes the optimal dose of HBO (i.e., number of sessions; treatment pressure; and treatment duration; etc). Usually 90 minutes at a pO_2 of 2.5 ata is sufficient. Most of the protocols used between 1 and 3 HBO sessions. In the Weaver's study, the greatest benefit was achieved in the first treatment. In clinical practice, it is usual to provide further HBO session if the patient has not recovered fully following the first session.

Patients with minor and/or subjective symptoms require high rate NBO using a mask for a minimum of 12-hours[66].

A further question that remains is the point after which treatment is no longer indicated. In a study performed by Goulon[18], the best results were obtained when the patients were treated within six hours. In clinical practice, it is usual not to treat after 24 hours from exposure if the patient is symptom-free.

6.3 Recurrence prevention

As most cases of CO poisoning are accidental, preventative measures are essential and must be addressed while the patient is still in hospital. In the author's experience, 4.5% of patients had recurrent poisoning within one year.

Preventative measures are required at three levels :

- patient level (including relatives; cohabitants; children and disabled or elderly adults potentially exposed). Information on the severity of poisoning; how it occurs; initial signs to detect recurrence; and the ways to avoid recurrence should be addressed. The information must be provided in writing as well as orally.
- at the environmental level: a professional technical assessment must be initiated to identify the CO source. This can be carried out by a health engineer from the health and social services. It should target all potential etiological causes. Depending on the outcome of the survey, local social services should be alerted if necessary.
- at the public health level: occurrences of CO poisoning including the cause and consequences, should be reported an appropriate statutory agency or authority (e.g., poison centre, local or regional health and social authorities). This is essential to promote a better understanding of epidemiological data and the human consequences of CO poisoning. This aspect of prevention is also crucial in order to make health authorities aware of the importance of the problem and for setting up adequate prevention programs.

7. SPECIFIC CASES

7.1 CO poisoning in pregnant patients

CO poisoning in pregnant women raises a very particular problem: CO poisoning has extremely harmful effects on the fetus, including death, fetal malformations and intellectual retardation. There is no strict parallel between the mother's clinical condition and the severity of fetal poisoning.

From a pathophysiological point of view, three facts must be considered:

- CO diffusion over the placental barrier has the effect of slowing both the uptake and elimination of CO relative to that of the mother[67],
- fetal hemoglobin has a greater to CO than adult hemoglobin,
- fetal hypoxia is much more severe than adult hypoxia in CO poisoning which favors CO binding to intracellular hemoproteins.

This explains why the severity of fœtal poisoning cannot be fully appreciated by an assessment of the mother's condition.

We performed a follow-up study over a 7-year period of 90 patients who were pregnant at the time they suffered CO poisoning and were all treated with HBO. Ninety percent of those pregnancies continued and ended with the birth of a normal child. In 5 cases, CO poisoning caused fetal death -- a 4-fold higher incidence than that of spontaneous abortions in our region. However, premature labour, fetal growth retardation and malformation rates were not higher than average.

We therefore recommend treating all pregnant patients suffering from CO poisoning with HBO, irrespective of the mother's condition. The pregnancy should thereafter be considered high risk and needs close monitoring; however, if HBO has been provided, elective termination is no longer recommended.

7.2 CO poisoning and pulmonary oedema

Pulmonary oedema reduces the effectiveness of HBO (pulmonary shunt effect) and in turn HBO may even aggravate it (hyperoxic cardiac decompensation).

In a 4-year series of 1,850 cases of CO poisoning, 120 patients (6.5%) suffered pulmonary oedema. These patients could be divided into two groups:

- cardiac-related: This included 92 cases (77%); patients were older (aged 71 ± 13 years), had frequently a previous history of heart

failure. For these patients, pulmonary oedema was an indication for HBO, since HBO accelerates myoglobin detoxification.

- non-cardiac related: The 2nd group included 28 younger patients (aged 18 ± 11 years), usually without previous heart pathology. The mechanism of pulmonary oedema was non-cardiogenic – either by toxic effect of the CO, or aspiration of gastric content (in 20 out of 28 patients). In these cases, the risk-benefit decision regarding HBO was made on the basis of reducing neurological risk in exchange for possibly increasing the pulmonary problems.

In our experience, comatose patients were always provided HBO without aggravating existing pulmonary oedema. However, the proviso is that only multi-place hyperbaric chambers that are equipped for intensive care should be used for such treatment so that potential complications can be managed (e.g., ventilation with positive end expiratory pressure; continuous positive pressure ventilation; haemodynamic monitoring, etc).

7.3 CO poisoning and smoke inhalation injury

It is now a well-known fact that a majority of deaths occurring in fires are not due to burns but due to asphyxia[68]. Smoke is a complex mixture of burning substances but nearly always includes CO and cyanide[69].

Beyond airway injuries (burns, obstruction by dust, necrotic debris, etc), CO poisoning must always be suspected in these patients, all the more if patients have lost consciousness or where neurological anomalies are observed. Metabolic acidosis should also lead clinicians to suspect CO poisoning[70].

Determining CO concentration in expired air in conscious patients enables selection of those requiring oxygen therapy.

If HBO is indicated, the pulmonary status should always be evaluated relative to the neurological risks of non treatment. Risk-benefit decisions should then be made.

7.4 Dichloromethane poisoning

Dichloromethane (e.g., methylene chloride) is a volatile solvent commonly used as an industrial solvent or paint stripper. Xenobiotic metabolism by the liver renders CO_2 and CO as byproducts with the latter causing a CO poisoning. The hallmark of this type of poisoning is secondary deterioration even after removal from fumes. This is because there is a continuous production of CO for some time after the methylene chloride has been absorbed, which is why COHb levels remain high[71].

Treatment consists of providing oxygen and can even justify HBO in the case of cardiac dysfunction or neurological impairment. Oxygen has to be administered over a longer period of time; COHb levels need to be monitored intermittently to confirm a downward trend and HBO sessions may need to be repeated.

8. CONCLUSION

CO poisoning remains a serious public health problem. Oxygen remains the principal treatment and HBO has proven to be more effective in preventing cognitive sequelae than NBO in patients at high risk for PNM. These include: comatose patient; history of loss of consciousness; neurophychometric disturbances; cardiac dysfunction and pregnancy. Such patients justify HBO therapy. However, other patients should be treated by an appropriate NBO regimen: 100% oxygen for at least 12 hours. A recent survey in our region showed that 50 % of CO poisoning patients requiring NBO did not receive this [32]. This may result in severe morbidity and socio economic costs.

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Chapter 2.2.4

NECROTIZING SOFT TISSUE INFECTIONS

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Abstract: Anaerobic soft tissue infections are still life-threatening infections. Even if uncommon nowadays, they remain severe conditions because often associated with major systemic effects leading to patient death if not promptly recognized and aggressively treated. Their origins are often traumatic or surgical but they can also develop from an ulcer or a small wound in patients at risk (i.e. diabetics, patients with peripheral vascular disease, etc). Hypoxia, traumatic muscle injury, heavy bacterial contamination as well as errors in antibiotic prophylaxis are major causes. Treatment includes antibiotic therapy adapted to both the anaerobic and associated aerobic bacteria; early and extensive surgical debridement; and intensive Hyperbaric Oxygen Therapy (HBO). Unfortunately, physicians are insufficiently aware of the first sign of these infections which explains why the management is often inadequate initially. Strict preventive measures must be taken to avoid their occurrence

Keywords: Anaerobic bacteria, anaerobic infections (soft tissue), gas gangrene, necrotizing fasciitis, Fournier gangrene, Ludwig angina, bacterial synergy

Anaerobic soft tissue infections are still life-threatening infections. Even if uncommon nowadays, they remain severe conditions because often associated with major systemic complications. Once established, they usually progress rapidly toward patient death unless promptly recognized and aggressively treated. Unfortunately, physicians are insufficiently aware of the initial presentation which explains why the management is often inadequate in the early phases.

Current points of interest include classification, pathophysiology and its implications on prevention, and function-sparing therapy (i.e., limb salvage).

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 263–289.

1. CLASSIFICATION OF SOFT TISSUE INFECTIONS

There has been multiple descriptions of soft-tissue infections due to anaerobic germs. Altemeier[1] and later Finegold[2] proposed classifications based on clinical and bacteriological criteria. However, these classifications offer little to the clinical diagnostic process necessary to expedite appropriate management[3]. Nowadays, more and more authors use a clinico-anatomic classification which offers more practical advantages (Table 2.2.4-1)[4,5].

Thus depending on the tissue initially infected, these infections can be divided into myonecrosis - whether due to C*lostridium* (gas gangrene) or not - and infections of the subcutaneous tissue. This later can be sorted into groups depending on their depth: (1) necrotizing fasciitis involves the deep fascia, the subcutaneous tissue and superficial fascia to variable degrees whereas (2) cellulitis involves the superficial fascia and the subcutaneous tissue to a variable extent but not the deep fascial layer.

Table 2.2.4-1. Anaerobic soft tissue infections clinico-anatomic classification

Initial infected tissue	Mode of Development	Germ	Disease	Specific Locations
Muscles	Acute	*Clostridium*	Clostridial myonecrosis (gas gangrene)	
		Other than *Clostridium*	Non clostridial myonecrosis	
Subcutaneous tissue & deep fascia	Acute	Mixed flora	Necrotizing fasciitis	Penis & scrotum : Fournier's gangrene Submandibular area : Ludwig's angina
Subcutaneous tissue	Progressive	Aerobic & anaerobic *Streptococcus* *Staphylococcus*	Cellulitis	

The striking elements common to all these infections are the fact that (1) they affect widespread areas involving various parts of the body, irrespective of the usual propagation barriers, and (2) that typical purulence is not present, usually replaced by a small amount of cloudy serous exudate. When incised, the tissue is pale, necrotic and there is little bleeding. It can be parted easily by hand or a blunt instrument. Microscopic examination reveals massive infiltration by leucocytes and the presence of both necrotic areas and developing micro-abscesses. Most of the time the causal organisms are found in these areas. The necrotizing aspect of these infections can be explained by a wide-spread thrombosis affecting practically all the small vessels in the infected area. The multiple thromboses cause extensive oedema and severe local hypoxia; even though blood

circulation is maintained in the larger vessels, it is not able to supply oxygen to the infected tissue.

Although these various infections have enough in common to be captured within a common framework, there are certain unique and distinguishing features that have clinical and therapeutic implications. They include (1) the tissue initially infected (muscle, subcutaneous tissue, fascia); (2) location on the body; and (3) mode of development[6].

1.1 Bacteriology

By definition, anaerobic bacteria are bacteria unable to grow in a medium containing more than 20 % of oxygen[7]. They produce energy by fermentation and most have none of the usual aerobic enzymes: cytochrome, catalase, peroxydase.

Even though many bacteria do not grow in 20 % oxygen – i.e. in ambient air – their level of susceptibility to oxygen varies widely. Some are extremely susceptible to oxygen and will not tolerate more than 0.1% of oxygen. These do not seem to have any pathogenic effects on man and are to be only saprophytic. Others only survive oxygen concentrations between 0.1 and 5% and are called strictly anaerobic. Other groups are optionally anaerobic or microaerophilic, tolerating higher concentrations in oxygen, even though their growth is increased in anaerobiosis. This concept of aerotolerance is important as it explains why some anaerobic bacteria are capable of surviving oxygen pressures equal to those found in human tissues[8-10].

Anaerobic bacteria classification is complex and there are still frequent changes in taxonomy. Briefly, and considering only those relevant to medicine, anaerobic bacteria can be sorted into the following groups : (Table 2.2.4-2)[2,7,11]:

- Spore-forming anaerobic bacteria belonging to the *Clostridium* genus. Their natural habitats are the soil, and the digestive systems of man and animals[12]. Most of them produce toxins which are partly responsible for their harmful clinical effects[13].

- Non spore-forming anaerobic bacteria, belonging to many other genera. These make up large proportions of the saprophytic flora of the mucosa[11,14].

Table 2.2.4-2. Classification of anaerobic bacteria and frequency of isolation in products of human origin[11]

SPORE-FORMING BACTERIA	
Gram-positive spore-forming bacilli : ***Clostridia***	11 to 14 %
C. perfringens *C. tertium*	
C. ramosum *C. sporogenes*	
C. difficile *C. histolyticum*	
C. septicum *C. novyi, C. tetani*	
C. paraputrificum *C. botulinum*	
NON SPORE-FORMING BACTERIA	
Gram-negative non spore-forming bacilli	24 to 39 %
Bacteroides *: B. fragilis, B. thetaiotaomicron*	
B. vulgatus, B. distanosis, B. uniformis, B. ovatus.	
Prevotella *: P. melaninogenica, P. intermedia,*	
P. oralis, P. disiens, P. oris, P. buccae	
Porphyromonas *: P. asaccharolytica, P. endodontalis, P. gingivalis.*	
Fusobacteria	4 to 5 %
F. nucleatum	
F. necrophorum	
F. mortiferum	
F. varium	
Gram-positive C*occi*	
Peptostreptococci	16 to 22 %
F. magna	
P. asaccharolyticus	
P. prevotii	
P. anaerobius	
Peptococcus	5 to10 %
P. niger	
Gram-negative C*occi*	(variable)
Veillonella parvula	
Gram-positive non spore-forming bacilli	
Actinomyces	rare
(A. israelii, A. naeslundii, A. odontolyticus, A. viscosus)	
Bifidobacteria	1 to 3 %
B. dentium	
B. adolescentis	
Propionibacterium sp.	6 to 17 %
P. acnes	
Eubacterium sp.	4 to 6 %
E. lentum	

1.2 Pathophysiology

1.2.1 Bacterial invasion

Anaerobic bacteria enter the body under 2 very different circumstances: either (1) by external invasion through direct inoculation or wound contamination by spores or bacteria in soil, or (2) by internal invasion by anaerobic bacteria originating from natural bacterial flora. Whenever the oral, intestinal or genital mucosa is broken, a septic cavity is brought into contact with the submucosal tissue which is normally sterile. Usually local and general immune mechanisms are able to limit bacterial contamination to the point of entry while the break in the mucosa is repaired. In some cases, however, they are overcome and an infection develops on the basis of germ virulence vs host immunocompetence.

1.2.2 Germ-related virulence factors[15]

Clostridia produce toxins – high molecular weight proteins with general or local effects – responsible of the severity of the clinical picture. The best known of these clostridial toxins is the *alpha toxin* secreted by *Clostridium perfringens*. It is a lethal, necrotizing and haemolytic toxin with predominant tissue effect due to great affinity for certain cellular structures not found in circulating blood. Alpha toxin is a C-type phospholipase (lecithinase) hydrolyzing lecithin into diglyceride and phosphoryl-choline. Lecithin is an essential component of the membranes of the eukaryotic cells. Its physiologic function is to stabilize the lipoprotein structure of cell membranes. So alpha toxin action affects all cells: muscle cells (myolysis); red blood cells (haemolysis); platelets (coagulation disorders); tubular renal cells (haemoglobinuria)[12]. Other toxins are also produced in varying amounts:[13] beta, delta and theta toxins.

Non spore-forming anaerobic bacteria are comparatively less virulent than *Clostridia* because they do not produce such powerful exotoxins. They are actually opportunistic germs which can become pathogenic under certain circumstances[16]. Like *Clostridia*, these bacteria excrete various substances into their environment, some of which play an important part in the fast development and the necrotizing effect of these infections. Hence, some of those enzymes damage the tissue constituents (e.g., procollagenase, hyaluronidase, proteinase, etc.) enabling the destruction of the support structures of subcutaneous tissue and causing bacterial diffusion into the spaces formed along the fascia. Other enzymes (e.g., coagulase) cause local

coagulation of the microvessels of the infected area followed propagating destruction as the local ischemia and promotes further bacterial proliferation.

Furthermore, some species of the *bacteroides* genus are enclosed in a polysaccharide capsule which protects them from phagocytosis. This constituent plays a major part in the pathogenicity of these bacteria. It has been experimentally proven that the intra-peritoneal injection of this purified capsular polysaccharide is all that is needed to induce abscess forming. This capsule also seems capable – at least in vitro – to inhibit the bactericidal activity of polymorphonuclear (PMN) leukocytes against certain aerobic bacteria and reducing their opsonization. This fact can account, in part, for the well-described synergy between aerobic and anaerobic bacteria[17,18].

1.2.3 Host-related susceptibility factors

By definition, anaerobic bacteria cannot survive in air. However it has now been proven that a large number of anaerobic bacteria can survive partial pressures of oxygen ranging from 15 to 60 mmHg, and even much more for some of them (*Bacteroides fragilis*)[8-10].

The tissue redox potential is a better index than the oxygen pressure to assess the development capacity of anaerobic bacteria in tissue. The redox potential actually measures the aptitude of a tissue to produce electrons. It is usually expressed in millivolts. A normal redox potential is +120 mV and is the most important mechanism to fight anaerobic bacteria infection[7,14,19]. If the redox potential is reduced, bacteria develop even if the pressure of oxygen in the tissue is around the normal range. Circumstances reducing the redox potential include: ischemia, tissue necrosis, development of associated aerobic bacteria.

Many other conditions or circumstances encourage the development of anaerobic infections: vascular disease (vascular atheromata, diabetic micro-angiopathy, vasculitis, etc.); vasoconstrictor drugs, cold and shock; trauma and surgery; haematoma and compressive oedema; foreign bodies; aerobic bacteria; and neoplastic proliferation. It is well known that anaerobic infection can develop jointly with cancer – it is not unusual for *C. septicum* infections to be the revealing sign of a cancer (rectocolon cancer in particular).

Lastly, some general systemic factors can encourage anaerobic infections: malnutrition, alcoholism, immunosuppressive treatments, granulocytopenia, etc.

1.3 Clinical aspects

1.3.1 Anaerobic myonecrosis or gas gangrene

A battlefield horror, gas gangrene, affected war wounds in around 5% of cases during World War 1; 1% in World War 2and in 0.016% of cases during the Vietnam War[20]. Its current incidence is low, although there has been an increase over the last 20 years, due to the increase of road injuries, errors in prophylaxis and mostly due to surgical practice where one-step repair procedures tend to be used[21]. Current incidence is estimated at 0.1 to 0.4 cases per year per 100 000 inhabitants[22]. In our own area, we have treated 165 cases in 15 years – in a recruitment area of 5 million inhabitants (Lille, Northern France).

1.3.1.1 Bacteriology

Out of the 150 we identified, six species of Clostridium were isolated in cases of gas gangrene, primarily *C. perfringens (C. welchii), C. novyi (C.oedematiens)*. Of these, *Clostridium perfringens* was the main agent in myonecrosis[2,23]. It was isolated in 80 to 90 % of cases.

Around 10 % of myonecrosis cases were not caused by Clostridia. In those cases, germs of the *Bacteroides fragilis* group and anaerobic Streptococci were most frequently involved.

1.3.1.2 Etiology

Bacterial inoculation is usually of external and traumatic origin – involving telluric germs. The well-known ecology of Clostridia relates to this: devitalised and bruised wounds; soiled with earth; inadequately disinfected; retained foreign bodies. Usually inoculation is extensive (road traumatology involving very severe injuries) and occurs jointly with lesions promoting anaerobic microbial proliferation (vascular disruption, open fractures, etc…)[21].

Etiology can also be of medical origin by contamination of cutaneous ulcers[20,22]. Diabetic foot lesions currently make up nearly 40 % of the lesions present when gas gangrene develops. Iatrogenic causes such as intramuscular or intra-articular injections are less frequent causes – mostly involving injections of corticosteroids or non steroidal anti-inflammatory drugs[24-25]. Contamination can also be surgical – particularly after amputations in vascular surgery or in diabetic patients. There have been rare cases occurring after “aseptic” procedures such as hip surgery[26].

Unlike anaerobic necrotizing fasciitis, contamination from endogenous intestinal or genitourinary flora is rare. When this does occur, colic or rectal cancer must be suspected[27].

1.3.1.3 Clinical presentation

Latency between contamination and signs of infection is usually short – between 12 and 24 hours. A pale and non-healing wound may sometimes prompt clinical suspicion. The first local signs are sharp and increasing pain – sometimes disproportionate to the size of the injury; anxiety and apprehension again exceeding the norm; cold and discoloured skin, extensive oedema, and a small amount of exudate. This is the stage where diagnosis must be considered and the wound investigated.

Radiography of the soft tissue can show gas bubbles or "feathering" in muscles thus providing an element of confirmation, but gas may not be present in the tissues at the onset and is not a reliable finding (i.e., only 20 % of cases, in our experience). Accordingly this element must not be a prerequisite for diagnosis. Bacteriological findings and surgical observation are the most important indicators. Moreover, the presence of gas is not specific: there are other gas-producing germs: (*E. coli, Proteus, Aerobacter*, etc.) and the trauma itself may have caused a misleading injection of air into soft tissue. The latter may be considered where gas is demonstrated by crepitus and radiographs taken very soon after the traumatic injury in the absence of developing sepsis.

The diagnosis of anaerobic myonecrosis is therefore first and foremost a clinical one. Bacteriological confirmation takes time and delay runs the risk of a rapid propagation with ensuing hypotension, altered consciousness, oliguria, jaundice and coagulopathy – all of which are signs of a poor ultimate outcome[28].

1.3.2 Anaerobic necrotizing fasciitis

Although the term "necrotizing fasciitis" was coined by Meleney in 1924 to designate "gangrene related to haemolytic *Streptococci*"[29], since Wilson (1952)[30] it is now used for a sub-cutaneous infection spreading along the deep fascia, causing secondary skin lesions and sparing muscles until late stages of infection.

Many terms have been coined: necrotizing fasciitis[31-34]; clostridial cellulitis[35,36]; non-clostridial crepitant cellulitis[37]; synergistic necrotizing cellulitis[3,38]; and for penis and scrotum infections, Fournier's gangrene[34,39-41].

1.3.2.1 Bacteriology

Although in his initial description, Meleney stated that beta-haemolytic *Streptococci* were isolated in all his patients[29,42], since then – as sampling and bacteriological culture methods have improved – many authors[30,43-46] have reported isolation of mixed flora where Streptococci are no longer the sole infective agents.

Rea & Wyrick[46] made the finding of mixed flora an essential sign of this type of infection. Their opinion was that improper handing and transport of samples and difficulties with culture of anaerobes were the explanation for the absence of detection of mixed flora in these infections.

After their work, most of the published series reported mixed flora as the cause of necrotizing fasciitis. Mixed flora refers to the presence of both anaerobic and aerobic germs, as well as Gram-positive Cocci and Gram-negative bacilli. In 1977, Giuliano[47] reported on a series of 16 patients in whom 75 strains of bacteria had been isolated. *Streptococci* were isolated alone or jointly with other bacteria in 15 of those 16 patients, *Bacteroides* in 10 and *Peptostreptococcus* in 8. This distribution is quite different from that reported by Stone & Martin[38] or from our own series[48], where no beta-haemolytic *Streptococci* were found. In both these series, Gram-negative anaerobic bacilli – mainly *Bacteroides* – were dominant, associated with Gram-negative aerobic bacilli and *Enterococci* (Table 2.2.4-3).

1.3.2.2 Etiology

Necrotizing fasciitis begins with a break in the skin or mucosa. It can be obvious, i.e., trauma, surgical wounds, infection of pre-existing lesions (arterial or venous ulcers, pressure ulcers, diabetic foot lesions, etc). Sometimes it is less obvious, idiopathic or goes unnoticed by the patient: e.g., skin abrasions, insect bites, etc.[33,35,44,45].

Rare indisputable cases have been observed after uncomplicated tooth removals[49]; conventional surgery[50]; and after sub-cutaneous or intra-muscular injections – mostly of corticosteroids or non steroidal anti-inflammatory drugs. Septic injections carried out by IV drug abusers are a frequent point of entry[51]; here the bacteria are quite specific and include several germs of the oral flora such as *Prevotella*)[52].

1.3.2.3 Clinical description

After the initial trauma, the phase of incubation is usually short (6 to 72 hrs), with discreet local signs in some cases: pale wound; local paresthesias; a feeling of fullness in the area, etc. Then an erythema appears. Soon after the area becomes swollen and painful. The infection develops rapidly and both local and generalised signs appear in a few hours.

Table 2.2.4-3. Anaerobic germ distribution isolated from 3 series of necrotizing fascitiis

	Brook[43]	Giuliano[38]	Own series[48]
*** Number of patients**	259	16	52
*** Total of isolated strains**	582	75	239
*** Strictly and aerotolerant anaerobic bacteria**	335	66	79
Gram-negative bacilli			
B. fragilis	59	2	16
Bacteroides sp.	17	15	19
Prevotella sp.	49	5	3
& Porphyromonas sp.			
Fusobacterium	11	1	3
Gram-positive bacilli			
Clostridium perfringens	21	3	26
Clostridia			
(except perfringens)	19	1	1
Eubacterium	5	1	3
Propionibacterium	23	4	2
Gram-positive *Cocci*			
Peptostreptococcus	116	12	1
Streptococci	36	22	5
(all groups)			
*** Strictly aerobic bacteria**	247	9	160

Locally, the affected area becomes erythematous, infiltrated, warm and painful; the swelling extends beyond the visible boundaries and beyond the borders of abnormal skin turgor. Usually there is neither lymphangitis nor satellite adenopathy. The lesion spreads quickly as observed by frequent clinical examinations. Crepitation can be found, indicating the presence of gas in the tissue, although it is less frequent than in the case of clostridial myonecrosis. Radiographic pictures of the soft tissue can show gas bubbles separating the sub-cutaneous tissue and showing the shapes of the muscles[53]. The local signs are remarkable for the speed at which they develop. It is quite possible for localized erythema in the immediate vicinity of a wound to develop into fasciitis involving a whole limb and spreading into the loin and abdomen within a 36 hour-period.

Systemic signs of necrotizing fasciitis often include a marked inflammatory response syndrome with fever, organ dysfunctions and extreme leukocytosis. Altered consciousness, oliguria and coagulopathy indicate that the infection is severe. However, it is essential to be aware that in some cases there is little or no infectious syndrome, even though the infection is rapidly spreading. This suggests a global fulminant infection and immunocompromise.

1.3.2.4 Site-related aspects

**** Perineal fasciitis***

In 1883, Fournier[39] described gangrene of the external genitalia in 5 men. Since then, fast-developing gangrene of the penis and scrotum has been designated as Fournier's syndrome. The category is divided into 2 sub-groups : Fournier's disease – in which the initial lesion is undetermined – and secondary Fournier gangrene in which there is a rectal or prostatic cause in the majority of cases [40,41,54,55]. Although Fournier's descriptions were sound there are cases of localised gangrene of the penis and scrotum spreading to the whole perineal area. Similarly there are cases of gangrene originating in the anal area spreading to the external genitalia. A similar pathophysiogical process also occurs in women so that today Fournier's syndrome is considered to represent any form of perineal necrotizing fasciitis[56-58].

From a clinical point of view, the perineal area is covered in a widespread and painful erythema. Cutaneous necrosis quickly develops. The infection spreads – more frequently in the case of secondary fasciitis – towards the abdomen, groin, buttocks and thighs. Systemic manifestations are also more common in the case of secondary fasciitis.

The search for a cause is an essential point of the management. In around 30 % of cases in men the search for a primary cause is fruitless or reveals only a folliculitis lesion in the scrotum. Nevertheless the fasciitis cannot be treated while the point of entry is left open. Abdomino-pelvic CT scan with a water-soluble contrast enema is a emergency mandatory examination. Many cases of seemingly spontaneous fasciitis ultimately lead to the discovery of an occult rectal or colic cancer[58].

Post-operative perineal fasciitis another potential cause – particularly after haemorrhoid or anal fistula surgery.

**** Necrotizing fasciitis of the neck and face***

Location of necrotizing fasciitis in the neck and face is less frequent[59,60]. As anaerobic bacteria form the majority of the mouth and throat flora[630], it is not surprising that this type of infection can develop after apparently ordinary disorders such as an abscess on a lower third molar[61] or in the tonsil[62], The absence of barriers to stop the infection from spreading[64,65] to the mediastinum[66,67] makes this type of infection particularly serious.

From a clinical point of view, the initial disorder (e.g., tooth or throat pain, sub mandibular swelling, etc.) quickly makes way to a rapidly-spreading erythematous swelling involving the whole sub mandibular area ultimately encroaching the other side and providing the well-known clinical picture of Ludwig's Angina[68]. The infection then spreads to the face, the lower part of the neck, the supraclavicular area and the thorax.

This is a serous condition mainly because the infection can spread to the mediastinum – an event which, in our experience, can only be detected by a cervical and thoracic tomodensitometry. The latter must be carried out as a matter of emergency to assess the development of the infection. The infection then spreads onward to the pleura, the lungs and the pericardium[61].

1.3.3 Anaerobic cellulitis

Quite the opposite from the florid presentation of necrotizing fasciitis, these infections of the sub-cutaneous tissue develop more slowly with only rare cases yielding generalised manifestations[4].

Known as progressive bacterial gangrene[69] or progressive synergistic gangrene[70], these infections initially affect sub-cutaneous tissue, often remaining in the superficial third upper-layer, leaving the deeper fascia unaffected[36,71].

1.3.3.1 Etiology

In most cases, anaerobic cellulitis develops after thoracic or abdominal surgery or around the drainage port of purulent pleurisy or of a peritoneal abscess. It can occur around the orifice of a colostomy or an ileostomy, or following an ordinary skin lesion. It can also appear spontaneously with no apparent initial lesion[69,72].

1.3.3.2 Bacteriology

Bacteria samples taken from the central zone show a large amount of bacteria with no particular relevance to the cellulitis and resulting from wound colonization. Samples taken from the peripheral zone reveal the presence of non haemolytic oxygen-tolerant anaerobic *Streptococci* combined with other germs: *Staphylococci, Proteus, Enterobacteria, Pseudomonas*, etc.

Streptococci seem to play a major role. Isolated in the furthest peripheral zones, they seem to prepare tissues for the infection by other germs. This is the reason why this infection has long been called synergistic[42]. However it can prove difficult to isolate the Streptococci, which means their role remains invisible and only the other germs are recognised.

1.3.3.3 Clinical aspects

Clinically, the lesion is revealed by pain, both spontaneous and when pressure is applied. Locally, an indurated dark red central zone can be observed, surrounded by erythema,. The cellulitis spreads and is typically made up of 3 zones: (1) the peripheral erythematous zone; (2) a dark red and painful intermediate zone; (3) and a gangrenous and necrotic central zone

which develops into a large ulcer where granulation and epidermal glands sometimes appear. A very specific fact is that the deep fascia around the muscles is unaffected. Hyperaesthesia of the intermediate zone is also a good sign[4]. The infection spreads slowly but continuously over a few days or weeks. Satellite lesions can occur due to sub-cutaneous propagation. General signs of infection are subtle and complications rare.

2. THERAPY

In view of the potential severity of these infections, patients in whom these conditions are suspected require immediate admission to intensive care units and emergency treatment combining 3 forms of therapy: antibiotics, surgery, HBO backed up by general intensive care.

2.1 Antibiotic therapy

Parenteral antibiotics must be started as soon as the condition is suspected and before the results of the bacteriological examination are known.

Penicillin G has long been the antibiotic of choice for treating and preventing anaerobic infections[2,19,23]. It reduces morbidity and mortality in experimental gas gangrene. It has changed the fate of war injuries. Therefore, to this day, penicillin G on its own and in high doses remains active against Group A *Streptococci* and a large number of anaerobic bacteria *(Clostridium, Fusobacterium* and *Peptostreptococcus*)[24]. In adults, daily dosage is around 30 million units in the absence of contra-indications. Trauma and oedema restrict antibiotic penetration which is why high dosage is necessary.

Unfortunately more and more bacterial strains are becoming penicillin G-resistant (*Bacteroides sp., Prevotella melaninogenica*, etc.). This has led to changes in this long-standing regimen[73-75]. In present times more stable betalactams are being used, such as carboxypenicillins (ticarcilline), ureidopenicillins (piperacilline) . Alternatively penicillin G is being combined with imidazole derivatives (metronidazole, ornidazole). Cephalosporins – with the exception of cephamycin – are usually much less effective than penicillin. Rifampicin, chloramphenicol, macrolides (erythromycine) or clindamycine can be used on patients with an allergy to penicillin. Clindamycin is very often recommended by North american authors because of its anti-toxin activity[76,77] but may be poorly tolerated and resistance is increasing so that its use has greatly decreased in Europe. Often

glycopeptides and imipenem are preferred when there are contra-indications to penicillin.

Although *Clostridia* infections would seem to justify monotherapy by high doses of penicillin G, the clinical management requires greater distinction: Firtsly there is no clinical difference (apart from frequency in relation to location and aetiology) between clostridial infections and non-clostridial infections (i.e, infections caused by anaerobic *Streptococci* or Gram-negative bacilli, particularly *Bacteroides sp*.). However the latter are becoming increasingly penicillin G-resistant. This means that where stopping the infection is a matter of urgency empirical therapy should cover these organisms as well. Secondly, many of these infections also involve a number of other bacteria. Aerobic germs – usually Gram-negative bacilli – are often present, either *ab initio* or by superinfection. The involvement of Gram-negative bacilli (Enterobacteria, *Pseudomonas,* etc.) should not only be considered because of a possible superinfection, but also because the are synergistic in that the beta-lactamase they produce reduce the effectiveness of penicillin on the anaerobes[17,78,79]. Combining these drugs with a beta-lactamase inhibitor may be helpful.

A combination of piperacilline, imidazole derivates and aminoglycosides (so-called triple therapy) has often been recommended. Piperacilline and imidazole derivates against anaerobes, the aminoglycoside being added for the Gram-negatives[4,28]. Combinations of ticarcilline - clavulanic acid - aminoside, or piperacilline - tazobactam – aminoside, or imipenem as monotherapy are other possible combinations.

There is no fixed duration for the initial antibiotic therapy. It should be continued at least until general and local signs of infection have ceased. Most authors recommend an average three-week duration. Unless infectious complications appear in other locations (pneumopathy, septicaemia, etc.), or a superinfection occurs, the results of subsequent bacterial samples does not justify changing the initial antibiotic therapy.

2.2 Surgery

2.2.1 General principles

Even before antibiotics, military surgeons had shown that radical, mutilating surgery, involving amputation at the root of the limb or even disarticulation could save a patient's life if carried out early on before the infection spread. This attitude, which is prevails to this day[80,81], is not

without significant mortality not to mention the severe functional sequellae[20].

Nowadays, with the development of antibiotic and HBO therapies, the approach has changed with surgery now being aimed at eliminating necrotic tissue and reducing oedema-related compression that exacerbates spread of the infection by reducing microcirculation and with that antibiotic penetration[82].

Basic surgical procedure includes wide and early debridement with incisions to open up the sub-cutaneous tissue to reach the fascia, and opening all affected tissue planes until the hand meets resistance which means uncleaved tissue has bean reached[4,5,20-22,28]. With the exception of dramatic life-saving amputations in lieu of alternative therapy, initial surgery is not mutilating. Only necrotic tissue must be removed, while doubtful but possibly viable tissue may be left in place. This approach is justified when HBO is combined with surgery, because HBO will save much of the otherwise doubtful tissue.

Extensive rinsing with antiseptic solutions completes the surgical management and drainage is left in place – usually liberally so. Antiseptics should be chosen for their lack of general or local toxicity but with effectiveness against all suspected bacteria and spores so that there are no spectrum gaps with subsequent selective bacterial contamination. Solutions of povidone iodine or chlorhexedine are usually preferred. Extensive rinsing with hydrogen peroxyde is no longer recommended as it does not increase the local oxygen tension and it may cause severe complications[83,84]. Lastly the point of entry requires specific treatment.

After initial surgery, wounds must be checked several times a day – in our practice, every 8 hours during the first 5 days. A form of mini-surgery is provided: necrotic tissue is removed as necessary and the remaining inflammatory tissues are extensively rinsed with antiseptic solutions and extra drainage provided. When the tissues become healthier (usually in the 2nd week), dressings can be reduced until they are performed daily and support of healing replaces the emphasis on cleaning. To this day the surgical approach to these wounds remains inconsistent. Although the emergent need for it is widely accepted[85], errors of judgement remain troublesome: In our study[48], initial surgery was unsatisfactory in 8 cases out of 10, either because immediate further surgery was required due to too little debridement, or because of an overly aggressive approach with extensive resections and even amputations that were not clinically indicated.

2.2.2 Site-related aspects

Abdominal locations complicate surgery. In the early stages reopening, cleaning all the residual purulent cavities and extensive sub-cutaneous rinsing are adequate. In later stages, the fact that the cavities must be kept open, and the necessity of extensive parietal sacrifices make the care of these patients considerably more difficult. The causal lesion requires relevant treatment of its own.

In cases of perineal locations, surgery will largely depend on whether or not a colostomy has to be performed. If intestinal resection requires a colostomy the decision is made automatically. More troublesome are the perineal infections where ongoing fecal drainage are at odds with wound management. Therefore colostomy is always to be considered as soon as an infection reaches the anal area[58]. The colostomy must be carried out in a healthy area to make sure neither the laparotomy scar nor the colostomy orifice become a causeway for the infection. The colic and rectal segment beyond the ostomy must be thoroughly emptied and cleaned. During the same surgical procedure, extensive drainage of the perineal infection must be carried in the same way, but quite separately from the colostomy.

In addition to all the relevant procedures on the point of entry, fasciitis of the facial and cervical locations must include extensive internal and external drainage of all the infected spaces of the face and neck. Considering the size of the incisions and the risk of necrosis of the cutaneous flaps, drainage on the neck should be carried out by long incisions along the sterno-cleido-mastoid muscles, rather than by transverse ones. Mediastinal drainage can be carried out using cervicotomy incisions if the infection is limited in the supra-aortic space. Right thoracotomy becomes a necessity if there is any extension beyond the aortic arch[61].

2.3 Hyperbaric Oxygen Therapy

Introduced by Brummelkamp & Boerema[86] in 1960 for treating gas gangrene, HBO is still a matter of debate even though its effects are clearly identified and many authors have reported its clinical effectiveness.

Since the end of the 1980's and the appearance of Evidence Based Medicine (EBM), an extensive process for revising and assessing medical practice has begun. This has concerned HBO together with many other forms of therapy. The authors agree that up to now, there are no double-blind randomized clinical studies providing A or B level recommendations for the use of HBO for acute soft tissue anaerobic infections. Nor are there any such studies for surgery or antibiotic therapy. But, considering the large

body of experimental and clinical studies published in the literature and their own experience, the jury of the ECHM Consensus Conference in 1994 and 2004 evaluated the use of HBO in anaerobic soft tissue infection as a type 1 recommendation based on the consensus of experts (level C).

We report here a summary of evidence supporting the use of HBO in the treatment of acute soft tissue anaerobic infections.

2.3.1 Physiological effects of HBO for the treatment of acute necrotizing soft tissue infections

The effects of oxygen on anaerobic bacteria and on tissue infection have been reviewed in the chapter 1.6.

In summary, the rationale for the use of HBO in the treatment of acute anaerobic soft tissue infection is based on :

- a direct toxic effect of oxygen of anaerobic bacteria,
- an indirect effect of oxygen on the microbicidal capabilities of polymorphonuclears in the infected area,
- an increase in the activity of selected antibiotics.

2.3.2 HBO in experimental models of infections

A certain number of experimental studies have been based on these mechanical effects. The earliest, carried out by Brummelkamp[86], Holland[87], and Demello[88], showed the usefulness – in a decreasing order – of antibiotic therapy, surgical drainage, and HBO for treating *Clostridium* infections.

The early work proved the effectiveness of HBO in experimental models of soft-tissue anaerobic infections. In a study performed by Hill[89], a standardized inoculum of *C. perfringens* and adrenaline was injected in the paws of mice to trigger ischemic infection. The animals were sorted into 2 groups which were subjected to repeated sessions of HBO at 2 or 3 ata of pure oxygen, and a 3rd group was kept as a control group. A significant difference in mortality was shown in favour of the higher pressure of oxygen.

Further work in this field was carried out by Demello[88] who assessed the effectiveness of antibiotic therapy, surgical drainage and HBO in a model of gas gangrene with *C. perfringens* in dogs (Table 2.2.4-4).

No survivals were obtained by surgery (extensive incision, drainage and rising with antiseptic solutions), HBO, or a combination of both. There was some improvement in survival after antibiotic therapy combining penicillin and another antibiotic with an effect on aerobic germs such as tetracycline.

But mostly, the best survival percentages were obtained by combining the 3 forms of therapy[88].

Table 2.2.4-4. Comparative study of different treatments against experimental gas gangrene in dogs (from Demello et al.[88]).

Therapy	Survival (%)
Surgery	0
HBO	0
HBO + surgery	0
Antibiotic therapy	50
Antibiotics + surgery	70
Antibiotics + surgery + HBO	95

These early data have been confirmed by more recent data: Hirn found a significantly more favourable effect on the survival of rats which had been injected with *Clostridium perfringens* to trigger experimental gangrene, in the group treated by a combination of surgery and HBO as in the group where surgery only was provided[90]. In a model of intra-peritoneal poly-microbial infection, Thom identified a significantly favourable effect on mortality in the group treated by HBO as compared to the control group[91].

Lastly, the usefulness of HBO was studied in a model of muscle infection involving *Streptococci* as a result of the general interest taken in soft-tissue *Streptococci* infections (these were described in the English press as "flesh eating bacterial disease")[92]. Conclusions were similar to those reached previously in other experimental models involving other bacteria: when used alone, HBO changes neither mortality nor bacterial proliferation; antibiotic therapy (in this case penicillin was used) is effective on both criteria; and combining antibiotic and HBO therapies was significantly more effective on both criteria than antibiotic therapy alone.

To conclude, animal models have proved that although pressures of oxygen play a part in the development of soft-tissue infections, a hierarchy exists regarding effectiveness of the different therapies available. HBO cannot be used on its own, and the best results are obtained when it is combined with antibiotic therapy and surgery.

2.3.3 Clinical experimentation

2.3.3.1 Published data

There are no double-blind randomized studies on the effectiveness of HBO combined with antibiotic therapy and surgery against anaerobic germ infections. However many open series have been published. Although they include a varying proportion of anaerobic myonecrosis and necrotizing

fasciitis infections, they provide useful data. These studies fall into two categories – the first where treatment included surgery and both antibiotic and HBO therapies, and the second where surgery was combined with antibiotic therapy only. The results provided by the first category were relatively homogeneous - recovery rates of 78 to 80 % and mortality rates of 20 %. In the second category, mortality was around 36 %, except in Altemeier's study of 1971 where gas gangrene affected mostly extremities limbs and over 50 % of amputations were carried out (Table 2.2.4-5)[65].

Table 2.2.4-5. Results of clinical studies sorted by the therapies used[21].

Author	Patients	Recoveries (%)	Deaths (%)
Arm surgery - antibiotics – HBO			
Roding, 1972	130	101 (78)	29 (22)
Hitchcock, 1975	133	100 (75)	33 (25)
Hart, 1983	139	112 (81)	27 (19)
Darke, 1977	66	46(70)	20 (30)
Holland, 1975	49	36 (73)	13 (27)
Unsworth, 1984	53	46 (87)	7(13)
Hirn, 1988	32	23 (72)	9 (28)
Gibson, 1986	29	20 (70)	9 (30)
Werry, 1986	28	21(75)	7 (25)
Kofoed, 1983	23	20 (87)	3 (13)
Tonjum, 1980	14	12 (86)	2 (14)
Total	696	537 (78)	159 (22)
Surgery and antibiotics only			
Altemeier, 1971	54	46 (85.2)	8 (14.8)
Hitchcock, 1975	44	24 (55)	20 (45)
Gibson, 1986	17	5 (29)	12 (71)
Freischiag, 1985	8	3 (37)	5 (63)
Total	123	78 (64)	45 (36)

In France, a multi-centre retrospective clinical study involving nearly 800 patients treated for soft-tissue anaerobic infections was published by Goulon in 1980[28]. Percentages of recoveries and mortality were more or less similar to those of the other studies for patients provided with triple therapy (i.e., surgery, antibiotics and HBO), whereas there was a significant difference in recovery percentages in those treated with surgery and antibiotics. To eliminate the bias that might have been introduced by a possible extra mortality in the group without HBO (the severity of some of these cases having possibly lead to patient death before they could be provided with HBO), only patients having survived longer than 8 days were included in the study. The difference of mortality for myonecrosis infections still remained in favour of those who received HBO.

Some studies of necrotizing fasciitis, although not randomized, have studies the effects of HBO on standard management with surgery and antibiotics. Shupak reported on a series of 37 patients, 12 without HBO, 25 with HBO, with no significant difference in mortality[93]. However, since decisions regarding the use of HBO were made by the surgeon, the proportion of patients with severe signs (i.e., coma, acute kidney failure, shock, and infection located on the trunk) was greater in the HBO group, even though this did not reach the threshold of statistical difference. Another series of 54 patients with necrotizing fasciitis of the trunk (24 without HBO, 30 with HBO) showed lower mortality in the group given HBO (30 %) than in the other group (42 %) Yet again this did not reach the threshold of significance[94]. However, Riseman reported on a study involving 29 patients (12 without HBO, 17 with HBO) where a significant difference was shown in mortality (23 % with HBO, 66 % without HBO, $p < 0.02$) and on the number of surgical debridements needed (1.2 with HBO, 3.3 without HBO, $p < 0.03$)[95].

The heterogeneity of these results can be explained by a number of facts. Studies were not randomized and the respective antibiotic, surgical and dressing regimens were not standardized. They were also not stratified for known prognostic factors making it impossible to compare the outcomes: the severity of sepsis; initial location; progression; ability to eradicate the sepsis focus; etc. were not specified. The enormous variability in mortality in groups without HBO (25 % for Shupak[93], 42 % for Brown[94] and 66 % for Riseman[95]) clearly shows the varying degree of severity of the infections considered.

The fact that the only positive study is the one where mortality in the control group is the highest confirms the impression given by clinical experience. The usefulness of HBO is most obvious when patients' conditions are most severe and the prognosis most serious. This was the decision of the jury of the Consensus Conference on indications for HBO that took place in Lille in 1994 and this was confirmed again in 2004. The jury strongly recommended the use of HBO in strictly anaerobic or mixed necrotizing infections (myonecrosis, necrotizing fasciitis) in view of the fact that this therapy could have a positive effect on survival. On the other hand, the jury was more doubtful about the usefulness of HBO for treating patients with milder disease and its use in cellulitis was therefore considered optional[96].

2.3.3.2 Research protocols and related problems

**** Randomizing studies***

Should we be promoting the idea of a randomized study of HBO? This question has a matter of debate for over 20 years and, the answer depends on

the characteristics of the evaluating team. For those already using HBO, it is inconceivable to deny one group of patients the benefit of HBO in combination with surgery and antibiotics. On the other hand, would a team unfamiliar with HBO be able to introduce this in the absence of any expertise using it? Many experimental and clinical issues that have arisen in recent times have lead to questioning the feasibility of such studies.

**** Choosing a protocol***

Actually the real problem is defining the best procedures for HBO. At present the pressure, duration and number of sessions are determined using few or no objective criteria. Although most teams use the procedures proposed in Hill's work on experimental gas gangrene in mice[89], there are no actual clinical studies on this point. Nor are the criteria for ending HBO indisputably determined. So depending on the teams in charge of managing patients, the total duration of this treatment can vary from 5 days for those using HBO strictly for its anti-infectious activity, to 2 to 3 weeks for those who aim to provide the benefit of the wound healing as well.

For the moment, there appears to be no value in arguing for an ideal sequence for using the various modalities of therapy. HBO can be provided before or after initial surgery, depending on the availability of hyperbaric chambers and surgical theatres. However the general recommendation is that it should be started as soon as possible. Some actually operate patients inside the hyperbaric chambers[4].

**** Improving results***

There are several ways of improving the use of HBO for treating soft-tissue anaerobic infections: (1) achieving consensus on the classification of anaerobic infections so that referrals are appropriate; (2) technical progress in measuring partial pressures of oxygen able to reach infected tissues, as this accounts for success or failure in using HBO; (3) evaluating bacterial clearance from the site of infection in response to treatment; and finally (4) controlled, multi-centre studies following strict methodology to allow objective assessment of therapeutic protocols, including the duration and frequency of HBO therapy.

2.4 General intensive care

There is nothing unique about caring for these patients: Septic shock, acute kidney, or respiratory failures require conventional treatment. The thrombotic element of these conditions favours the use of small doses of heparin. Nutrition is important and must cover the energy expenditure of these patients which is often enormous. Finally, in all cases of infections of traumatic origin, anti-tetanic prophylaxis must be a matter of routine

whenever the patient's vaccination status (active immunization) is in doubt or no longer valid.

2.5 Preventive therapy

The current rare occurrence of post-surgical or traumatic soft-tissue anaerobic infections demonstrates the effectiveness of preventive therapy. This is based on correct surgical care of the lesions combined with preventative antibiotic therapy by penicillin G – combined with imidazoles when the presence of *Bacteroides sp* is suspected (e.g., in colic or rectal lesions)[97]. However absolute prevention is not assured. Anaerobic infections can develop under antibiotic treatment – either because they have been provided too late or because surgery has been unable to restore antibiotic penetration due to vascular injury or compression, high compartmental pressures, devascularised tissue, contamination or foreign bodies remaining. In cases of particularly soiled wounds or late referrals, preventative therapy can combine preventative HBO (5 to 7 sessions over a period of 2 to 3 days) with antibiotic therapy. However, this reasonable but as yet empirical recommendation is not supported by evidence.

3. CONCLUSION

Despite the progress made in therapy, the prognosis for soft-tissue anaerobic infections remains poor. Global mortality varies between 20 and 50 % in the various series and depends on initial location (Table 2.2.4-6).

Table 2.2.4-6. Mortality of anaerobic soft tissue infections depending on location (from our own series of 30 cases)[5].

. Neck only	12.5 %
. Limb only	18 %
. Perineum	32 %
. Abdomen	45 %
. Neck & Mediastinum	50 %
. Abdomen & Thorax	68 %

When infection affects only one limb, mortality is around 5 to 10% for necrotizing fasciitis and a little higher for myonecrosis: 10 to 20 %. Once it affects the abdomen & thorax it can reach 60% for necrotizing fasciitis. Sadly, survival is sometimes secured at the cost of extensive mutilation. Here HBO seems particularly effective in reducing functional sequelae related to loss of tissue or extremities.

Beyond the initial location, a number of factors exacerbate these infections: older patients; poor general health (e.g., alcoholism, diabetes, neoplasia); coagulation disorders (i.e., decreased prothrombin time, thrombocytopenia); hypothermia; jaundice; kidney failure; acute respiratory failure; shock; altered cconsciousness; and lastly late referral – perhaps the most obviously important factor[85].

Given the therapeutic and anti-infective strategies available over the past ten years and in active use today, results are still not universally satisfactory. Further progress will depend on physicians carefully considering the following: (1) aggressive prophylaxis against and (2) immediate intensive treatment upon discovery of anaerobic infections[98].

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Chapter 2.2.5

INTRA-CRANIAL ABSCESS

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Abstract: Intracranial abscesses (cerebral abscess, epi- and subdural empyema) are described in the literature to have an overall mortality of 10 - 36 %. A high percentage of the surviving patients is persistently suffering from neurological deficits. Starting from on anecdotal case, up to now, our group treated 21 consecutive unselected patients with intracranial abscesses (ICA) by adjuvant hyperbaric oxygen therapy (HBO). We found a 0.0 % mortality with only one patient remaining severely handicapped.
Based upon these facts, both the ECHM and UHMS have approved the use of HBO when, at least, one of the following criteria is met: multiple abscesses; abscess in a deep or dominant location; compromised host; in situations where surgery is contra-indicated or where the patient is a poor surgical risk; where there is no response or further deterioration in spite of standard surgical (e.g. 1-2 needle aspirates) and antibiotic treatment

Keywords: Intracranial abscess, mortality, anaerobic bacteriology, intracranial pressure, peri-focal brain swelling, adjunctive HBO

1. INTRODUCTION – AN ILLUSTRATIVE CASE[1]:

History: While playing on a farmyard, a five years old boy accidentally was hit by a hayfork at his left eye. No injury was observed to the eye or surrounding tissue so that the true diagnosis was missed by a GP and an ophthalmologist the same evening[1].

High temperatures up to 40° C (= 104° F) occurred during the following 24 hours and these were misdiagnosed as a summer flu. Another 24 hours later, the child was admitted to pediatric infirmary, now being in the state of a severe meningitis including sings of an orbital empyema (figure 2.2.5-1A).

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 291–304.

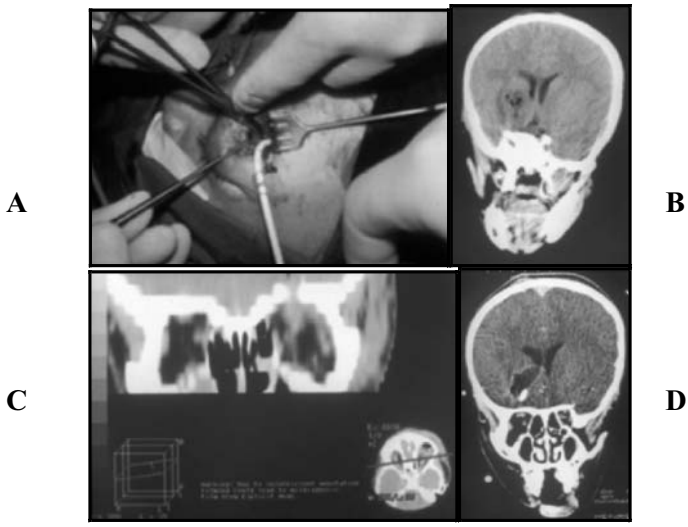

Figure 2.2.5-1. Physical aspect and radiological findings (see text for details)

Diagnoses: ***Bacterial meningitis*** (cerebro-spinal-fluid culture: *Clostridium perfringens*). ***Gas formation*** of unknown origin in the basal parts of the left frontal cerebral lobe (figure 2.2.5-1B). ***Orbital empyema.***

Course: Five days after the initial injury, the child was transferred to our facilities. Computed tomography revealed the penetrating injury of the left-side orbital roof (figure 2.2.5-1C). This established the link between the initial trauma, the meningitis, and the radiological signs of an early cerebritis.

Because of the localization of the cerebral process as well as its stage, the neurosurgical approach was limited to drainage only. In spite of effective drainage combined with broad-spectrum antibiotics, a large cerebral abscess emerged over the next three days. The abscess was adjacent to the Broca center, capsula interna, and A. cerebri media with resulting ventricular rupture (figure 2.2.5-1D).

Figure 2.2.5-2. Picture of the boy one year after treatment. Note the complete recovery in coordination and hand ability

HBO-Therapy: Because of the abscess being in a dominant location, the organism involved, and the progression in spite of standard therapy, adjuvant HBO was started (1 session of 60 minutes per day at 2.5 ata).

Continuous improvement followed: body temperatures, orbital empyema, subsided and systemic inflammatory parameters returned to normal within one week. The boy completely regained his alertness within three days.

Seventeen HBO-sessions were administered on 17 consecutive days. No complication resulted from the pressure or hyperoxygenation. At the end of HBO treatment, the child was discharged from the ICU following a total stay of 20 days. Close neurosurgical surveillance was maintained.

Outcome: There were no permanent neurological deficits and the boy was able to go to school at the age of six according to national regulations (figure 2.2.5-2)**.**

2. MORBIDITY / MORTALITY

Intracranial abscesses (i.e. cerebral abscess, epi- and subdural empyema) account for not more than 3 to 5 admissions per year even at larger medical centers[2]. Thus, the incidence is low and roughly in the same range as that of e.g. gas gangrene in former years.

However, the overall mortality described in numerous series from different countries around the world for the years 1981 to 2005 (table 2.2.5-1) varies from 0 to 36 %, averaging at 19.2 %! Even if the mortality has significantly decreased over the past three decades to about 13 % at present, it still remains unacceptably high.

Table 2.2.5-1. Mortality rates from intracranial abscesses treated by means of standard management (time span studied: 1981-2005 [year of publication])

1981 – 1986

Author	Published	Country of Origin	Nb	Deaths	Mortality	[Ref.]
Yang	1981	PR China	400	91	23 %	[3]
Alderson	1981	Great Britain	90	9	10 %	[4]
Dohrmann	1982	Australia	28	10	36 %	[5]
Britt	1983	USA	14	5	36 %	[6]
Cowie	1983	Great Britain	89	24	27 %	[7]
Harris	1985	USA	15	3	20 %	[8]
			636	**142**	**22.3 %**	

1987 – 1993

Author	Published	Country of Origin	Nb	Deaths	Mortality	[Ref.]
Ferriero	1987	USA	17	1	6 %	[9]
Pattisapu	1987	USA	8	0	0 %	[10]
Miller	1988	Great Britain	100	20	20 %	[11]
Schliamser	1988	Sweden	54	17	31 %	[12]
Basit	1989	Saudi-Arabia	21	5	24 %	[13]
Szuwart	1989	Germany	38	10	26 %	[14]
Witzmann	1989	Austria	38	7	18 %	[15]
Pathak	1990	India	41	10	24 %	[16]
Kratimenos	1991	Great Britain	14	2	14 %	[17]
McIntyre	1991	Australia	14	3	21 %	[18]
Bagdatoglu	1992	Turkey	78	16	20 %	[19]
Seydoux	1992	Switzerland	39	5	13 %	[20]
Bok	1993	South-Africa	21	5	24 %	[21]
Stapleton	1993	Great Britain	11	3	27 %	[22]
Yang	1993	PR China	140	11	8 %	[23]
			634	**115**	**18.1 %**	

1995 – 2005

Author	Published	Country of Origin	Nb	Deaths	Mortality	[Ref.]
Sharma	1995	India	38	12	32 %	[24]
Takada	1998	Japan	13	0	0,0 %	[25]
Stephanov	1999	Switzerland	17	2	11,8 %	[26]
Mamatova	2000	Uzbekistan	13	1	7,6 %	[27]
Liliang	2001	Taiwan	15	4	26,7 %	[28]
Marchiori	2003	Italy	20	1	5 %	[29]
Jansson	2004	Sweden	66	3	4,5 %	[30]
Ozkaya	2005	Turkey	25	4	16 %	[31]
			207	**27**	**13.0 %**	

No. of series	Nb	Deaths	Mortality
29	1477	284	19.2 %

The factors responsible for a decreasing mortality certainly include:

- earlier and more accurate diagnosis by means of modern imaging,
- options of minimally invasive surgery, e.g. CT-guided fine needle aspiration,
- better knowledge of the bacteriological origins of intracerebral abscesses, resulting in a improved selection of antibiotics.

Nevertheless, **one** out of **eight** patients still die due to intracranial abscesses, and a high percentage of survivors suffer from severe neurological sequelae, mainly of epileptic origin[7].

2.1 Bacteriology

Knowledge of the bacteriological sources of intracranial abscesses has improved over the past 25 years: Anaerobes account for up to 90% of the isolated bacteria, depending on the culturing technique. The fact that (in the past) several studies (e.g. Yang 1981[3]) found a high percentage of sterile cultures may be deceptive. One explanation may be that anaerobic culturing either had not been done or had not been successful.

Brook[32] reported the differential bacteriological findings in 19 children with intracranial abscesses as follows: in 63.2 %, anaerobes were cultured exclusively; in 26.3 % both aerobes and anaerobes were found; and only 10.5 % of the cultures were purely aerobic. Typically, several microorganisms were found simultaneously.

These results are consistent with our own (table 2.2.5-2 and 2.2.5-3): In 21 sequential patients, 32 microorganisms were identified. Nine patients had more than one organism cultured from the intracranial focus. In 15 patients, the cultures were purely anaerobic, including micro-aerophilic streptococci. In 5 patients, staphylococci were found, mostly in combination with other microorganisms.

The therapeutic effects of HBO on anaerobic and mixed aerobic/anaerobic flora are well known, and delineated[33-37].

Table 2.2.5-2. Bacterial isolated (own patient series, N = 21): In 15 patients exclusively anaerobic/microaerophilic pathogens, in 9 patients more than one germ isolated

Strictly anaerobic		
Peptostreptococci	6	
Bacteroides spp.	4	53 %
Fusobacteria	2	
Clostridium perfringens	1	
Veillonella	1	
Streptococci (anaerobic)	3	
Intermediate		
Streptococci (microaerophilic)	9	31 %
Enterobacter	1	
Aerobic		
Staphylococci spp.	5	16 %

2.2 Perifocal Brain Edema

The formation of perifocal edema around an intracranial abscess may result in secondary hypoxic lesions in surrounding brain tissues or, at worst, lead to a life-threatening increase in intra-cranial pressure (ICP).

The effects of HBO on perifocal brain edema and elevated ICP have been well documented over the past 40 years[38-45], and has now been shown in a prospective, randomized, controlled clinical trial[46] involving 168 patients with severe closed head injury:

HBO acts directly on autoregulated small blood vessels: elevated arterial oxygen tension results in vasoconstriction leading to a decrease in cerebral blood volume and consequently to a reduction in intracranial volume. The effects are additive to hyperventilation. This in turn results in a reduction of an increased ICP. When compared to normobaric normoxic hyperventilation, HBO has the benefit of overcoming the vasoconstrictive effect on oxygen delivery by virtue of the additional physically dissolved oxygen in plasma: hyperoxygenation is achieved. These combined effects of vasoconstriction and hyperoxygenation may be of major importance in the prevention or treatment of secondary brain injury[47-49].

2.3 Host Defence

The effects of HBO in enhancing leukocyte mediated host defence mechanisms are described elsewhere (see chapters 1.6 and 2.2.4) and therefore are not described in this section.

2.4 Blood-Brain-Barrier

Since intracranial abscesses often demonstrate no or only a slight inflammatory reaction of the meninges, antibiotic penetration may pose a problem due to a functional blood-brain barrier. Interestingly, preliminary results[50] show a reversible opening of the blood-brain-barrier by HBO, leading to an improved penetration of antibiotics through the non-inflamed meninges.

2.5 Antibiotics and Tissue Partial Pressure of Oxygen

Antibiotics, especially aminoglycosides, are oxygen-dependent[51]. Abscesses, particularly anaerobic ones, have low oxygen partial pressures, which add to resistance. HBO is able to increase abscess oxygenation and potentiate the effects of antibiotics.

2.6 Series treated by adjunctive HBO

At present, the authors have reported on 21 sequential patients with intracranial abscesses treated at their intensive care unit with adjunctive HBO from 1983 to 2003 (table 2.2.5-3).

The decision to provide HBO was based on at least one of the following criteria being met:

- multiple abscesses,
- abscess in a deep or dominant location0,
- early abscess stage (without need for surgery),
- poor patient's condition (“high risk“ patient),
- anaerobic or miscellaneous bacteria found.

In severe cases, HBO therapy was provided twice a day; otherwise, we recommend one treatment per day at 2.5ata. The duration of each hyperbaric session was between 60 and 90 minutes. The total number of HBO sessions varied from 4 to 27, with an average of 13.4. Usually the number of treatments depended on the patient's recovery, including neurosurgical evaluation and repeated cranial CT scans. In two cases, the patient's compliance proved to be a problem, so that fewer treatments were given than medically indicated. Nevertheless, a 0.0 % mortality was observed with a complete recovery in 76 % of our patients (table 2.2.5-4).

Table 2.2.5-3. Data and diagnosis, underlying disorders and bacteriological findings in 21 unselected patients with intracranial abscesses (own cases)

No.	Age	Sex	Diagnosis	Underlying Disorder	Bacterial Isolate
1	31	f	multiple abscesses left hemisphere	septic tonsillectomy	*Bacteroides fragilis, peptostreptococci*
2	22	m	epidural empyema	pansinusitis	*Fusobacteria, streptococci* (microaerophilic)
3	34	m	parietal abscess	pulmonary angioma	*Bacteroides fragilis, peptostreptococci, streptococci* (microaerophilic)
4	13	m	frontal abscess	sinusitis frontalis	*streptococci* (microaerophilic)
5	15	f	frontal abscess	pansinusitis	*peptostreptococci*
6	26	m	frontal abscess	sinusitis frontalis	*Veillonella parv., Bacteroides spp.*
7	47	m	parietal abscess	apical ostitis tooth 3/5	*peptostreptococci*
8	36	m	frontal abscess	???	*Staph. epidermidis*
9	27	m	subdural empyema	sinusitis maxillaris	*peptostreptococci* (blood culture)
10	42	f	frontal abscess	progressive osteomyelitis	*Enterobacter, Staph. aureus*
11	48	m	multiple abscesses left hemisphere	sinusitis frontalis	*Staph. epidermidis*, *streptococci* (microaerophilic)
12	52	m	frontal abscess	sinusitis maxillaris?	*streptococci* (anaerobic)
13	21	m	multiple abscesses right hemisphere	pansinusitis	*streptococci* (microaerophilic)
14	5	m	frontal abscess	penetrating injury	*Clostridium perfringens*
15	45	m	subdural empyema	pansinusitis	----
16	47	f	subdural empyema	osteomyelitis femur (?)	*Fusobacteria*, *Staph. Sp.*
17	17	m	epi-/subdural empyema	open skull base fracture	*Staph. epidermidis* *Streptococci* (anaerobic) *Streptococci* (microaerophilic)
18	57	f	subdural empyema	mastoiditis	*Streptococci* (microaerophilic)
19	22	m	subdural empyema	pansinusitis	*Bacteroides sp. Peptostreptococci*
20	4	m	multiple abscesses both hemispheres	pulmonary abscess	*Streptococci* (anaerobic) *Streptococci* (microaerophilic)
21	19	m	multiple abscesses	sinusitis maxillaris	*Streptococci* (microaerophilic)

Table 2.2.5-4. Number of HBO sessions and outcome in 21 patients with intracranial abscesses (own cases)

No.	Age	Sex	HBO'	Outcome	
1	31	f	14	slightly disabled	*
2	22	m	4	complete recovery	*
3	34	m	10	severely disabled (lost follow-up)	
4	13	m	16	complete recovery	*
5	15	f	10	complete recovery	*
6	26	m	10	complete recovery	*
7	47	m	6	brachio-facial hemiparesis (in recovery, lost follow-up)	
8	36	m	27	complete recovery	*
9	27	m	7	moderate motor-dysphasia, minimal brachial hemiparesis (in recovery, lost follow-up)	
10	42	f	19	complete recovery	*
11	48	m	12	complete recovery	*
12	52	m	13	complete recovery	*
13	21	m	12	complete recovery	*
14	5	m	17	complete recovery	*
15	45	m	22	complete recovery	*
16	47	f	16	persistent aphasia	
17	17	m	20	complete recovery	*
18	57	f	7	complete recovery	*
19	22	m	20	complete recovery	*
20	4	m	6	complete recovery	*
21	19	m	14	complete recovery	*

* patients returned to his / her former occupational work or school

Table 2.2.5-5. Mortality rates from intracranial abscesses, managed by adjunctive HBO (time span studied : 1976 - 2003)

Author	Year	Country of Origin	Nb	deaths	Mortality	[Ref.]
Mathieu	2000	France	8	1	12.5 %	[52]
Sutter	1996	Austria	18	0	0.0%	[53]
Kemmer	2001	Germany	10	1	10.0 %	[54]
Kindwall	2001	USA	8	0	0.0 %	[55]
Lampl	2003	Germany	21	0	0.0 %	[56]
			65	**2**	**3.1 %**	

The favourable results of adjunctive HBO have been confirmed by other investigators (table 2.2.5-5). This is especially true for the series by Mathieu from Lille, France, in which the inclusion criterion was deterioration of the

patient's neurological condition, due to the lack of response to conventional therapy[52]. Similarly the Graz team, in Austria, was able to offer a longitudinal perspective in mortality before and after the use of HBO[53]. The unpublished data from Kemmer, Germany[54], also support the findings as do those of Kindwall[55] and a number of individual case reports.

2.7 Utilization Review

As in other life-threatening conditions such as e.g. gas gangrene, it is mandatory in intracranial abscesses to apply HBO only in combination with currently accepted standard procedures[57,58]. Above all, treatment must include appropriate neuro-surgical management (e.g. puncture, drainage, or even resection of the abscess, depending on the individual situation) as well as antibiotics and steroids, and - if needed - standard intensive care treatment in order to stabilize endangered or disturbed vital functions. It has to be emphasized that HBO must not interrupt these intensive care measures, and full intensive care treatment must be continued inside the hyperbaric chamber.

The early administration of HBO is of utmost importance, however. To delay the onset of HBO or to start it as a last-ditch attempt when everything else has failed obscures its true benefit and run the risk of otherwise avoidable and perhaps irreversible secondary brain damage.

Since we consider the infectious component of intracranial abscesses to be of primary importance, we recommend a treatment pressure of 2.5ata, 60 - 90 minutes on oxygen, repeated one or twice daily, depending on the urgency of the situation given. The total number of treatments has to be assessed on an individual basis in accordance to the patient's clinical response and the radiological findings.

2.8 Cost Impact

In view of the high morbidity and mortality of intracranial abscesses, and due to the fact that HBO is a non-invasive method and carries a low rate of adverse effects, the risk-benefit and cost-benefit ratio are compellingly low: the number of treatments required are relatively few, and the costs of HBO are trivial in comparison to the overall costs of managing these critically ill or otherwise potentially chronically disabled patients.

3. CONCLUSION

The patient series listed in tables 1 and 5 were treated conventionally or by adjuvant HBO during similar time spans. As such, they are a fair basis for comparison.

Taking mortality as the criterion, and applying the one-sample test for binomial proportion (normal theory method), the results are significantly superior ($p < 0.01$) when HBO is applied as an adjunctive component to the otherwise standard therapeutic principles of ICA-management.

Based upon all these results, HBO has been approved by the Undersea and Hyperbaric Medical Society as well as by the ECHM in its last 2004 Consensus Conference for the treatment of intracranial abscesses under the following conditions:

- multiple abscesses, distributed all over one or both hemispheres,
- abscess in a deep or dominant location, where surgery would result in additional irreversible damage to neuronal structures of vital importance,
- immune compromised host (e.g. postoperative, post-traumatic or septic patients),
- situations where surgery is contraindicated or
- where the patient is of poor surgical risk,
- where there is no response or even deterioration in spite of standard surgical and antibiotic treatment procedures.

HBO as an adjunct therapy in ICA management is so effective that the next step should be a large multi-centre trial, comparable to a phase three study in pharmacology.

The full benefit of an HBO-based protocol is expected to become even more significant once additional study criteria, such as epileptic seizures and outcome measures such as the ability to return to work are properly documented in addition to the surveillance of the mortality rates.

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Chapter 2.2.6

CRUSH INJURY AND OTHER ACUTE TRAUMATIC ISCHEMIA

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Abstract: Crush injury and other acute traumatic ischemia are characterized by a vicious circle of ischemia, hypoxia, oedema, disturbed microcirculation, and secondary ischemia in the border area of the tissue affected by the primary trauma. In hypoxic tissues mechanisms of infection control and healing are impaired so that the risk of infection and wound healing problems are definitely higher than after other kinds of injuries. Restoration of perfusion can lead to reperfusion injury. Hyperbaric oxygen ameliorates the effects of acute traumatic ischemia through four mechanisms: hyperoxygenation, vasoconstriction, influence on reperfusion and host factors. Besides adequate shock management, direct surgical intervention with debridement and repair of soft tissues and of any damaged vessels and stabilization of bony elements are of paramount importance. Adjuvant hyperbaric oxygen therapy (HBOT) should be administered as soon as possible; when it is given early it can prevent large expanses of ischemic necrosis, minimize the frequency and extent of amputations, reduce oedema, control infection, support healing, and prevent reperfusion injury. However, an early start of HBOT and an uncompromising application without restrictions to established surgical treatment and intensive care therapy is essential

Keywords: Hyperbaric oxygen; Crush injury; Traumatic ischemia; Wound healing; Oedema

1. INTRODUCTION

Severe trauma to the body, like fractures, soft tissue trauma, burns, but even complex surgical interventions may lead to acute traumatic ischemia of tissues. The compromise of the circulation to tissues can result either from injury to major blood vessels, as in open fractures with interruption of

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 305–327.

arteries or at the microcirculation level can be caused by oedema, as in severe crush injuries, muscle compartment syndromes or burns. The consequence is insufficient oxygen availability for tissues to meet their metabolic needs. Cell dysfunction and sometimes cell death are the consequences. Furthermore tissue hypoxia in these cases leads to a self-perpetuating process such that a gradient of injury continues even after primary surgical management. The risk of necrosis or amputation and secondary complications such as infection, non healing wounds and non-union of fractures frequently develop.

Desired Outcomes in crush injury management:

- Reduced tissue loss
- Reduced complications as:
  - Functional loss and scarring
  - Infection
  - Non union
  - Chronic pain
- Accelerated rehabilitation
- Reduced operations
- Reduced length of stay and lower costs

The rationale for using hyperbaric oxygen therapy (HBO) in acute traumatic ischemia is based on the direct influence on the pathophysiology of these injuries by hyperbaric oxygen (HBO). The role of HBO in the adjunctive treatment of crush injury and other acute traumatic ischemias has been proven by a large number of experimental studies and growing clinical experience. HBO is accepted as an adjuvant treatment modality by UHMS[1] and EUBS. In this chapter the main emphasis will be given to crush injury and compartment syndrome. Compromised flaps, burns and replantation will be discussed in chapter 2.2.7.

2. PATHOPYSIOLOGY OF ACUTE TRAUMATIC ISCHEMIA

2.1 Compartment syndrome

Compartment syndrome is defined as “a condition in which increased pressure within a limited space compromises the circulation and function of the tissues within that space”[2]. It is most commonly seen after crush injuries of the limbs, but may also occur in abdominal trauma. It typically follows traumatic injury, but is also seen after ischemic reperfusion injuries, burns and prolonged limb compression due to poor positioning of the limb, as in

toxic coma. Surgical interventions as bone nailing may increase oedema formation and devascularisation, leading to compartment syndrome.

2.1.1 Diagnosis of compartment syndrome

An important element in the diagnosis of compartment syndrome is the history of injury, which generally focuses on a mechanism of massive crush trauma. The physical examination must emphasize:

1. Pain out of proportion to the injury
2. Pallor of the extremity
3. Paralysis
4. Paresthesia (early loss of vibratory sensation)
5. Pulseslessness
6. Progression of symptom

Progression of symptoms and objective findings on repeated examination at hourly intervals confirm the diagnosis of compartment syndrome. Particularly important findings are continued severe pain that is unresponsive to usual analgesics, increased paraesthesia and hypaesthesia, and increased pain on attempted passive stretch testing of the involved muscles.

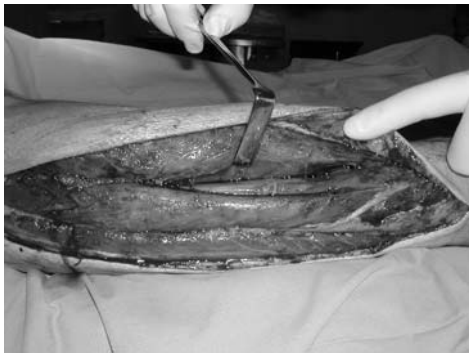

Figure 2.2.6-1. Lower limb compartment syndrome - Fasciotomy

A model to explain the development of compartment syndrome premises that ischemia begins when local blood flow cannot meet the metabolic demands of the tissue. The rise in intracompartmental pressure is due to oedema or haemorrhage from soft tissue injury or fracture. As volume increases, venous return becomes hindered but large arterial vessel flow is relatively unaffected. As the intracompartmental pressure rises, the intraluminal venous pressures also increases leading to a reduction in the arteriovenous pressure gradient with subsequent diminished or absent local

perfusion. The resulting reduction in venous drainage causes a further rise in interstitial tissue pressure with the formation of tissue oedema. It is only in the late stages of a compartment syndrome that the arterial flow into the compartment is seriously compromised. The continuing flow of blood into the compartment augments the swelling and oedema throughout the early stages of the syndrome. Both the magnitude and the duration of increased tissue pressure adversely affect the perfusion of the compartment. As normal perfusion pressure of capillaries is in a range of 30–35 mmHg, the critical compartment pressure seems to be 30 mm Hg or higher, for duration of six hours or longer. There is still no conclusive answer as to the critical threshold of intracompartmental pressure at which fasciotomy should be performed. The comparison of diastolic blood pressure and compartment pressure is a relative indicator of tissue perfusion. If there is a fracture, compartment pressure measurements should be taken as close to the fracture site as possible and in multiple locations. Compartment measurements within 30 mmHg of diastolic pressure are commonly seen as an indication for fasciotomy.

Since the pressure is not a direct measure of tissue damage and there is considerable variation among individuals as to their tolerance to a given pressure, it may not be possible to define the critical level more satisfactorily nor to establish the duration of raised intracompartmental pressure which results in an acute syndrome. According to Tscherne[3], the more severe the initial soft-tissue injury, the greater the probability is that soft-tissue complications, including compartment syndrome, will develop. Monitoring of the intracompartmental pressure should be routine, in patients in whom subjective clinical assessment is not available, i.e. in unconscious or uncooperative patients, and in those under the age of 35 years with injuries to the lower leg[4]. Close observation is required until the acute swelling begins to subside.

2.1.2 Therapy

Primary therapy of the compartment syndrome is fasciotomy. Fasciotomies must be extensive enough to completely relieve the constrained internal pressure, and therefore must extend into normal tissues proximally. In III° degree burns, escharotomy alone is usually insufficient and fasciotomy also must be performed. Physiologic skin incisions are performed with care to avoid damage to deeper structures (ulnar nerve at the elbow, median and ulnar nerves at the wrist, digital nerves in the fingers) and to prevent unnecessary secondary scar contractures.

The well known effects of HBO generate a favourable gradient from functioning capillaries to compromised cells with an increment in oxygen

supply. This may allow compromised tissue to survive. Inhibition of oedema is the second fundamental effect of HBO in early adjunctive treatment of compartment syndrome.

2.2 Crush injury

Crush injuries occur when a part of the body is subjected to a high degree of energy or pressure. It happens usually after being hit by a heavy object or being squeezed between two objects. The greater the energy involved the more severe the tissue damage.

Definition of Crush Injury:

- Two or more tissues (muscle, bone, skin, nerve) involved
- Injury severe enough that tissue survival is questionable
- If tissue recovers, functional deficits are likely
- Gradient of injury from minimal to irreversible with a partial viable grey zone between the two

Crush injury involves severe trauma to two or more tissues as bone, soft tissue, nerve, and vascular structures. Damage includes: laceration (open wound), fracture, bleeding, bruising, compartment syndrome, and others.

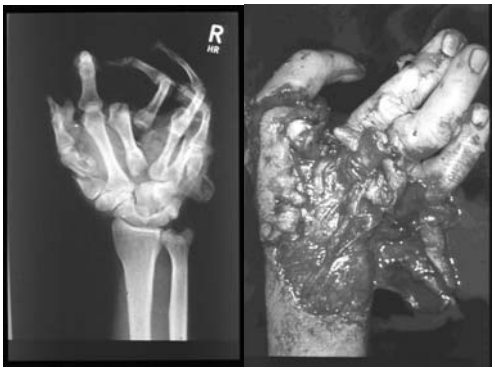

Figure 2.2.6-2. Severe crush injury of the hand

There is a gradient of injury from minimal to irreversible with a grey zone of partial viable tissue between the two. When crush injuries are severe, the rate of complications including infection, non-healing of fractures and tissue range up to 50 to 60 percent with a high amputation-rate. The main target of the therapy is to take measures to help the partial viable tissue to recover and to prevent further generalized tissue damage.

The immediate threat to the tissue after crush injury is whether perfusion is sufficient to maintain oxygenation and viability of tissues. Blood flow is

most important to tissue viability. A decreased blood flow and thrombosis of micro vessels compromise tissue perfusion and cause tissue hypoxia. Cellular hypoxia disturbs the cellular metabolism. Hypoxic cells are unable to resist bacteria and loose their water content because of insufficient energy production needed for active transport mechanisms in the cell membrane. Leakage of intracellular fluid to the extracellular space and extravasation of plasma from ruptured blood and lymph vessels promote oedema formation. Posttraumatic oedema contributes to reduced microcirculation and ischemia of the partially viable tissue. Oxygen availability to tissues is further reduced.

Massive posttraumatic oedema has detrimental effects on wound healing and infection control in the traumatised tissue. The diffusion distance from the capillary to the cell is increased, reducing furthermore the oxygen availability to cells that already have increased oxygen needs. Oxygen diffusion decreases by an approximately three-fold factor as the diffusion distance is increased. Furthermore oedema leads to collapse of capillaries because of increasing interstitial pressure around the capillaries from the oedema fluid (see compartment syndrome).

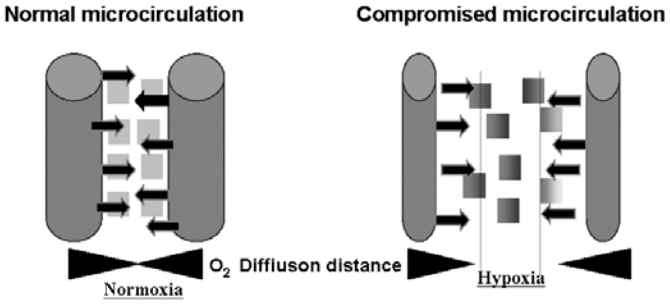

Figure 2.2.6-3. Effect of oedema on oxygenation of cells

In situation with severe oedema oxygen supply is maintained only by physically dissolved oxygen in plasma. Usually this fraction of oxygen under normobaric conditions is insufficient for tissue needs. HBO allows oxygenation of cells only by high levels of physically dissolved oxygen in plasma even when the red cell blood flow is disturbed

Crush injuries are characterized by a vicious circle of ischemia, hypoxia, oedema, disturbed microcirculation, and secondary ischemia in the border area of the tissue affected by primary trauma. Hypoxia plays a central role in this vicious circle. Is it possible to interrupt this circle, partially viable tissue may recover; otherwise there will be a loss of function due to cell death.

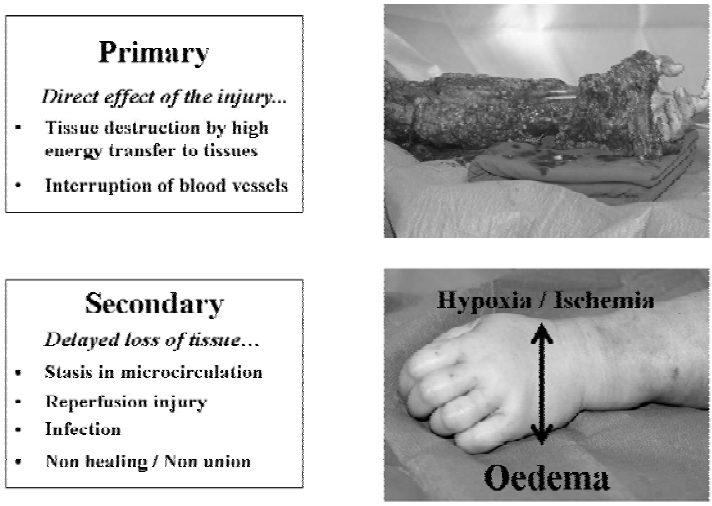

Figure 2.2.6-4. Causes of tissue destruction in crush injury. Self perpetuating circle where hypoxia plays the main role

In the initial phase of tissue repair and infection control the metabolic needs of tissues increase by a factor of twenty or more[5]. The host responses to infection and ischemia are compromised when tissue oxygen tension falls below 30 mmHg. Specifically white blood cell killing becomes defective or nonexistent and host repair processes such as fibroblast secretion of collagen are arrested[6]. Without a collagen matrix in the wound, neovascularization and wound healing cannot occur. Thus hypoxic tissues lose the ability to resist infections and their self-healing possibilities.

2.2.1 Classification of crush injuries

The most widely used classification system for crush injuries is Gustilo's[7] classification of open fractures (see Table 2.2.6-1). It should be used as a reference comparing treatment interventions with the severity of injury and to give prognostic indications. In the most severe grades III B and III C the complication rates reach 50% with standard surgical interventions as described below.

In 1996 the 3rd Consensus Conference of the European Committee for Hyperbaric Medicine in Milano[8] recommended a combination of Gustilo´s classification with a host scoring (Strauss[9], see table 2.2.6-2) as objective criteria for using HBO as an adjunct in the treatment of crush injuries. For the uncompromised host, HBO is recommended for all Gustilo Grade III B

and III C fractures. In the compromised host the indication for using adjunctive HBO should start at Grade II (see Table 2.2.6-1.).

Table 2.2.6-1. Gustilo Classification and HBO Indication for Crush Injuries

Type	Mechanism	Expected outcome	Infection rate	Amputation rate
I	Small laceration < 1 cm	Usually not different from a closed fracture	minimal	
II	Large laceration, but minimal soft tissue damage	Usually not different from a closed fracture	3%	
III	Crush injuries:			
A	Sufficient soft tissue to close wound (primary or delayed)	Complication rate < 10%	4%	0%
B	Flaps or grafts required to cover bone	> 50% incidence of complications	52%	16%
C	Major vessel injury	About 50% incidence of complications	42%	42%

These recommendations correspond to the UHMS committee report[1] which states that when ever HBO is used for acute traumatic ischemia the injury should be classified by a Standard Classification Method such as the Gustilo Grading System or the Mangled Extremity Severety Score (MESS).

Table 2.2.6-2. Criteria for using HBO as an adjunct in the treatment of crush injuries

Type	HBO Indication
I	None
II	Only in compromised hosts, such as diabetics, advanced peripheral vascular disease, collagen vascular disease, etc., concern about primary healing of flaps
III A	See Type II fractures
III B	All injuries
III C	All injuries

Table 2.2.6-3. Evaluation of host status (Strauss[10])

Factors	Scoring criteria		
	2 Points	1 Point	0 Point
Age	< 40 years	40-60 years	> 60 years
Ambulation	Community	Household	None
Smoking/Steroid Medication	None	> 5 years ago	Current
Cardial/Renal	Normal	Compensated with medication	Decompensated even under medication
Neuropathy/Deformity	None	Mild to moderate	Severe

Comments

1. Use ½ points when severity of involvement is between two scoring criteria
2. For ambulation scoring criteria subtract ½ point if walking aids are required
3. When two factors are listed, use the scoring criteria which reflects the more severe involvement

Score	Severity of compromise
8-10	Normal host
4-7	Impaired host
3 or less	Severely compromised host

The mangled extremity severity score (MESS) is an other classification system originally used to select which severely injured extremity should undergo primary amputation. It can offer objective criteria for the use of HBO as adjunct treatment in crush injuries[11].

2.2.2 Treatment

Crush injuries must be diagnosed without delay and treated aggressively to prevent or minimize irreversible damage not only to the injured tissue. Multidisciplinary treatment by emergency physicians and surgeons as well as intensivists is mandatory. Even under best conditions the risk of complications is high with a need of reoperation in more than 50% of severe injuries. Many of those patients end up with poor outcome.

In the treatment of crush injuries, priority should be given to the restoration of circulation. In limb trauma with large vessel damage, vascular reconstructive surgery has to be considered immediately. The survival of the limb may depend on anatomical reconstruction of damaged vessels and on the time period between injury and repair. Sufficient blood supply to traumatized tissues is mandatory to avoid secondary complications. Ischemia is the primary cause of tissue hypoxia in acute traumatic ischemias.

Haemodynamics must be stabilized mainly by correcting hypovolaemia and blood loss.

Primary surgical treatment of crush injuries consists of meticulous cleansing to the depths of the open wounds. Debridement of all nonviable tissue and foreign material is mandatory, but marginally viable tissue should be retained and protected. Debridement to clean-bleeding, normal-appearing bone, eliminating foreign material regardless of the skeletal defect created is important.

Bacterial colonisation is common especially in open fractures. Hypoxia favourites bacterial grow in two ways:

- The reduction of local oxygen partial pressure in wounds reduces the neutrophil phagocytic activity. The rate of free radical production and hence the oxidative bacteria killing depends mainly on local oxygen tension.
- Anaerobic bacterial grow is increased in hypoxic tissue.

Calculated antibiotic treatment in open fractures therefore has to be carried out immediately. HBO has a direct bactericidal effect mainly to anaerobic bacteria. A bacteriostatic effect on Escherichia coli, Staphylococcus and Pseudomonas species is reported with even synergistic effects when combined with certain antibiotics[12].

The next therapeutic step is the reestablishment of skeletal stability, by external fixation. Plate fixation or nail fixation is usually postponed to second step interventions. Temporary physiologic resurfacing by an allograft (artificial skin) or a vacuum sealing may be helpful, particularly with large, contaminated defects. Primary tendon or nerve repairs are contraindicated in the majority of crush injuries. At one- to three-day intervals, dressings are changed and, if open treatment was used initially, redebridement of the wound is carried out until only viable healthy tissue remains

HBO should be considered as an important adjunct in this early management of severe crush injuries to reduce oedema formation and increase tissue oxygen tensions in hypoxic tissues to levels which make it possible for the host responses to become functional.

The recommended treatment schedule is three treatments at a pressure of 240 kPa for 90 minutes of oxygen therapy at pressure within the first 24 hours of treatment, followed by twice daily HBO for three days (i.e. a total of 7 treatments). After the acute phase of the first three days therapy should be continued for at least five days or longer if clinical judgement suggests that HBO treatment should continue (for instance because of infection, delayed wound healing or ischemic complications of flap repair surgery).

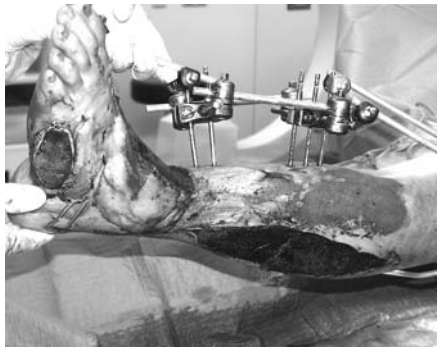

Figure 2.2.6-5. Typical crush injury after primary surgical debridement and stabilisation with fixateur externe

Bone reconstruction is undertaken only after oedema has subsided. Ideally, delayed primary wound closure or resurfacing by split-thickness skin graft is performed four days to one week after initial treatment if the wound remains clean and shows no evidence of contamination, infection or further necrosis. HBO can help to shorten this time interval.

2.3 Reperfusion injury

Restarting blood flow after more than about ten minutes of ischemia (depending on the kind of tissue) is typically more damaging than the ischemia itself because the ischemia sets the stage for oxygen to generate free-radicals rather than contribute to cellular energy production. Membrane damage is the most important consequence.

For reperfusion, the focus of membrane damage is more on endothelial cells as well as platelets, leucocytes and other cells in the blood stream. Where as ischemic damage is focused more on organ tissue. Even if the physicochemical causes of ischemia reperfusion are still under investigation it seems that Eicosanoids generated by arachidonic acid (especially leukotrienes) greatly increase the adhesion of leukocytes & platelets to capillary walls, plugging them up. Superoxide also increases the adhesion of leucocytes to vessel walls. Eicosanoids and associated oxygen free-radicals make capillary walls more "leaky", causing oedema with the consequence of a vicious circle of hypoxia and oedema. In reperfusion these effects quickly become pronounced enough to block capillaries entirely resulting in the no reflow phenomenon (*see chapter 1.7*)

2.4 Rationale for use of hyperbaric oxygen in acute traumatic ischemia

Clinical and experimental evidence indicates, that HBO therapy used as an adjunct for management of acute traumatic ischemia may improve outcome. The appreciation of the potential applications in management of trauma cases requires an understanding of the mechanisms of potential action and of oxygen effects on various types of tissues.

The immediate effect of HBO therapy is hyperoxygenation. The effects of HBO therapy result from the increased amount of physically dissolved oxygen in plasma under hyperbaric conditions. Oxygen dissolves in plasma in direct proportion to the partial pressure of oxygen in the inspired gas. Oxygen is thus delivered to all perfused tissues of the body via systemic circulation. Under HBO treatment this supplement of the oxygen-carrying mechanism of haemoglobin becomes most important when stasis of cellular elements restricts red blood cell flow through the microcirculation.

In most cases trauma patients are treated at a pressure of 240 to 280 kPa. A patient breathing 100% oxygen at that pressure is exposed to pO_2 of approx. 1600 mmHg. This increase of partial pressure of oxygen supports gas diffusion for a much greater distance than under normobaric conditions. Thus hyperbaric oxygen allows oxygenation of tissues even when the blood flow is disturbed.

A considerable elevation of the arterial pO_2 provides protection against the vicious circle created by ischemia, hypoxia and oedema. The oedema reducing effect of hyperbaric oxygen was demonstrated in limb muscle after 3 hours of ischemia[13]. In the same model Nylander et al[14] showed, that repeated hyperbaric oxygen in the early postischemic phase stimulated the aerobic metabolism resulting in higher levels of adenosine triphosphate (ATP) and phosphocreatinine and lower lactate levels than in untreated ischemic animals. Haapaniemi[15] from the same working group found that repeated hyperbaric oxygen treatment had positive effects for at least 48 hours after severe ischemic injury. HBO erased the levels of high energy phosphate compounds, indicating stimulation of aerobic oxidation in the mitochondria. They found a diminished degree of skeletal muscle injury 48 hours after the ischemic insult which was explained by restoration of energy content, maintaining the transport of ions and molecules across the cell membrane and optimizing the possibilities of preserving the muscle cell structure.

Sufficient oxygen becomes dissolved in plasma while breathing pure oxygen at 240 kPa to meet almost normal tissue oxygen requirements. Under these conditions compromised tissues can stay alive without haemoglobin bound oxygen only by oxygen dissolved in plasma. This effect is important

when microcirculation is compromised by stasis of cellular elements restricting red blood cell flow. Oxygenation of the tissues is restored by high levels of plasma dissolved oxygen. (Ten fold increment at 240 kPa).

The consequence of this systemic hyperoxygenation is a threefold increase of diffusion distance of oxygen through the tissues. Thus even cells suffering from ischemia (as result of impairment of the microcirculation) are able to survive. This anti-ischemic effect can prevent further evolution towards tissue necrosis.

Injured but viable cells in the penumbra have increased oxygen needs. At a time when oxygen delivery is decreased by impairment of the microcirculation survival of the cells is directly dependant on oxygen tension. However hyperbaric oxygen therapy can help ischemic tissue to survive only if an effective arterial flow persists in order that oxygen transport to the cells is maintained.

Tissue hypoxia caused by decreased blood flow and thrombosis of microvessels leads to undesirable swelling. If severe oedema occurs the diffusion distance of oxygen from the vessels to the injured area is increased. Both cytogenic and vasogenic oedema results in increased interstitial pressure. Retarded venous outflow along with continued or even increased arterial inflow causes further fluid transudation at the capillary level. Even vessels that are not directly damaged may alter their permeability and contribute to oedema formation and further ischemia. As a result of this secondary injury, tissues completely remote and unaffected by the primary injury are at risk of necrosis.

Compartment syndrome is the classic example of this pathologic process of secondary injury. HBO induces vasoconstriction in hyperoxygenated tissues that reduces blood flow by 20%, leading to oedema reduction[16]. This effect would seem to be undesirable especially in relative ischemic tissue, but the high oxygen content of the blood flow more than compensates for any blood flow reduction. Since resorption of extracellular fluid continues the net-effect is oedema reduction and improved oxygenation of tissues.

The vasoconstricting effect seems to be induced by direct action of the increased pO_2 in blood vessel walls[17]. In an animal model hyperbaric oxygen reduced the formation of the oedema by approximately 20% in injured muscle tissue[18]. The anti-oedematic effect explains the efficacy of HBO in compartment syndrome. The oedema reduction in treating compartment syndrome is only effective when HBO therapy is started early. This explains the importance of the time factor in starting HBO therapy after crush injuries.

2.5 Literature review

The rationale for using HBO in acute traumatic ischemia is to increases tissue oxygen tensions in hypoxic tissues to levels which make it possible for the host responses to become functional. With HB0 at 240 kPa the haemoglobin-borne oxygen content is increased only from 19,8 ml of oxygen per dl blood to 20,4 ml O_2, whereas plasma and tissue oxygen tensions increase tenfold. The resulting effect is that oxygen diffusion distance from capillaries is increased by a threefold factor (Krogh[19]). Sufficient oxygen becomes physically dissolved in plasma to keep tissues alive despite inadequate haemoglobin-borne oxygen delivery[20,21]. Oedema reduction secondary to vasoconstriction is the second important effect of hyperbaric oxygenation. The benefit of this vasoconstriction that occurs only in non-hypoxic tissue is a 20% reduction in posttraumatic vasogenic oedema and an improvement in microcirculation[22]. HBO maintains oxygen delivery while the blood flow that contributes to oedema formation is reduced.

HBO may reduce the effects of reperfusion injury in acute traumatic ischemias, especially in those injuries where tissue ischemia is severe and prolonged. HBO prevents sequestration of neutrophils on the endothelial wall, lipid peroxidation of cell membranes, and it provides sufficient additional oxygen for reperfused tissue to generate oxygen radical scavengers (Thom[23,24], Zamboni[25]).

In summary, the immediate effects of HBO in acute traumatic ischemias are fourfold:

- Increased oxygen delivery per unit of blood flow
- Enhanced oxygen tension at the tissue level
- Oedema reduction
- Protection from reperfusion injury

Clinical experience with HBOT in acute traumatic ischemia is growing within the last years. But still there are only two randomised controlled trials of crush injury management assessing effects of HBO (Lindstrom[26], Bouachour[27]). Most clinical reports describe the benefits of HBO in a very subjective way as „helpful“, or state that amputation could have been avoided by the use of HBO. In this context it must be admitted that randomised clinical trials are difficult to perform due to the complexity and diversity of trauma injuries.

Strauss in 1981 did review the international literature on HBO in crush injuries[28]. 93 cases using HBO were reported in the English speaking literature, none were controlled studies. They all showed benefits from HBO for traumatic ischemias. Most of the clinical reports were case reports with limited numbers of patients, except the Russian and Eastern Europe reports. The reports of 634 cases from the Eastern European literature included

benefits as "positive effects on local reparatory processes," "reduction of tissue damage," "accelerated recovery of neutrophil phagocytic activity," "accelerated diminution in oedema," and "healing without suppuration". The review showed that the more frequent the HBO treatments, the greater the likelihood of success.

Shupak et al in 1987 reported that in 75% of the patients who were at risk of limb amputation after acute ischemic injury, the limb was solved using adjunctive HBO[29]. Only one patient out of 13 did not benefit from HBO. Similar reports come from Radonic[30] who treated lower limb trauma associated with popliteal vessel damage using adjuvant HBO.

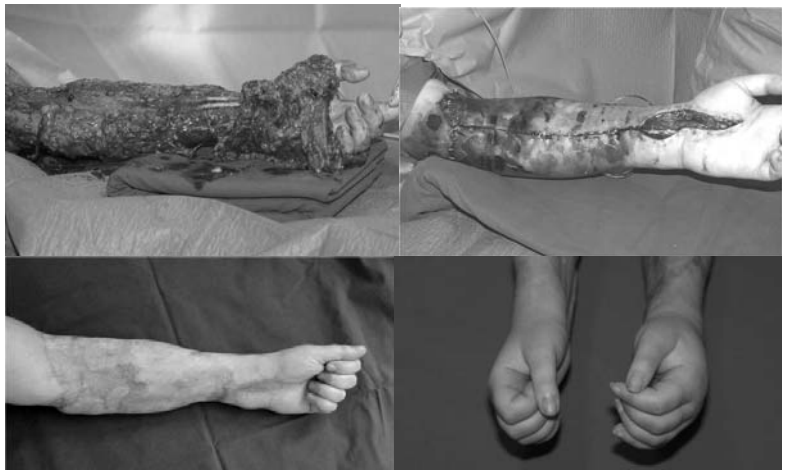

Figure 2.2.6-6. Severe crush injury of the arm; therapeutic progress under HBO therapy:
a: day of accident;
b: day 7, after 11 HBO treatments;
c, d: functional outcome after 2 years; 20 hyperbaric oxygen treatments in total

In 1996 Bouachour et al. published a randomized double-blinded, placebo-controlled study of the effect of HBO therapy in the management of severe crush injuries[27].

Thirty-six patients with Gustilo Grade 2 or 3 crush injuries were assigned in a blinded, randomised way to receive HBO therapy or placebo within 24 hours of surgery and subsequently twice daily over 6 days. 17 patients (94%) in the HBO group versus 10 (59%) in the placebo group achieved complete healing ($p<0.01$). None of the 18 patients treated with HBO required amputation, but two of the control patients did. Further surgery was required in 1 of the HBO group (6%) versus 6 (33%) in the placebo group ($p<0.05$). Fracture healing in patients over 40 years of age was significantly improved with HBO ($p<0.05$). The authors found transcutaneous oxygen

measurements significantly improved in the HBO group as compared to the control group. They found transcutaneous measurements a valuable discriminator for wounds that healed completely versus those that progressed to tissue necrosis. In patients with complete healing, $tcpO_2$ values on air rose from 21,6 ± 5,7 mmHg to 90 ± 20 mmHg over a series of 12 HBO treatments, no significant increase in $tcpO_2$was seen after 12 sham treatments.

This study has been welcomed as providing randomised controlled trial based evidence both of the efficacy of HBO therapy in severe limb injury and the importance of transcutaneous oxygen values as an objective predictor for wound healing during hyperbaric oxygen therapy.

33 consecutives patients with Grade III crush injuries were treated with adjuvant HBO at the University of Miami/Jackson Memorial Medical Centre from 1999 to 2002 by Matos et al.[31]. The patients' injuries were categorized according to the Gustilo´s classification: Grade IIIA[7], Grade IIIB[23] and Grade IIIC[3]. The HBO was delivered in a multiplace chamber at 240 kPa for 90 minutes on 100% oxygen on a BID and QD schedule. HBO was discontinued with the development of a healthy granulation bed or resolution of ischemic changes in tissues. All patients received initial surgical management within 24 hrs. 88%[29-33] of the patients had a successful outcome with preservation and good functional recovery of the threatened limbs. The average time from injury to initiation of hyperbaric oxygen treatments was 48 hours and a mean of 15 HBO was performed. Only 48% of the patients required reconstructive procedures (14 STSG and 2 free flaps) to address the soft tissue defect. All four failures underwent amputations (2 transmetatarsal, 2 transtibial). Incidence of soft tissue infection was minimized and osteomyelitis prevented in all cases.

Our own experience is reported in a prospective non randomised study on 88 patients with crush injuries and severe open fractures of the upper and lower extremity, Gustilo grade IIIB and IIIC[32]. In order to compare the results with former studies the patients were divided into four groups:

- Up to 40 years (Gustilo grade IIIB 25 patients, Gustilo grade IIIC 20 patients),
- over 40 years old (Gustilo grade IIIB 21 patients, Gustilo grade IIIC 22 patients).

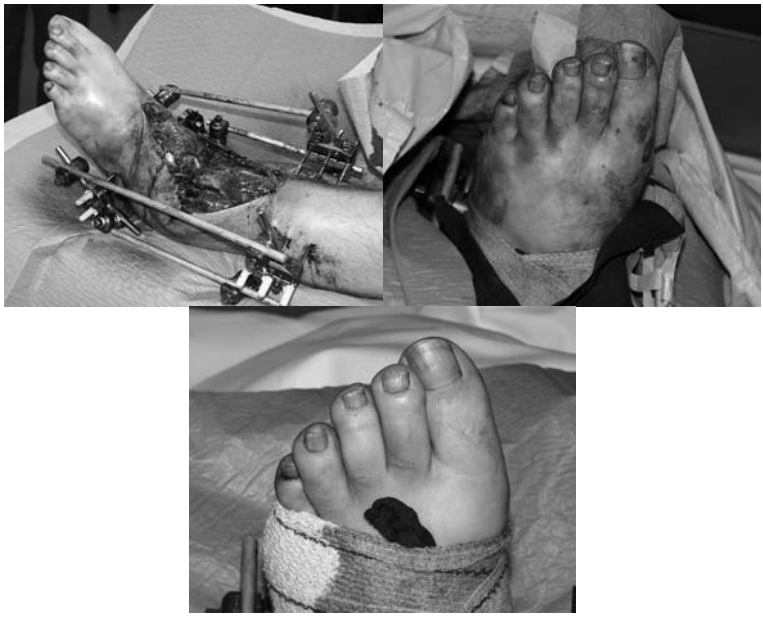

Figure 2.2.6-7a-c. Severe crush injury with replantation of the foot. Reduction of oedema and restoration of microcirculation after 48 hours

Patients' ages raged from 11 to 70 years. Open fractures of the tibia and crush injuries of the hand were most common. Stabilization was mostly done by external fixation. The number of HBO treatments ranged from 2 to 42 sessions (mean 11.7). More than half of the patients were under artificial ventilation when referred to the hyperbaric unit.

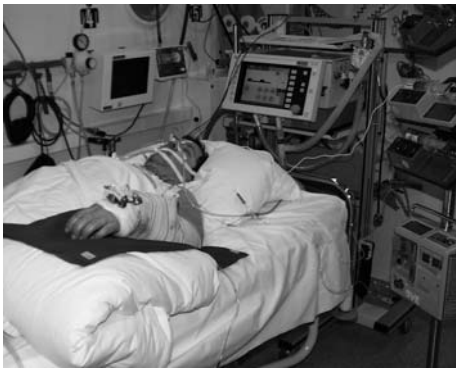

Figure 2.2.6-8. Immediate HBO therapy after primary surgery. Patient under Intensive Care

Even there was no placebo group in this study, the results of an adjuvant HBOT show an excellent outcome. In the upper limb trauma subgroup there was a significant loss of function (ability to work) in only 21 patients, 18 patients kept mild impairments. Major amputations (fingers I/II, hand or lower leg) had to be performed in 8 patients, minor amputations (finger III/IV/V) in 9 patients. All secondary amputations had to be performed in patients with grade IIIC injuries, mostly after primary replantation of an amputated limb or due to chronic infection.

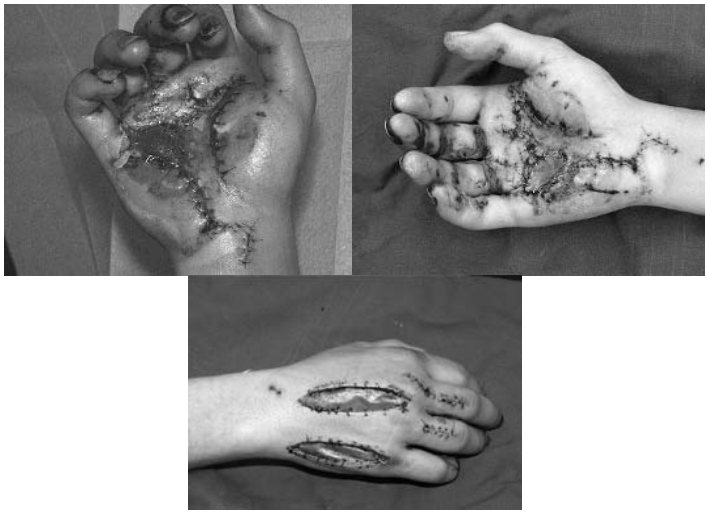

Figure 2.2.6-9.Case report: Severe explosion injury. Significant reduction of oedema after 15 HBO therapies. Functional outcome without loss of function

In upper extremity injuries the number of severe complications, mainly infections was much lower than in lower extremities. The total infection rate was 31,8% (group c,d,e). The infection rate of grade IIIB injuries was 23,9%, of grade IIIC injuries 40,5%. The rate of severe clinical infections (chronic, repeated debridement and prolonged antibiotic therapy necessary) was 10,2% in total (group d,e).

Table 2.2.6-4. Infection Rate

Infections:	< 40 y		> 40 y		
	IIIB	IIIC	IIIB	IIIC	total
a. no bacterial growth	12	4	11	7	34
b. detection of bacteria	7	6	5	8	26
c. mild local infection	4	6	5	4	19
d. severe local infection	2	4	0	1	7
e. chronic infection	0	0	0	2	2

In contrast to Bouachour et al. there was no difference in the complication rates and outcome of patients up to 40 years and older than 40 years.

Recent advances in orthopaedic, vascular and plastic surgical management including HBO have seen a move towards attempting limb salvage where amputation would previously have been performed. However significant debate exists regarding criteria for early amputation versus limb salvage. HBO could be helpful in distinguishing viable from non viable tissue in those cases.

Table 2.2.6-5. Limiting Factors for HBO therapy in acute traumatic ischemia

• Lack of trauma management experience in HBO Centre • Lack of Intensiv Care experience in HBO Centre
• Patient instability • Risk of transport to Hyperbaric Centre
• Logistic difficulties – Few Hyperbaric Centres at Trauma Centres – Chamber remote from ICU/trauma ward – Many patients can't be moved from bed – Time conflict
• Lack of referrals – Lack of acceptance by trauma community – Financial aspects

Further randomised controlled clinical studies are required to explore the potential benefit of HBO in acute traumatic ischemia. Of particular interest would be long term outcome data for both the injury and the patient in functional terms. The design of the HOLLT study[33], a multi-centre randomized controlled trial of HBO versus non HBO as an adjunct to the normal trauma care will use severe lower limb fractures as the form of crush injury to study the adjunctive short- and long-term effects of HBO.

2.6 Criteria for using HBO in acute traumatic ischemia

The jury of the 7th ECHM Consensus Conference organised by the European Committee for Hyperbaric Medicine (ECHM) issued recommendations on the use of HBO treating crush injury and other acute traumatic ischemia. They used a 3 grade scale according to the strength each recommendation has been evaluated:

Type 1 : Strongly Recommended. The jury considers the implementation of the recommendation of critical importance for final outcome of the patient.
Type 2 : Recommended. The jury considers the implementation of the recommendation as positively affecting final outcome of the patient.
Type 3 : Optional. The jury considers the implementation of the recommendation as an option.

The jury also reported the level of evidence which supports, in its view, the recommendation.

Level A : Recommendation supported by level 1 evidence
Level B : Recommendation supported by level 2 evidence
Level C : Recommendation supported only by level 3 evidence

Following these principles the jury came to the following recommendations regarding acute soft tissue ischemia:

- HBO_2 is recommended in post traumatic crush injury following open fracture Gustilo type III B and C (Type 1 recommendation, level B)
- HBO_2 is optional in reperfusion syndromes following invasive vascular procedure (Type 3 recommendation, level C)
- HBO_2 is recommended in compromised skin grafts and myo-cutaneous flaps (Type 2 recommendation, level C)
- HBO_2 is optional in the replantation of traumatically amputated limb segment (Type 3 recommendation, level C)
- In every case, the measurement of transcutaneous oxygen pressure is recommended as an index for the definition of the indication and of the evolution of treatment (Type 1 recommendation, level B)

2.7 Treatment protocol

The recommended treatment schedule is three treatments at a pressure of 220-280 kPa for 90 minutes of oxygen therapy at pressure within the first 24 hours of treatment, followed by twice daily HBO for three days (i.e. a total of 7 treatments). After the acute phase of the first three days therapy should be continued for at least five days or longer if clinical judgement suggests that HBO treatment should continue (for instance because of infection, delayed wound healing or ischemic complications of flap repair surgery).

It is most important to begin with adjuvant HBO therapy as soon as possible after the trauma, because the majority of damage to microcirculation from ischemia occurs within the first four to six hours of reperfusion. It is important to understand that not only primary ischemia time is crucial, but even time from reperfusion to HBO treatment.

The treatment regime in our institution therefore warrants an immediate start of HBO treatment after the first surgical debridement. Patients are kept under anaesthesia at least during this first HBO treatment and only extubated – according to their clinical situation– after their return to the ICU. We are placing myringotomy tubes in those patients prophylactically to avoid problems with ear clearing. During the following days these patients sometimes have to be treated after surgical interventions when they are still drowsy from anaesthesia. Position of the myringotomy tubes has to be controlled daily.

3. CONCLUSION

HBO therapy should be considered as an important adjunct in the management of severe crush injuries. Besides adequate shock management and direct surgical intervention with debridement and repair of soft tissues, damaged vessels and stabilization of bony elements, supplemented by antibiotic and antithrombotic therapy, HBO therapy should be administered as soon as possible. Hyperbaric oxygen therapy must be seen as part of a therapeutical continuum, without any interruption of the chain of treatment. An early start of HBO therapy and an uncompromised application without restrictions to established surgical treatment and intensive care therapies is essential. Adjunctive treatment using hyperbaric oxygen requires not only a high standard of technical equipment in the hyperbaric chamber, but also a good amount of well trained medical personnel available 24 hours a day.

Still further clinical trials including controlled randomized trials are necessary to further prove the role of HBO therapy as an adjunct in the treatment of crush injuries.

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Chapter 2.2.7

COMPROMISED SKIN GRAFT AND FLAP

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Abstract: Hyperbaric oxygen has been effectively used as adjunct therapy in wound healing treatment of acute or chronic surgical conditions. Covering or reconstructing complex wounds is accomplished by skin grafts or flaps. Transferred tissues may be compromised due to different etiologies requiring proper therapy. Hypoxia due to inadequate grafted tissue oxygenation, involves hyperbaric oxygen use as adjunct therapy. Experimental and clinical studies concerning hyperbaric oxygen have shown results favoring the attachment of threatened grafted tissues. Capillary proliferation, protection from reperfusion injury, anti-edema action, rheological capillary improvement and protection from infection are among the demonstrated effects of hyperbaric hyperoxia. Definition of the etiology and proper timing of hyperbaric oxygen therapy through a collaboration of the plastic surgeon with the hyperbaric physician are considered necessary for the desired final outcome

Keywords: compromised skin graft; compromised flap; hyperbaric oxygen; reperfusion injury; plastic surgery

1. INTRODUCTION

Plastic surgery has a predominant role in the management of complex wounds and is indispensable for covering areas where important loss of tissue has taken place.

Wound healing is a delicate balance process related to many factors that may interfere with the reparative tissular response both to acute traumatic ischemia or chronic hypoxic wounds.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 329–361.

There are numerous surgical choices in order to close any kind of wound which may be divided in multiple categories depending on surgical complexicity and patient factors.

Proper wound management is related both to the perfusion correction and oxygen tissular delivery and to the local environment of the lesion, as are the regular debridement, the anti-bacteriological control through local or systematic antibiotic therapy and the suitable dressings to the wound nature. The wound healing is completed by either primary or secondary intention through granulation, epithelization and contraction.

Complex wound reconstruction is accomplished by transferring tissues like skin grafts or flaps from a different part of the body to the wound area.

The survival of these transplanted living tissues depends on many factors of which the most important is an adequate blood supply.

In normal conditions hyperbaric oxygen is not required for the survival of non-compromised flaps and grafts and may be useful only when viability of the transplanted tissue is doubtful or uncertain.

When the local microcirculation is inadequate to support the transplanted tissue, oxygen tissular improvement is of critical importance.

Today it is clear that hyperbaric oxygen (HBO) may provide a distinctive enhancement of the wound healing process by optimizing the tissular oxygen level in cases where a decreased microcirculation or hypoxia is present.

Furthermore the experimental and clinical experience of HBO therapy provide strong evidence not only in the collagen maturation and the angiogenetic stimulus but also in many important phenomena related to the wound microenvironment during the wound healing period as are the reduction of the ischaemia – reperfusion injury, the enhancement of growth promoting factors, the improvement of hemo-rheological status and the resistance to infection.

In order to analyze the principles of Hyperbaric Medicine and identify the common physiological aspects with Plastic Surgery in the wound healing process, a review of basic terms is necessary.

2. SKIN GRAFTS

A skin graft is a segment of skin detached completely from its bed and transferred to another site. Composed by epidermis and dermis, skin grafts are quite different from flaps as they are avascular where as the flaps have an innate vascular support.

The transplanted tissue placed on the host basis survives primarily as oxygen diffuses into it from the underlying wound bed and later relies on the promoted angiogenesis of the basis and the wound margins.

According to the thickness of dermis, skin grafts can be either full thickness or split thickness. The split thickness grafts are often used to cover granulated wound areas as they require less ideal conditions and they may survive a diminished vascularity[1]. Full thickness grafts are preferred in wounds with well-developed vasculature, non-contaminated and of small size.

Composite grafts contain more than one kind of tissue (skin, fascia, muscle, bone).

According to the donor origin, grafts are defined as autografts, (skin transferred from the same body) allografts, (skin transplanted from a different body) xenografts, (animal grafts) or biologic skin grafts (combination of living cells in collagen matrix).

Whether the plastic surgeon will choose to apply a skin graft depends on the vasculature status of the wound bed and the survival of the graft depends on rapidly acquiring an effective blood supply[1].

Thus the possible adjunctive enhancement of HBO application in skin grafts should be related to the promotion of adequate granulation tissue development in the wound area.

3. FLAPS

Unlike a graft a flap is transferred with its own essential blood supply or is connected to the recipient site vessels.

Although the skin graft is often simpler, there are cases in which a flap is required or may be more desirable. Flaps are usually needed for covering recipient beds that have poor vascularity so blood supply is the critical factor to select the proper type of flap.

Classification of skin flaps is related to three distinct groups[2]:

- ***Method of movement***

Local or distant flap, according to the distance between the donor and the recipient site. *Local flaps* include *advancement, pivot* (often a graft is required to close the donor site) and *interpolation* (more complex). *Distant flaps* are divided into *direct, tube or free.* A *free* flap permits the immediate transfer of composite tissue supported by its own blood supply in a basis of detached blood vessels which are attached at the existing vessels at the recipient area of the wound.

- ***Blood supply***

Flaps are also divided according to the existing vessels, which are the musculocutaneous (major branches supplying muscle and dermal plexi) and septocutaneous arteries (supplying fascia and skin).

In the *musculocutaneous* flaps belong the *random cutaneous* (composed of skin, fat and the synonymous arteries) subdivided in: *advancement, pivot,* and *interpolation* flaps, and the *myocytaneous* (plus the presence of muscle). The last ones have a vascular bed of greater length and credibility

In the *septocutaneous* belong the *fasciocutaneous* flaps (incorporation of deep fascia into a skin flap) and the *axial* or *arterial* flaps (nourishing by a direct cutaneous artery and vein)

- ***Composition***

A simple skin flap is usually efficient for the majority of defects but in complicated cases more tissues need to participate in the composition of the flap.

According to the involved tissues flaps are divided in: *cutaneous, fasciocutaneous, myocutaneous, skin graft and muscle,* and *specialized flaps* subdivided in *sensory neurovascular, osseocutaneous,* and *composite flaps.*

4. SKIN GRAFT SURVIVAL

Skin grafts, being avascular, are particularly susceptible to hypoxic insult. Graft survival depends on the recipient site blood supply.

When the skin graft is detached from the donor site its biological behavior is dramatically changed as its circulation, lymphatic drainage and nerve continuity are acutely interrupted.

Consequently the survival of the threatened graft is dependent on restoration of blood supply and the time till the reestablishment of circulation plays a critical role.

In the first 24-48 hrs post-transplantation the graft is nourished from the host bed via “plasmatic circulation” by serum imbibition.

Imbibition is supported by animal studies in which skin graft gained weight in the first 20 hours through fluid absorption[1].

Despite histologic, biochemical, tissue chamber, microangiograhic and vital microscopy studies, revascularisation of skin grafts is still an issue of argument.

A combination of three processes is related to revascularisation of the graft[3]:

a) Direct anastomosis of the graft and host vessels known as “inoculation”

b) In-growth of host vessels into the endothelial channels of the graft and

c) Random penetration of the host vessels into the graft dermis creating new endothelial channels.

Enzyme studies of markers for viable endothelium indicate degeneration within the first 4-5 days and then a restart of activity suggesting in-growth of vasculature stemmed from the host bed.

Updated interpretation is that early filling of the graft endothelial spaces with serum-like fluid and erythrocytes follows the anastomosis of graft vessels with host vessels, coupled with early in-growth and penetration of host endothelium.

During the imbibition period there is edema of the graft due to entrance of nourishing fluid. Progressively and in parallel with the reestablishment of circulation the edema is reduced.

5. FLAP SURVIVAL

As soon as the flap is elevated a complete disruption of blood flow takes place.

The functional loss of sympathetic innervation and the presence of ischemia compose a new status of hemodynamic imbalance for the isolated flap as flow decreases and vasoconstriction occurs by the release of sympathetic substances.

In order to survive the flap should restore an adequate nutritive process within the first 12 hrs postoperatively.

Initially, there is an increase in the size and the number of the small arteries of the subdermal plexus and of the dermal venous channels, plus a dilatation of preexisting anastomoses between transversely lying vessels [2, 4].

Tissue metabolism is switched to anaerobic as hypoxia occurs, resulting in decrease of oxygen, glycose and ATP and increase of lactate production, toxic superoxide radicals, prostacyclin, thromboxane and platelet aggregation.

The produced metabolic vasodilators enhance the flow and with the depletion of sympathetic vasoconstrictors there is a further increase from 12 – 48 hrs.

Angiogenetic “response” from the host tissue usually occurs 3-7 days after the transfer by direct in-growth and inoculation. Reorientation of vessels along the long axis and creation of functionally significant anastomosis take place in this period[4].

Through the action of angiogenetic factors, a dilatation of the vessels at the edge of the flap occurs, basal membrane is thinned and there is migration of endothelial cells from the neighboring vascular lumen. Additionally, endothelial cells replicate in order to spread-out the new microvascular net and concomitantly anastomosing the capillaries forming loops and finally

the new vascular "tree"[4]. Inoculation also occurs as some recipient capillaries are anastomosed with those of the flap [5].

After two weeks the circulation is well established between flap and recipient bed; the third week maturation of anastomoses continues and the third week flap achieves 90% of its final circulation[4].

6. COMPROMISED (FAILING) SKIN GRAFTS AND FLAPS

Complications may arise in both kinds of transplanted tissues resulting in partial or total loss of graft or flap.

The presence of doubtful viability tissue is described as compromised. The term failure is mostly related to technical errors during the perioperative period.

Many factors may contribute in order for a transplanted tissue to become compromised.

Causes of graft complications beyond the technical surgical problems are an improper host wound bed due to hypoxia or infection and lack of new tissue development.

In compromised flaps the contributing factors are: ischemia - hypoxia, edema, arterial vasospasm, arterial or venous occlusion, congestion and dehiscence or infection.

A factor of major importance is also the reperfusion injury syndrome when re-establishment of circulation follows prolonged tissular hypoxia as in complicated free flaps.

Patents health factors like age, smoking, systemic disease and/or relative therapy may interfere with the flap prognosis.

Clinical evaluation is of major importance and is tested according to the flap condition taking into account flaps characteristics like color, temperature, capillary fill up and bleeding.

The appearance of cyanotic color in graft is related with delayed revascularization and hypoxia, white color with lack of blood supply and red color with presence of infection.

Follow up of the flap "take" is critical for the first 48 hrs. Observation of the flap color may determine the leading factor of the complication.

The primary cause of flap demise is not an inadequate arterial inflow but rather a venous insufficiency through a compromise venous outflow[4]. Clinically flap is edematous, colored deep purple or dark blue, (in total venous occlusion) capillary refill is missing and the flap temperature is low.

Assessment of possible compression in grafted tissue is necessary to investigate the presence of tight sutures, hematoma, twisting / kinking of vascular pedicle or venous thrombosis.

Recognition of venous hypertension is very crucial as venous drainage occlusion is much more deleterious for flaps survival judged against low arterial inflow[2].

Proper surgical intervention (decompression, medicinal / chemical leeching) must be performed soon.

Arterial insufficiency is related to a pale color, deprived capillary refill, low temperature and lack of pinprick bleeding. The presence of edema, hematoma, kinked pedicle or vasospasm are routinely responsible for low blood flow.

Vasospasm may occur intraoperatively in arterial anastomosis following free tissue transplant or later, (48 hrs) ensuing pathogenesis of thrombosis. Surgical investigation has to be performed on time for the restoration of arterial inflow.

Transcutaneous oxygen pressure ($TcPO_2$), tissular pH, photoplethysmograpphy, laser Doppler, oxymetry and radioisotopic techniques are among the methods for prognosis of objective flap judgement[6].

A variety of conservative complementary treatments is proposed according to the cause of the compromised tissue including vasodilators, pentoxiphylline, dextranes, radicals scavengers, fibrinolytics, medicinal or chemical leeching and hyperbaric oxygen therapy (HBO).

7. HYPERBARIC OXYGEN

In well - perfused wounds where the healing process is sufficient through a balanced cellular metabolism HBO therapy is not necessary.

The proposed use of HBO as supplementary therapeutic intervention in the management of compromised flaps or grafts was based on the acquired experience of wound healing enhancement after HBO application in wounds and injuries of hypoxic soft tissues[7, 8, 9, 10, 11].

Compromised tissues are usually hypoxic thus the necessity for improved oxygenation. HBO has been shown experimentally/clinically able to support and restore healing mechanisms in hypoxic cellular environment[7, 12, 13].

Reduced perfusion and hypoxia are expressed with diminished tissular oxygen thus preventing cellular energy requirements involved in wound healing restoration.

Although the absolute limit of tissular hypoxia for healing is difficult to be defined, a level of 40 mmHg of wound oxygen is considered necessary[14].

In compromised tissues a value of oxygen tension below 15 mm Hg is often detectable[15].

7.1 Hypoxia - Free radicals – Reperfusion Injury (RI) – HBO

Inadequate oxygen supply in compromised flaps according to Kerrigan and Daniel[16] is the result of three hypoxic insults: a) direct ischemia from the interruption of cutaneous vessels, cell death within 13 hrs in cases of non restored flow and initiation of post-ischemic inflammatory process resulting in endothelial swelling b) expansion of the inflammatory reaction from the surgical injury itself c) vasoconstriction due to the release of catecholamines as nerve continuity is interrupted through the alpha adrenergic receptors.

Skin grafts survive only if enough oxygen diffuses from a non- hypoxic underlying bed at least for 24-48 hrs until the appearance of revascularization.

Hypoxia, through the interruption of aerobic metabolism, initiates catabolism of ATP to adenosine creating anaerobic metabolites like hypoxanthine an electron donor which in the presence of oxygen mediates the formation of free radicals: superoxide anion, and hydroxid peroxide or hydroxyl radical (if more electrons are added).

There are many types of radicals but those of most concern in biological systems are derived from oxygen and known collectively as reactive oxygen species.

Another important source of free radical production is the neutrophils through the cell membrane NADPH oxidase and degranulation.

The resumption of blood flow after a prolonged period of flow cessation causes an inflammatory reaction in the microcirculation the so-called ischemia reperfusion injury, (RI) or "no-reflow" phenomenon where the free radicals play an important role[17].

The restoration of perfusion and oxygen delivery to hypoxic tissues after a certain period of ischemia normally should be related with re-establishment of aerobic metabolic balance and depletion of free radicals but instead of it far greater production of reactive oxygen intermediates may occur[18].

Endothelial cellular injury, prostaglandins release, inflammatory cytokine secretion and presence of interstitial edema due to capillary leakage are some of the hypoxia and the RI induced effects[19].

Zamboni et al.[20] have demonstrated in a rat sceletal muscle "in vivo" after 4hrs of ischemia the important role of neutrophils in the apparition of RI. Leucocytes presented an increased adherence to the endothelium resulting in the occlusion of postcapillary venules and additionally in a significant

vasococonstriction of arterioles. The adherence phenomenon was proved to be moderated by the action of "intercellular adhesion molecules" (ICAM -1), known as b_2 integrins on the corresponding receptors (CD-11a, b, c, CD-18 chain) of the expressing neutrophils membrane surface[21, 22].

As demonstrated in several studies[23,24] ICAM-1 expression is not mediated by hypoxia alone but requires the co-existence of cytokines or a reperfusion period.

A cascade of interactions is induced by the action of free radicals, molecules highly unstable, upon the cellular membranes or on the membranes receptors, channels, proteins and nucleic acids.

The clinical effects depend on the involved area of the transplanted tissue as the hypoxia intensity varies between the central region and the distal parts the last ones being the most sensitive.

The role of free radicals and the phenomenon of RI have a very distinctive role in the pathophysiology of compromised flaps.

Experimental and clinical studies have demonstrated the improvement of skin /muscle flap survival subjected to hypoxia and RI after the administration of various free radical scavengers[25, 26].

As the role of oxygen in the RI is the key factor it could be assumed that the use of HBO would enhance further the generation of free radicals and the rate of deleterious cascade in local microcirculation.

However, clinical and experimental experience has demonstrated that HBO not only does not promote RI but on the contrary it acts as antagonist[20, 27, 28, 29].

Thom et al.[30] as well as Suzuki[31] revealed that HBO may stop the neutrophil adhesion and the interaction of b2 –integrins on the CD-18 surface receptors expressed on neutrophils and endothelium.

Zamboni et al.[20, 32] demonstrated also the efficacy of HBO in inhibiting leukocyte adherence. Thus in a study[32] of a reperfused rat skin flap model after 8hrs of ischemia a significant improvement of tissue survival has been shown, after application of HBO. Using quantitative analysis Zamboni also showed that HBO impaired the leukocyte adherence on endothelium in post-ischemic skeletal muscle[20].

Buras et al.[33] recently suggested that the beneficial effect of HBO in RI through a decreased expression of ICAM-1 may be related to an induced eNOS synthesis, which may help explain also the protective effect of HBO treatment, if applied before RI in a rodent liver model[34] .

Compromised free flaps are mostly submitted to RI and HBO use may be of major clinical value according to the experimental[35] and clinical studies[36].

7.2 Vasospasm – oedema – HBO action

Vasospasm is one of the main causes for the genesis of compromised cutaneous and musculocutaneous flaps due to diminished blood flow. Although the mechanism is unclear, it seems that it is induced through a myogenic irritation by trauma or strech.

Microcirculatory events take place similar to those in R. I. which are: vasodilation followed by vasoconstriction, low flow, increased vascular endothelial permeability and edema formation.

The adjunct application of HBO usually promotes vascular constriction explained as a defense mechanism against hyperoxia, thus diminishing the arterial flow by 20-30% as demonstrated experimentally and clinically[37, 38].

The "hypoperfused" tissues are compensated from the increased amount of carried oxygen through the hyperoxygenated plasma. However this unique event flow reduction – more oxygen delivery known as "HBO paradox" is applied only to normal vasculature without any influence on the problematic microcirculation[39].

Acquired therapeutic experience with HBO proposes that the induced vasospasm is a collateral effect of major importance in treating injuries complicated with presence of edema.

Zamboni et al.[20] using intravital microscopy showed that in hypoxic tissue treated with HBO arteriolar diameter had no significant change.

In another study the same author using Laser Doppler flowmetry demonstrated that HBO improved distal microvascular perfusion in rat ischemic flaps[27].

Hammarlund et al.[40] showed that blood supply on microcirculation of acute derma wound was increased through HBO instead of being suppressed or maintained.

The vasoconstriction of intact skin vasculature under the HBO stimulus results in redistribution of arterial content in favor of the problematic areas and counteracts the hypoxia from impaired local blood flow[39, 40].

High-pressure arterial oxygen is indispensable for oxygen to diffuse and overpass interstitial liquids in order to reach the distal ends of hypoxic and hypovascular tissues as the oxygenation of nearby tissue volume depends on the capillary integrity. This may explain the too often observed complication in distal flap necrosis.

Under HBO, plasma oxygen content increases directly as a function of its inspired partial pressure. Oxygen gradient in arterioles represents the driving force for tissular supplementation and normal cellular metabolic balance. In clinically applied HBO treatment arterial PO_2 may be elevated up to 1500 mmHg or more, increasing the transfer of oxygen into tissues by 20 fold, corresponding in 300 mmHg or more of tissue partial pressure[41].

Hypoxia enhances the installed vasodilation of occluded venous microcirculation, the inflammatory metabolite secretion and the free radical production, promoting furthermore the endothelium cellular injury leading to increased permeability and edema formation. The presence of edema acts like a mechanical diffusion barrier in oxygen movement from arterioles to cellular components.

HBO through induced vasospasm reduces the arterial-arteriole flow thus leading to diminished venous stasis and better draining, permitting the reduction of pressure in the free flap compartment and restoring a low arterial inflow.

The less edema is present the more enhanced is the diffusion range of oxygen.

The "antiedematic" effect of HBO may jeopardize the vicious circle of ischaemia, hypoxia and edema and restore or even improve the capillary flow.

The combined therapeutic action of HBO on vasospasm and swelling reduction in hypoxic tissues is of major importance in compromised tissue transfers in order to improve normal capillary function.

7.3 Capillary hemo-rheological status – HBO

Kerrigan[16] proposed a capillary model including three phases (post-hypoxic vasodilation, hemoconcentration and a vasoconstriction induced suboptimal flow) to explain the pathophysiological changes in flap microcirculation.

Rheologic properties of blood at the microvasculature level have a predominant role in the pathogenesis of compromised flaps and skin grafts as partial or total arterial occlusion may occur.

Zamboni[6] reports that especially in free tissue transfer, where the accepted thrombosis rate is at least 5-10 %, there is a secondary ischemia prior to the one of revision anastomosis, resulting in desperate situation.

After the tissue detachment, microcirculation is acutely interrupted and hemo–rheological disturbances appear like local vasoconstriction, vasodilation, alterations of fibrinolysis and blood viscosity as a result of hypoxia.

Augmented plasma exudation in compromised microcirculation is followed by hemoconcentration in parallel with the existing endothelial edema favoring capillary occlusion.

The fibrinolytic system possesses a strategic role in the pathogenesis of thrombi. Endothelial cells produce plasminogen activator (t-PA) to allow fibrinolysis to occur and plasminogen activator (inhibitor type one PAI-1) as antagonist. PAI-1 antagonises t-PA, regulating fibrinolytic activity.

HBO was shown clinically[42] to enhance t-PA activity favoring fibrinolysis and decrease of PAI-I. Another study[43] using cultured human endothelial cells following anoxia demonstrated HBO to affect the fibrinolytic response preventing thrombosis or microembolization.

Platelet aggregation is enhanced by thromboxane A_2 coming from the cell membrane released arachidonic acid as a result of hypoxic insult.

An animal study[44] showed that the maximal rate of ADP and collagen-induced platelet aggregation decreased after hyperbaric exposure.

In hypoxia free radicals have a direct effect upon red blood cells, like the peroxidation of membranes lipids resulting in structural changes of red cell membrane. This results in red cellular deformability which promotes furthermore the rheological disturbance of blood flow enhancing tissue subperfusion. The grade of this deformability may be evaluated through the erythrocyte filtration index.

In an experimental controlled animal study[45] exposure to hyperbaric oxygen demonstrated a decrease in RBC deformability confirmed with electron microscope and a significant increase of the filtration index. The authors suggested that rheological alteration of red cells might affect their flow through small-caliber blood vessels.

Mathieu et al.[46] also demonstrated the improvement of red cells filtration index after HBO treatment. Dise et al.[47] proposed that HBO inhibits erythrocyte phospholipid fatty acid turn over.

HBO has been shown clinically[48] to increase prostacyclin (PGI2) products (6-Keto-PG F) and in parallel to decrease thromboxane (TxA2) sub-products, (TxB2) thus promoting vessel dilation.

In summary, although the evidence is mostly from experimental studies HBO seems to favor the decrease of thrombotic occlusion in capillary or microcirculatory level.

7.4 Flap – graft wound healing microenvironment – HBO

The acquired experience and the detection that oxygen is a pivotal nutrient component of healing procedure has implicated the importance of insufficient oxygen supply in all the phases of wound repair.

Traditionally wound healing involves an inflammatory, a proliferative, and a remodeling phase. As oxygen participates in all phases, the demand for sufficient oxygen tension levels is the rational for HBO treatment in compromised tissues.

The role of HBO in compromised grafts or flaps concerning the stage of healing is usually referred as the same in both categories, although their pathophysiology is different.

Graft is especially susceptible to hypoxic insult, as initially it is completely dependent upon oxygen diffused from the base and wound margins, until the vascular net is re-established. Flap has its own vasculature and in order to survive an adequate nutritive process is necessary after the first postoperatively hours until the progressive promotion of angiogenetic response.

Despite the fact that insufficient blood supply is not favoring HBO action in hypoperfused tissues, there are studies in which skin flaps almost totally anoxic have been shown to present reduced necrosis extension after hyperbaric hyperoxia[32].

Proliferative phase is the real healing part including fibroblast mediated collagen deposition and the formation of new blood vessels.

Increased hypoxia and lactate levels are considered to be the trigger for the attraction of activated macrophages which release angiogenetic stimulating factors, orchestrating fibroblast and endothelial cells migration and proliferation.

Today a lactate level is acknowledged as the most important factor far more than hypoxia to lead the repairing cascade actions. It is also acknowledged that its levels remain high in the wound area even in the presence of local raised PO_2 [50].

Lactate stimulates many cells to release cytokines and growth factors e.g.IL1, 6 and 8, trasforming growth factor β, (TGF β) platelet-derived growth factor, (PDGF) or vascular endothelial growth factor, (VEGF) which dominate angiogenesis. Oxygen presence in parallel seems to encourage their production and excite their action, a property not shared by hypoxia[51,52].

Passaniti et al[53] proposed that fibroblast proliferation - migration and new capillaries development act in unison both demanding adequate oxygen.

Collagen synthesis from fibroblasts and deposition to extracellular space requires adequate oxygen as substrate for the post-translational hydroxylation of pro-collagen. The proper wound PO_2 for this extraction was estimated to be close to 100 mmHg, where this oxygen tension influences also the cross-linking of collagen enhancing its tensile strength [51, 54].

In the zone of dividing fibroblasts, the mostly confined to the front capillary line, PO_2 is in the range of 30-80 mmHg. Fibroblasts deposit collagen providing a structural matrix crucial for the development of angiogenesis.

The effect of HBO on human skin cells in culture and in human dermal and skin equivalents was studied by Dimitrijevich et al[55]. Beyond the increase in fibroblast proliferation, (up to 2 ata oxygen) HBO dramatically enhanced keratinocyte differentiation and epidermopoiesis in the complete

human skin equivalent (up to 3 ata). The authors suggest utilization of HBO during repair of peripheral human tissue.

Angiogenetic response, the sprouting of new blood vessels from pre-existing vessels, takes place through migration of the activated endothelial cells, cell division, tube formation, and neo-capillary net development.

Strong clinical evidence supports HBO inducement of angiogenesis although the mechanism of its biological action is not clear.

Gibson and Hunt[52] demonstrated in a Matrigel model angiogenesis to be stimulated paradoxically by both hypoxia and oxygen through released endothelial growth factor, (VEGF) although the long HBO acquired clinical experience has provided indirect evidence supporting this co-existence. This study shows further beneficial effects of HBO upon angiogenesis as seem to influence the interaction of VEGF and its cellular target.

Li et al.[56] proposed that although lactate and hypoxia stimulate macrophages to produce VEGF, lack of oxygen up-regulates VEGF receptors and the expressing cells may grow faster when exposed to hyperoxia.

Sheikh et al.[57] used a rat wound model to show that HBO induced VEGF production by 40% suggesting that this explains in part the angiogenetic action of HBO.

Recently Lin et al.[58] presented an impressive study to further clarify the angiogenetic HBO effect. They have noted that VEGF in order to promote vessel formation must act synergistically with specific angiopoietins, specifically the A2 one. HBO was observed to selectively enhance its action through e-NOS related signaling pathway.

Summarizing, adequate tissular oxygen appears to have a key role in the expression of healing, although the mechanism of angiogenetic stimulation is not clearly defined.

7.5 Resistance to infection of transferred tissues – HBO

Although the infection rate in transferred tissues is rare mainly in well blood-supplied flaps, the presence of hypoxia may often be adjacent with the insult of infection. A reduced host defense from underlying diseases also enhances and predisposes to the genesis of infection.

The results of infection can be deleterious for the compromised tissue leading to enhancement of hypoxia, dehiscence, sepsis, and necrosis. The increase of oxygen concentration has been shown to reduce the incidence of surgical-wound infection[59].

The presence of oxygen is necessary for the phagocytosis and extermination of bacteria by polymorphonuclear leucocytes through the production of superoxides. Inside phagosomes membrane "oxidative burst"

includes the formation of a variety of oxidants through a NADPH oxygenase from the available oxygen.

Allen et al.[60] reported that if local oxygen tension is below 30mmHg, the leucocyte bacteriocidal action is dramatically reduced; also bactericidal activity in wounds could be enhanced by three to four folds if tissue PO_2 levels would raise up to 100 mmHg, as it usually happens if supplementary oxygen is provided.

Johnson et al.[61] demonstrated in dogs that in composite flaps a zone of 50-75 mmHg is the most important clinically.

Leucocytes exposed to high oxygen levels after HBO application improved their phagocytic properties, even more than the relevant one in normoxic levels[62].

HBO is used as an adjuvant way to surgery and antibiotic therapy to expand the therapeutic armamentarium in compromised wound healing.

Niinikoski and Hunt[51] report a clinical study of surgical patients where wound infection occurred in inverse proportion to the proxy wound PO_2 levels.

Anaerobic bacteria are extremely vulnerable to HBO as they lack antioxidant capacity. HBO has a bacterostatic or bactericidal effect when is used in anaerobic infections[63].

Additionally aerobes are shown to be susceptible in raised oxygen's tissular levels.

Hunt et al.[64] demonstrated that Pseudomonas Aeruginosa counts have been shown to decrease in animals wound chambers by inspiring high fractions of oxygen.

Knighton et al.[65] showed also in animals that skin lesions from Escherichia coli, induced through dermal inoculation, varied according with inspired FiO_2. Oxygen raised tension has diminished also the extension of random pattern skin flaps necrosis in dogs after their inoculation with Staphylococcus Aureus.

Furthermore experimental research[66] reports possible HBO enhancement of antibiotics action due to an additive intracellular effect. Some antimicrobial agents like quinolones, macrolides, and rifampycine act within the phagocytes where an endocellular synergy between oxygen dependent reactive species and antibiotics may occur.

Regarding the above studies it is assumed that oxygen tension has a predominant role in wound's resistance to infection.

8. HBO STUDIES IN COMPROMISED TRANSFERRED TISSUES

In 1963 Pr. Boerema, the pioneer of Hyperbaric Medicine, has noticed an apparent beneficial effect of HBO on a compromised skin graft[67].

Since then many experimental and clinical studies have confirmed the efficacy of HBO to enhance survival of compromised transferred tissues.

8.1 Animal Experimental Studies

Many different animal models have been used to investigate the underling mechanisms of transferred tissues survival in order to simulate them with the relevant in humans.

Although Kernahan et al in 1965 reported no beneficial effect of HBO in island skin flaps in pigs, in 1966 Mc Farland and Wermuth[69] used some shortcomings from the previous study and examined the HBO action on experimental pedicle flaps and composite skin grafts in rats. Their conclusion was that HBO had a definitive role to prevent necrosis extension in both grafts and flaps. The possible explanation for the opposing results of those studies is that pig flap is a true random flap, while the one of rat is myocutaneous with incorporated blood supply.

In 1967 Champion et al[70] exposed pedicle flap in a rabbit model for 2 hrs, twice a day for five days, and achieved survival 100% of HBO flaps versus 50 % in the control group. Flap survival was relevant to alveolar and skin oxygen tension. None of the flaps treated with compressed air survived. HBO was proposed to maintain flaps viability until the restoration of microvasculature.

The following year Shulman and Kron[71] showed in a rat model that HBO combined with repeated grafting reduced in half the necessary healing time for partial thickness wounds comparing it with the relevant of control group. In parallel, the possibility to prevent infection through high oxygen levels was demonstrated in transferred tissues, while the rats in the HBO group were not infected, although bacterial contamination occurred in all the studied animals.

In 1968 Wald and Georgiades[72] studied intensive HBO therapy in experimental rat skin flaps, demonstrating a 22% increase in flap survival.

Perrins and Winter[73] in 1970 used pigs with shallow wounds to test the HBO efficacy in skin covering in order to compare this model with human healing rhythm of the recipient bed after grafts were detached. The results were 80% skin coverage in the HBO group versus 49% in the control group.

In a study[74] comparing PO_2 in rat skin flaps between HBO at 3 ata and 100% FiO_2 in normobaric conditions, oxygen tension in hyperbarism raised up to 600 mmHg whereas in 1 ata no raise occurred.

Niinikoski[75] and Hunt in 1970 also used tubed rat skin flaps to compare the size of viable area in a HBO group versus a similar control group breathing normal air. The HBO group showed 51% extension in length of survived flap versus the control.

In a study from Jurrel and Kaisjer[76] pedicle rat flaps were compared concerning the survival area according to the onset of HBO. Better results were obtained when HBO was started immediately after the surgery compared to those when HBO was delayed more than 24hrs. Even though the results of the delayed HBO use were still of statistical importance, the prompt onset of HBO was emphasized.

Using a model of provoked and predictable necrosis in rat skin flaps, Arturson et al.[77] demonstrated that in the HBO treated group there was a statistical important improvement in flap survival in comparison to the control group.

In 1973 irradiated rats were studied by Greenwood and Gilchrist[78] to evaluate the HBO effect in skin flaps 6 months post radiation. The HBO treated group showed a significant flap survival compared with the control group treated with air.

Niinikoski and Kivisaari[79] in 1975 performed a controlled study in rats with HBO at 2 ata to evaluate the healing rate in open wounds with intact or disturbed circulation. Improvement has been shown only in the devascularized wounds of HBO group, implying the role of hyperoxic healing enhancement in compromised wounds.

Manson et al.[80] in 1980 studying pedicle flaps in Guinea pigs demonstrated that animals treated with HBO had a three fold increase of capillary net when compared to controls.

Caffee and Gallagher[81] in 1981, using modern flap designs in pigs have not shown effectiveness of HBO use in improving flap survival.

Tan et al.[82] in 1984 examined the HBO effect in island flaps in rats, in comparison with a control group treated with air under pressure and normobaric 100% oxygen. Significant flap survival was noticed only in the HBO group. The authors suggest that as oxygen tension is lower in flaps compared with skin tension, proper tissue oxygenation may be restored only through hyperbaric hyperoxia .

Nemiroff and Lungen[83] in 1987 performed a controlled randomized study to examine the possible HBO action in irradiated skin flaps in rats, comparing as well ordering effects of HBO and effects of flap elevation and radiation (in 15 groups). HBO was performed before flap elevation, soon after surgery, (4hrs) or later. Authors reveal that the sooner the HBO is initiated after the “surgery”, (in the study "surgery" represents a programmed flaps failure) the better are the results for flap survival. Thus, in case of a diagnosed problematic flap HBO should be administered on time.

In the same study authors used flap histopathologic analysis to show that the number and possibly the size of capillaries were significantly greater in the HBO group. They conclude that HBO enhances flap survival through promotion of microvasculature.

Composite skin grafts in rabbits were used by Rubin et al[84] in 1988 to examine the HBO effect. The HBO group was submitted in hyperbaric exposure twice a day for ten days, resulting in significant grafts survival compared with the control group.

A protocol including HBO combined with pentoxyphylline, known to increase red cell flexibility was used by Nemiroff and Ryback[85] in 1988 on rats skin flaps. Animal groups included a control group, two HBO groups (one with and the other without pentoxyphylline) and one group treated only with pentoxyphylline. Statistically important results concerning flaps survival were achieved in the group where HBO was combined to pentoxyphylline, although both the remaining groups showed improved results versus the control group.

Zamboni et al.[32] in 1989 experimented on axial pattern flap survival in rats with HBO, administered during or just after prolonged flap ischemia of 8 hrs. It was a controlled study comparing the control group versus sub-groups, using HBO during ischemia or reperfusion. HBO was shown to increase flaps viability when administered both during or just after ischemia.

Kerwin et al.[86] in 1992 used a cat model to evaluate HBO efficacy on pedicled skin flap after having clamped the nourishing artery. HBO was performed once a day at 2 ata, whereas in most experimental studies it was used twice a day. Beyond the improvement in flaps color and exudation after HBO use, survival was similar both in HBO and control group. Pellitteri et al.[87] in 1992 performed a controlled study on random skin flaps in swine with the application of intensive and tapering HBO. Flaps were designed to obtain a predictable length of necrosis. Their results demonstrated a diminution of 35% in flap necrosis when HBO was administered.

The HBO effect in preserved free flaps of rats was studied by Tai et al.[88] in 1993. After 18hrs of flap preservation HBO administration induced flap survival from 10% (in air) to 60%. Authors presume that HBO application inhibited the role of xanthino-oxydase, improving flap survival.

Zamboni et al.[27] in 1993 used Laser Doppler flowmetry to evaluate HBO effect on ischemic skin flaps in rats during reperfusion. They revealed that hyperbaric hyperoxia enhances distal microvascular skin perfusion, responding in improvement of flap survival.

Xenon washout method for measuring blood flow and vital fluorescein microscopy as index of functional capillary density was used by Sirsjo et al.[89] in 1993 to detect the efficacy of HBO, to treat postischemic muscle tissue. Their results suggested that HBO enhances the recovery of blood flow and functional capillary density in post-ischemic muscle tissue, indicating attenuation of the microvascular dysfunction or of the damage in the postischemic period.

Stewart et al.[90] in 1994 examined the effect of free-radical scavengers combined with HBO on random-pattern skin flaps in rats. 10 treatment groups of rats were randomly assigned. Superoxide dismutase, catalase, alphatocopherol acetate and the inhibitor allopurinol were used to combat or scavenge radicals. HBO was performed daily at 2,5 ata. The goal of the study was to increase the oxygen delivery to the flap and simultaneously reduce or prevent the action of free radicals. The combination of treatments resulted in significantly increased random-pattern flap survival in all HBO groups, except in the allopurinol one, compared to untreated controls.

Recently in 2002 Prada et al.[91] used a model of axial pattern skin in rats to evaluate the effect of allopurinol, superoxide-dismutase and hyperbaric oxygen. The percentage of flap necrosis was significantly smaller in all-experimental groups when compared to controls.

Erdmann et al.[92] in 1995 used a highly immunogenic skin allograft mouse model to determine the HBO effect as an immunosuppressive agent. The controlled study used three randomized groups with varying dose of HBO. Authors suggest that low dose and intermediate HBO treatment delayed skin allografts rejection, confirmed also histologically.

A controlled study by Zamboni et al.[93] in 1996 evaluated in a microcirculation model on a rat gracilis muscle flap the HBO action on flap arterial neutrophil concentration and the relevant pulmonary neutrophil sequestration. Acquired results demonstrated that HBO significantly reduced concentration to sham levels without inducing pulmonary sequestration.

The result of HBO use in free tissue transfer was extensively studied by Stevens et al.[94] in 1996 on abdominal adipocutaneous island flaps in rats. Vascular pedicles were clamped twice for 6 hrs each, followed by a 2 hr interval of reperfusion; then ischemia was reapplied for different periods (6,10,14 hrs). After the second period of performed ischemia animals were randomly assigned in groups treated with air, 100% normobaric oxygen, and HBO. A statistically significant increase in flap survival was reaffirmed only in the HBO group.

In a study by Ramon et al.[95] in 1998 concerning single-pedicle transverse abdominis myocutaneous flap in a rat model and possible HBO effect, results suggested that in the treated group flap survival differed significantly from the controlled animals.

Bayati et al.[96] in 1998 evaluated the HBO effect in the stimulation of angiogenesis to improve the viability of prefabricated flaps. Two modalities, basic fibroplast growth factor (BFGF) and HBO were used separately and together on prefabricated myocutaneous flaps in rats. Laser Doppler skin perfusion and histological examination were performed to evaluate post stimulation vascularity. Both HBO and BFGF used separately, increased significantly the survived area of the prefabricated flap. The combined

application of these two modalities induced furthermore the effect, leading to near complete flap survival through improved vascularity.

Zhang et al.[97] in 1998 demonstrated in a controlled study that postoperative HBO increases neovascularisation (documented histologically) and the acquired survival of the rat ear composite graft was significantly important (82% versus 26,5% in control group).

The question for the use of HBO to attenuate lipid peroxidation on free skin grafts was posed by Lemarie et al.[98] in 1998, as in their study HBO exacerbated the degree of oxidative stress in relevant rat flaps.

Axial skin flaps in rats subjected to total venous occlusion were used by Lozanno et al.[99] in 1999 to evaluate the effect of HBO and medicinal leeching. Arterial inflow was left intact. Five animal groups were randomly assigned according to combined or single treatment. The study demonstrated that although HBO alone was not effective, when it was combined with leeching it resulted in significant flap survival compared with leeching alone.

The effect of HBO on microvascular anastomosis healing and patency was studied by Shi et al.[100] in 1999 in a rat model. The authors using eighty anastomosed femoral arteries in five groups concluded that HBO might be useful in improving the healing of microvascular anastomoses, mainly in vessels that have undergone crush injury.

Yucel et al.[101] in 2000 examined the effects of HBO and heparin, used combined or separately on epigastric venous flap in rats. Their results imply that flap survival rate in the combined modalities group was significantly higher than in the control, or in the heparine group.

Gampper et al.[102] in 2002 studied the potential for HBO to decrease the effects of a secondary ischemic event on epigastric flap model in rat. Cross clamping of the vascular pedicles for 2hrs was followed 24 hrs later by flap reelevation and reocclusion for 5hrs. Rats were divided into three groups. The first group received HBO immediately before primary ischemia, the second underwent similar treatment prior to secondary ischemia and the third group used as control. The results showed that all control flaps were nonviable, where complete (20% versus 31%) or partial flap survival (48% versus 55%) occurred respectively in the two treated groups. In conclusion, HBO significantly increased the survival of flaps subjected to a secondary ischemia even if administered before the primary ischemia.

Survival of distal skin paddle through HBO was evaluated by Richards et al.[103] in 2003 in a rat tubed pedicle flap model. Their results showed that at 5 days after pedicle division flap survival in the HBO groups was of statistical importance, as compared to the relevant of control groups.

Ischemia reperfusion injury (RI) and HBO action on the mechanism involving the expression of adhesion molecules was studied extensively by

Hong et al.[104] in 2003 in a rat musculocutaneous flap. The study consisted of gross examination for flap survival, histology, immunihistochemical staining, myeloperoxidase assay, flow cytometric study of CD18, and Northern blot analysis on ICAM-1 messenger RNA expression. Their results suggest that HBO does not alter the expression of CD18, but decreases the expression of ICAM-1. The point of HBO application, whether applied before or after RI, did not show any differences in outcome. HBO increased flap survival against RI through a protective mechanism involving downregulation of ICAM-1 on endothelial cells.

Recently Li et al.[105] in 2004 experimented on auricular composite grafts in rabbits with HBO. They suggest that HBO enhanced graft survival mainly in the larger composite grafts.

In conclusion, the last 40 years several experimental studies were performed concerning the possible role of HBO on compromised tissues, using different animal models as also various types of transferred tissues.

Although this variety of studies includes non-homogenous models regarding flat or graft type, blood supply, tissue origin, procedure for programmed "failure", host immune status making comparison not reliable, it is certain that the common denominator is the presence of hypoxia. Statistically important improvement of compromised tissue survival was reported in almost all the controlled studies, thus indicating that HBO counteracts the hypoxic insult.

8.2 Clinical studies

Although animal studies considering the reported evidences on compromised grafts and flaps confer a high degree of validity, relevant human studies for HBO as adjunct therapy are essential to enroll it in the therapeutic armamentarium.

In 1966 Perrins reported the use of HBO to enhance flap survival reducing the failure rate in a series cases and next year he presented a controlled study[106] of HBO effect on skin split grafts. The protocol included 48 patients randomly assigned to a control and HBO treated group. The graft survival rate in the HBO group was 64% versus 17% in the control, statistically important, although the low percentage in untreated patients was not explained.

Greenwood et al.[107] in 1973, having already experience with HBO use in irradiated rats on skin flaps[78], studied the action of HBO on healing of compromised wounds in irradiated patients with laryngectomy. They concluded that HBO enhanced the restoration process.

Wilkox et al.[108] in 1976 conducted a study with thirty-eight osteotomy patients treated with HBO to determine clinically its effect on the healing

acceleration. Data accumulated from this clinical investigation indicated that HBO augments clinical healing subsequent to osteotomy procedures.

Perrins[109] in 1983 reported that in graft donor site, when a secondary hypoxia is present, HBO enhances the healing rate e.g. in burns, making grafts transfer possible in a shorter period than expected. HBO use in normal conditions, concerning graft bed healing, is neither necessary nor recommended.

In 1986 Bowersox et al.[110] in a retrospective analysis reviewed a series of 105 patients with ischemic flaps and grafts, where HBO had been used as adjunct therapy. In 90% of the grafted patients and in 63% in those with flaps, conditions appropriate for failure of transferred tissues were recognized. HBO contributed to avoid creation of "compromised tissues", as the survival rate in grafts was up to 91% and the relevant in flaps up to 89%.

Davis et al.[111] in 1987 reported a series of 4 patients suffering from pyoderma gangrenosum wounds, unhealed for many years even after intensive treatment with all therapeutic modalities (debridement, steroids, antibiotics and multiple skin grafts). Authors used HBO combined with skin grafting and all patients healed with a follow-up period of 4-6 years, free of recurrences. Prior of this report, in the presence of pyoderma gangrenosum, graft prognosis was unfavorable.

Ueda et al.[112] in 1987 in a retrospective analysis in a series of 26 patients with oral deformations, after removal of mouth or tongue cancers, reported that the developed compromised flaps achieved a 95-100% recovery.

In 1993 Waterhouse et al.[36] in a clinical controlled retrospective review described the effect of HBO in compromised free tissue transfer and replantation. Patient inclusion criterion was the presence of 6 hrs of primary or any secondary ischemia. Salvage in the HBO group (16 cases) was 75% versus 46% in the control group (13 cases). Timing of HBO application proved mostly significant for salvage rate, being 100% when free flaps and replants were treated within 24 hrs after the injury. On the contrary, when HBO was performed later than 72 hrs, failure occurred in all transferred tissues. Thus, the author proposes that HBO therapy should be initiated as soon as possible in order to avoid a post injury prolonged period of ischemia leading to irreversible lesions.

Marx and Ames[113] in 1982 proposed the efficacy of HBO in radiation injuries. Reconstructions of the mandible or maxilla using a newly defined and specific hyperbaric oxygen protocol were combined with grafts in irradiated tissue, into scarred and deficient tissue beds. Eleven of 12 grafts in irradiated tissue met six rigid criteria for a 91.6% rate of success. Neovascularity and neocellularity were demonstrated histologically (by human biopsy specimens) and were valid for the excellent results of reconstruction in irradiated and/or deficient tissue beds. Davis et al[114] in

1981 had also presented a study proposing HBO as a new adjunct in the management of radiation necrosis with surgery and antibiotics. Fifteen of the 16 cases of soft-tissue radionecrosis of the head and neck were successfully managed.

Reconstructive attempts in studies by Marx et al.[115, 116] as also by others[117] have demonstrated extensively the close relationship of HBO to bone graft healing.

For over half a century HBO application in radio-injuries to treat late complications is widespread in literature through retrospective trials and case reports, even if most of the studies results were more than encouraging.

In 1994 Marx[118] reported that in a series of 104 patients with hemimandibular reconstruction, success percentage was up to 92% in the HBO group with 52 patients versus 65% in the controlled group. The author links the success to induced angiogenesis and fibroblasia by HBO, implying that live bone cell transplantation into HBO treated tissue produces a greater survival of cellular elements and greater bone formation.

Furthermore, as soft tissues are also influenced by radiation injury, microvascular free flaps were introduced in the field of osteoradionecrotic lesions in a combined effort to restore in parallel soft tissues and bones defects. The most often involved areas are in the neck and head, followed by the pelvic region.

Although free flaps carry their own vascular support, the prognosis for a normal rate adherence with the radio –injured underlying tissue is not always favorable. This possibility of poor outcome establishes HBO use an important supportive procedure as adjunct therapy.

Marx et al.[118] had accomplished a randomized prospective study in irradiated patients, dealing with three aspects of the problems related to soft tissue flaps and wound healing:

a) delayed wound healing b) minor or major wound dehiscence and c) infection.

106 irradiated patients, with a dose greater than 64Gy, participated in two groups of 80 each, one group with HBO therapy and one as control. All patients were submitted to a flap or a major tissue surgery. In the HBO group the results were:

a) wound healing delay only 11 % versus 55 % in the non treated group

b) “minor” rate of wound dehiscence (defined as one that healed in 3 weeks) of 7.5 % versus 15 % in the control group and “major” (unhealed in 3 weeks or requiring secondary surgery or HBO) of 3.5 % versus 33 % respectively

c) “minor” rate of wound infection (defined as the one responding to antibiotics, culture specific and local irrigation) of 3.5 % versus 7.5 % in the

control group and “major” rate (surgery debridement in addition to minor) of 2.5 % versus 16 % respectively.

The study, according to the author, clearly confirms the value of HBO performed protocol to reduce additional surgeries, disability and total cost of car.

In summarizing studies review, several articles have been published in the medical literature concerning the experienced use of HBO to improve viability in "uncertain" transferred tissues. The acquired results have shown that a beneficial effect was evident in most of the experimental and clinical studies.

Inclusion or acceptance of any new therapeutic approach is related to “evidence based medicine”, meaning properly organized protocols through double-blind controlled randomized studies, or strong evidence of beneficial action.

Human flap variety techniques is similar to the one in animal models, making protocol standardization design almost impossible, thus comparable analysis of the results is not practical or feasible. Furthermore in light of the last controlled animal studies, patient inclusion in the non-treated groups may raise ethical matter.

Rapid strides in modern plastic surgery on transferred tissues imposes the need for further research of HBO action in the survival of "compromised" grafts and flaps.

9. HBO CLINICAL APPLICATION

According to Zamboni[6] HBO should be applied on compromised transferred tissues, if appropriate criteria exist such as: definition of problem, documentation of flap perfusion, suitable pre -HBO surgical procedures (if required) and minimal timing of HBO initiation.

The responsible plastic surgeon should define the underlying problem, providing the hyperbaric physician with the relevant information about the compromised tissue.

HBO treatments are performed at a pressure of 2.0 to 2.4 ata, in periods of 90 min. every 12 hrs for 2-3 days and then, as soon clinical stabilization occurs, once per day to a total of 20-30 treatments.

In case of total venous or arterial occlusion, specifically in free tissue transfer, treatments are given any 8 hrs for 24 hrs and then any 12 hrs for 48hrs followed by once daily.

Although clinical judgment is the most objective criterion for prediction of tissue survival outcome, Wattel et al.[119] proposed transcutaneous oxygen measurement ($TcPO_2$) in hyperbaric conditions to evaluate oxygen

availability and therefore healing probability. Authors compared transferred tissue measurements under three successive conditions, first breathing normal air, then breathing pure oxygen by facial mask in normobaric and finally in hyperbaric conditions (2.5 ata). Only the measurements in hyperbaric conditions showed a significant difference and these values were predictive to the response of HBO treatment. Furthermore they have found that the flap failed if $TcPO_2$ was lower than 50 torrs in HBO conditions.

Alternatively, others[6] have found microvascular perfusion monitoring through Laser Doppler being more predictive of outcome than $TcPO_2$, since in case edema is present acquired values may not be accurate.

Continuous Laser Doppler measurement depicts the dynamic condition of skin blood flow and may be of predictive value, whereas a single even normal value is not an adequate index of flap perfusion.

10. ATTACHMENT OF GRAFTS – FLAPS IN SELECTED COMPROMISED WOUNDS

Etiology of unsuccessful covering of non-healing areas in compromised tissues is related to pre-existing hypoxia, predisposing the negative outcome of transferred tissues in case a flap or graft is required.

HBO should be considered as an adjunct therapy, both preventive and supportive, for the attachment of transferred grafts or flaps in hypoxic tissues where the diminished local oxygen delivery is inadequate to satisfy the high-energy demands.

Acute injuries like thermal burns and necrotic lesions or chronic ones like irradiated tissues and diabetic wounds may benefit from HBO, applied in parallel to the primary treatment to optimize the conditions for restoration of the local metabolic balance and promotion of healing.

In acute injuries the presence of edema, hypoxia, microcirculation impairment, enlargement of the damaged area and high risk for infection are usual predisposing for HBO application, to improve outcome of transferred tissues.

Ketchum et al.[120] in an experimental study on rats, regarding the HBO effect on small burns (1^{st}, 2^{nd}, 3^{rd} degree), reported an improvement in microvascular growth. Author through micro-angiographic studies supported the hypothesis that HBO had an ameliorating effect on the revascularisation of the injured area.

In a clinical series of 20 patients with severe burns (20-80% surface area) Hanquet et al.[121] demonstrated that HBO use resulted in acceleration of wound healing and better integration of grafts versus a control group.

Waisbrein et al.[122], performing a clinical retrospective study on 36 patients with burns, reported an important reduction in grafted skin area in the HBO group equal to ¼ of the relevant in the control group.

Necrotizing lesions (crushes syndromes, complicated open traumas) or infections (anaerobes, mixed) are often accompanied by aggressive surgical debridements requiring a tissue transfer for healing. Bouachour et al[123] in a controlled series of severe limb injuries reported among other results that skin grafting was reduced in the HBO group.

Chronic injuries like irradiated tissues and diabetic wounds have been demonstrated clinically and experimentally to be favored by HBO application.

After radiation therapy, tissue hypoxia is installed through induced capillary endarteritis. This secondary ischemia was shown to be restored through the HBO promotion of neovascularity. An enlarged microvascular net in the irradiated receptor bed is mandatory for an uncomplicated tissue transfer process, as Davis and Heckman[124] have shown in a series of myocutaneous flaps. In a clinical series of soft tissues radiation injuries Hart and Strauss[125] reported successful skin grafting after HBO use.

Diabetic ulcers, the most favored wounds treated with HBO, may benefit further when a tissue transfer is required to cover a defective area. A multidisciplinary approach in this kind of wound is obligatory (diabetic balance, regular debridements, use of proper antibiotics, HBO use) in order to establish a sufficient granulation and support the attachment of a graft or flap.

11. SUMMARY

Plastic surgery may repair many defects using a transferred tissue through different techniques concerning blood supply, types of flaps, and involved tissues, matching the patient's local needs and conditions. An increasing element of risk is related to the degree of any present hypoxia, thus creating suitable conditions for "compromised" transferred tissues.

HBO appears to posses unique physiologic effects for healing promotion, when hypoxia is present at the wound site, but seems to be of no benefit in normal healing process.

Primary goal of HBO application is to enhance tissue oxygen delivery and ATP balance, thus promoting its established effects as are: protection from reperfusion injury, edema reduction, neo-capillary formation, micro-wound environment improvement and infection resistance.

HBO may be used for preparing a granulating host base or when tissue viability is doubtful, or when previous "takes" of transferred tissues have failed.

Threatened grafts and flaps have been experimentally and clinically proved to benefit from HBO adjunct use, when it has been applied on time and in suitable cases.

As in the majority of HBO approved indications, the efficacy of HBO is still controversial in the relevant community of plastic surgeon, due to the lack of properly performed controlled, randomized clinical studies.

Despite of the above issue, recent experimental and clinical acquired experience of HBO action may confirm its specific role as adjunct treatment in the "compromised" transferred tissues, thus inviting for further application of HBO therapy in Plastic and Reconstructive surgery.

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Chapter 2.2.8

RADIO-INDUCED LESION IN NORMAL TISSUES

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Abstract: Late complications are one of the major factors limiting radiotherapy treatment, and their treatment is not codified. Hyperbaric oxygen (HBO) has been used for over half a century in an attempt to treat late complications. This prompted European Society for Therapeutic Radiotherapy and Oncology and European Committee for Hyperbaric Medicine to organise a consensus conference in October 2001, dealing with the HBO indications on radiotherapy for the treatment and prevention of late complications. This updated literature review is part of the documents the jury based its opinion on. Despite the small number of controlled trials, HBO may be indicated for the treatment of mandibular osteoradionecrosis in combination with surgery, haemorrhagic cystitis resistant to conventional treatments and the prevention of osteoradionecrosis after dental extraction, whose level of evidence seems to be the most significant though randomised trials are still necessary

Keywords: radiotherapy, late complications, osteoradionecrosis, soft tissue radionecrosis, post radiation proctitis, post radiation cystitis, post radiation laryngeal necrosis

1. OSTEORADIONECROSIS

Osteoradionecrosis is one of the most serious complications arising from head and neck radiation therapy, and so one of the most studied. Mandibular bone is by far the first site concerned, with a few cases reported involving maxilla or temporal bone[1,2]. Since its description in the 1920s, its incidence, causality, contributing factors and management have been a topic of debate.

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Most authors define the entity in terms of clinical parameters in their studies. Incidence reporting for osteoradionecrosis may not be as accurate as for other diseases due to the lack of standard definition. Certain authors define osteoradionecrosis as an bone exposure longer than 3 months[3-6]. Marx and Johnson[7] define it as an area of exposed bone that has failed to show any evidence of healing for at least 6 months. Radiographically, periosteal thickening and lytic destruction are common[8]. A tumor recurrence must be excluded. Necrosis or irritation of adjacent tissues are common. As necrosis persists, secondary infection, fistula formation or fracture may ensure.

1.1 Incidence and pathophysiology

The reported incidence is variable. Comparison is difficult because of differences between studied population (radiotherapy alone, technique of radiation, brachytherapy, surgery more radiotherapy, policy of dental management…). Overall the incidence has considerably decreased for the last twenty years and in recent series the incidence is inferior to 5 %[5,9-12].

Early the role of vascular damage in the pathophysiology of osteoradionecrosis has been advocated[13,14]. Its pathogenesis has been studied in a animal model in which high dose, fractionated megavoltage (equivalent to 70 Gy in 35 fractions of Cobalt 60) was administered to the mandible of rhesus monkeys[15]. Blood vessels in the periodontum, periosteum, haversian bone and marrow were reduced in number and calibre (by obliterative endarteritis, fibrosis, periarteritis).

Similar histologic changes have been observed in human specimens, with fibrosis of the marrow spaces[7,16,17]. The vascularisation of the mandible is precarious. All areas of the craniofacial skeleton other than the mandibular body are supplied by periosteal and muscular perforators that are very redundant. The entire posterior segment of the mandible receives most of its blood supply from the surrounding musculature[18]. In contrast, the inferior alveolar artery has been shown to be primary nutrient source of the mandibular body[18,19]. Additionally, the atherosclerotic changes in the inferior alveolar artery precede those in the others vessels of the head and neck[20].

Initially sepsis was considered as an very important factor of the pathogenesis of osteoradionecrosis. Meyer[21] defined the classic triad as radiation, trauma and infection. Osteoradionecrosis and osteomyelitis were synonym. Introduction of sepsis by a trauma in avascular bone produced osteomyelitis. Irradiated bone was thought to be susceptible to infection because of its inability to defend against bacteria due to decreased vascularity[13-15,22-26]. The presence of bone sepsis hasn't been clearly demonstrated in early studies. Epstein[5] cultured the necrotic sites of 26 cases of osteoradionecrosis with aerobic techniques, however no pathogens has

were identified. Happonen[27] used immunocytochemics methods to detect microorganisms in osteoradionecrosis : *Actinomyces sp*. was found in all five cases, whereas its presence has been detected with conventional method (microbiologic culture) in only one case. In all patients mixed infection was found in microbiologic cultures (*Streptococcus viridans* was the most common). Others publications report cases of Actinomycosis in osteoradionecrosis[28,29]. Nevertheless the presence of microorganisms in necrotic bone does not prejudge their role in pathogenesis. Marx[7] studied the necrotic bone: no organisms (aerobic, anaerobic or fungal) could be cultured or observed in the deep bone, although many different organisms were identified in all cases of osteomyelitis and infected bone grafts, both superficial and deep. In osteoradionecrosis the organisms were limited to the surface of bone exposed to the oral environment. He concluded by replacing the classic sequence of radiation-trauma-infection with a sequence of radiation, hypoxic-hypovascular-hypocellular, tissue breakdown induced or not by trauma (collagen lysis and cellular death exceeding synthesis and cellular replication), chronic non-healing wounds. The same author, recording TcPO2 of central radiation port, has shown there was no evidence of spontaneous microvascular revascularization with time[17]. It was recently suggested that osteoradionecrosis may be induced by a predominantly fibro-atrophic mechanism[30].

1.2 Risk factors

An important risk factor associated with osteoradionecrosis is the total radiation dose. Several authors found a total radiation dose greater than 65-70 Gy as increasing the risk of osteoradionecrosis[25,31-38]. Bedwinek[31] found no osteoradionecrosis when the dose was less than 60 Gy, and 9% for doses greater than 70 Gy. Morrish[37] found 0% incidence less than 65 Gy, 27.6% (dentulous patients) and 6.6% (edentulous patients) for 65 to 75 Gy, and 84.6% (dentulous patients) and 50% (edentulous patients) for doses greater than 75 Gy. Murray[25] found an incidence of 14% for 50-60 Gy, 23.2% for 60-70 Gy, 19.5% for 70-80 Gy and 28.6% for doses greater than 80 Gy.

Volume of mandible irradiated is also a risk factor of osteoradionecrosis[11,13,32,33,35,36,39,40]. For Beumer[32], for doses above 65 Gy, the risk of osteoradionecrosis increases significantly with the volume of the mandible irradiated. For Emami[35], the TD 5/5 (probability of 5% complication within 5 years from treatment) is 65 Gy for a small section of the mandible (1/3), and 60 Gy for a larger volume; the TD 50/5 (probability of 50% complication within 5 years from treatment) can be projected as approximately 77 Gy for a small volume with 72 Gy for the 2/3 and full volume.

Hypofractionation significantly increases the risk of osteoradionecrosis[34,40]. A randomised trial of CHART (Continuous Hyperfractionated Accelerated Radiotherapy: 54 Gy in 36 fractions over 12 days) versus conventional radiotherapy (66 Gy in 33 fractions over 6.5 weeks), including 918 patients found similar incidence of osteoradionecrosis in the two arms[41]. Using hyperfractionated radiotherapy, a short interfraction interval (< 6 hours) is a significant risk factor for osteoradionecrosis[42].

The technique employed for irradiation can be a risk factor. The association of external beam therapy and brachytherapy increases the risk of bone complications[25,34,43-47]. With this technique, total dose is also a risk factor[11,44] : doses superior to 80-90 Gy significantly increase the risk of osteoradionecrosis.

The modalities of brachytherapy merit to be studied. A dose rate superior to 0.55 Gy/h is a risk factor for osteoradionecrosis[44,48-50] (0.7 Gy/h for Pernot[11]). The volume irradiated is also one[11,48-50]; for some authors the risk significantly increases for volumes superior to 25-30 cm^3 [11,51]. It is now clearly established that a leaded protection decreases the dose to the mandible to 50%, and so decreases the risk of osteoradionecrosis[11,44,45].

Several risk factors are related to the tumour. Osteoradionecrosis is more frequent when the tumour is adjacent to bone[3,25,31,36,38,39,52]. The floor of the mouth is the location for which the risk is greatest[4,11,50,53]. Dental management has been a topic of debate, and the practices have dramatically changed since twenty years. Before, all teeth or teeth in radiation port were extracted. This “aggressive“ management is a risk factor for osteoradionecrosis; extraction of only unsalvageable teeth with primary closure, restoration of remaining teeth as needed, and daily fluoride application is the most adapted practice[3,10,25,31,32,39,52-55]. A minimum delay between extraction and initiation of radiotherapy of 10-21 days is necessary[17,56,57]. Daily fluoride application significantly decreases dental caries and periodontal infection[10,51,53,56,58-60].

One of the most important risk factor is dental extraction after radiotherapy[3,4,11,26,33,53,54,59,61,62]. Marx[62] in a randomized trial showed that hyperbaric oxygen therapy before and after teeth removal in irradiated patients versus penicillin significantly decreases osteoradionecrosis (increasing angiogenesis and cellular density). Seventy-four patients having received irradiation to doses of 60 Gy or greater were randomised in two groups. One group of 37 patients, in whom a total of 135 teeth had to be removed, received 1 million units of penicillin G intravenously just before surgery and 500 mg of phenoxymethyl penicillin four times daily for 10 days after surgery. The other group of 37 patients, in which a total of 156 teeth had to be removed, received no antibiotics but twenty sessions of hyperbaric oxygen before tooth removal and 10 sessions after tooth removal. Sessions of

HBO (2.4 ata, 90' each session) were conducted once daily, 5 or 6 days each week. In the penicillin group eleven patients (29.9%) developed osteoradionecrosis, whereas in the HBO group only two patients (5.4%) developed osteoradionecrosis. This difference is statistically significant, however the incidence of osteoradionecrosis in non-HBO group seems high. Using a similar protocol of hyperbaric oxygen therapy (20 dives before, 10 dives after teeth extraction), Lambert[63] in a retrospective study found no osteoradionecrosis in 75 patients.

However, some authors have demonstrated that post-radiation extraction without hyperbaric oxygen is safe with very strict precautions[53,56,64,65]. Horiot[56] reported one osteoradionecrosis in 22 patients who required post radiation dental extractions (with peri antibiotic coverage, alveolectomy, primary closure). In Maxymiv's study[65] (196 removed teeth included within the treatment volume in 72 patients), no osteoradionecrosis occurred. Clayman[66] in a literature review estimates that the incidence of post-extraction osteoradionecrosis is relatively low: 5.8% for studies published since 1968, and 2.1% for studies published between 1986 and 1995.

The randomised trial by Marx[62] showed the efficacy of HBO in the prevention of osteoradionecrosis following dental extractions in the irradiated territory. Indications should nevertheless be considered for each individual case and could be reserved for patients with the most significant risk.

1.3 Treatment

1.3.1 Conservative treatment

It is often the first stage of treatment. In most of the series it associates local application of antiseptic (chlorhexidine), analgesics if necessary, oral hygiene, systemic antibiotics, eventually sequestrectomy and smoothing sharp of bony projections[3,4,6,9,33,39,53,67-71]. However the optimal scheme of antibiotherapy is not determined and its efficiency has not been demonstrated in controlled studies. Penicilline is often used. Tetracycline is incorporated into bone crystals and then is for Coffin[9] the antibiotic of choice for clinical aseptic lesions. Conservative measures allow healing from 15 to 100% of the cases without the adjunct of hyperbaric oxygen therapy, but after several months of treatment[3,4,6,9,33,39,53,67-71]. In certain series, up to 57 to 100% of the patients healed, or had lesions stabilized or improved[4-6,53]. Nevertheless it is difficult to judge the efficiency of conservative treatment because of the lack of standard definition, classification of osteoradionecrosis, and controlled trials.

1.3.2 Surgery

Most of the authors reserve radical surgery to the following indications: intractable pain, fistulae, pathological fracture, no response to conservative treatment[3,4,6,9,26,28,31,67,70,72,73]. Mandibular resection is necessary in 12 to 40% of patients initially treated with conservative measures without hyperbaric oxygen therapy[3,11,13,26,31-33,52,70,74]. Hemimandibulectomy with an intra oral approach is the most employed technique, with rapid healing and few complications. Koka[73] in a study of 104 hemimandibulectomy for osteoradionecrosis (100 intra oral approach, 4 extra oral approach) found 18 % of post-operative complications: minor sepsis in 8.6 % cases, major sepsis in 2.9 %, hemorrhage in 2.9 %, fistula in 3.8 %. All the complications were effectively controlled. Fracture and pain were the major indications. All the patients who had pain (54 %) and trismus (17%) became asymptomatic following surgery. Alimentation was reestablished within 2-3 weeks in 65 % cases, and for the rest delayed beyond a month.

Multiple techniques of reconstruction have been documented in surgical literature and include myo-osseous or myo-cutaneous flaps; microvascular iliac crest or fibular graft is a more recent technique, with good aesthetic and functional results[11,73,75-79].

1.3.3 Hyperbaric oxygen therapy

HBO stimulates angiogenesis, increases neovascularization, cellular levels of oxygen, fibroblast and osteoblast proliferation and collagen formation in irradiated tissues. In an animal model, 20 sessions at 2.4 atmospheres absolute (ata) pressure, 90 minutes each day, significantly increase angiogenesis and cellular density in irradiated mandibles versus normobaric oxygen and air breathing control ($p=0.001$)[80]. In an human model, transmucosal oxygen tension in irradiated gingiva increases from 50 to 86 % of the oxygen tension of healthy gingiva after 30 dives (90 minutes/day at 2.4 ata)[81]. A study showed that angiogenesis rapidly progresses to a plateau at 80 to 85 % of non irradiated tissue vascularity by 20 sessions; transcutaneous oxygen measures remain at that level during several years[62]. Improvement of angiogenesis and cellular density has been histologically proved too[17,62,82].

HBO has been used in the management of ORN since the 1960s. Hart and Mainous suggested as early as 1976 that its action may be due to an enhancement of vascular proliferation[69]. Several investigators have reported the use of HBO as an adjunct to the conservative treatment or to radical surgery in non controlled trials[3,5,28,68,69,71,77,83-86]. The modalities of HBO and

conservative measures are variable. The rates of healing range from 30% to 100%; all these studies conclude that HBO is an effective adjunct.

Marx[82] established a protocol associating surgery and HBO; it consists of three stages. In stage I, after 30 sessions (100% oxygen, 2.4 ata, 90 minutes/day, 5 day/week), wound is re-examined: in case of improvement, the patient completes a full course of 60 sessions. If there is no improvement, the patient is advanced to stage II: a sequestrectomy with primary closure is accomplished, with HBO if healing progresses without complication. If the wound dehisces, the patient is advanced to stage III: a resection is accomplished. In a patient whose initial presentation includes pathologic fracture, orocutaneous fistulae, or radiographic evidence of resorption to the inferior border, an initial course of 30 sessions is given, and the patient directly enters in stage III. In stage III-R, 10 weeks after resection, the patient is given an additional 20 sessions in preparation for bone graft reconstruction. With this technique, resolution was achieved in stage I for 15%, in stage II for 14%, and in stage III (radical surgery) for 70% of the patients (total= 58). The same rates have been retrieved with 268 patients[87]. London[84] using the same protocol showed clinical improvement with decreased pain in all sixteen patients. Marx proposed HBO as an adjunct to bone graft reconstruction too, with a 91.6 % rate of success[88].

Recently Annane[89] reported on a prospective randomized trial comparing HBO to placebo in the treatment of patients with mandibular ORN. Patients were included in the study if they had (at least 2 months after optimal conservative treatment, including antibiotics, local irrigation, and surgery) one of the following clinical criteria: pain, dysesthesia in the distribution of the inferior alveolar nerve, areas of bone exposure, trismus, fistula; and one of the following radiographic criteria: increased density, periosteal thickening, diffuse radiolucency, mottled areas of osteoporosis, and sclerosis sequestration. Exclusion criteria included fracture or radiographic evidence of bone reabsorption to the inferior border, ongoing cancer, previous treatment with HBO, or contraindication to HBO. Patients were assigned to receive 30 HBO exposures preoperatively at 2.4 ata for 90 minutes or a placebo, and 10 additional HBO sessions postoperatively or a placebo. The hyperbaric sessions were delivered twice daily. Patients received either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (placebo). Before randomization, patients were graded by the same surgeon in group A: areas of exposed bone <20 mm in diameter, no cutaneous fistula, and no a priori need for surgery; and in group B: areas of exposed bone of > 20 mm, cutaneous fistula, or an a priori need for surgery. Sixty eight patients were included. At one year recovery was not significantly different in the two groups. Time to pain relief in the 60 patients who presented with pain at inclusion was similar in

the two treatment arms. Of the 54 patients in stage A at enrolment, 26 (48.1%) progressed to stage B, 14 (56%) of 25 in the HBO arm and 12 (41.4%) of 29 in the placebo arm (p=0.41).

In conclusion uncontrolled trials are supporting HBO use in the treatment of ORN. A recent double blind randomized controlled trial did not show positive effect with HBO. However HBO regimen was atypical (2 sessions a day to a total of 25 sessions instead of the usual 30 + 10 regimen). At the present time, the efficacy of HBO in the treatment of ORN is unclear and further investigation is warranted. Nevertheless HBO should be useful in patients with more severe ORN.

2. SOFT TISSUE RADIONECROSIS

2.1 Rectum

Late rectal morbidity is principally observed in patients treated with radiotherapy using curative doses for cervical, prostate and rectal cancers.

During radiotherapy, inflammatory changes are prominent and consist in migration of leucocytes through the crypt wall, crypt abscesses, inflammatory cell infiltration in the surface epithelium and lamina propria, and a striking accumulation of eosinophilic granulocytes. These histologic changes are maximal 2 weeks after the beginning of the treatment[90]. Later radiotherapy induces swelling of the fibroblasts, a subendothelial deposition of hyaline material, an endothelial proliferation with endarteritis of the arterioles. The most marked changes are noted in the submucosa, contrary to the acute radiation injury which is most prominent in the mucosa[91]. Superficial neovascularization (telangiectasia) can be observed even in asymptomatic patients[92]. These pathological changes can result in rectal tissue ischemia and fibrosis, leading to bleeding, ulceration, stricture or fistulae[93].

Patients with increased acute toxicity during radiotherapy significantly increase the risk of late rectal morbidity[94,95]. Around 80 % of late rectal complications occur within 30 months after the end of the treatment[94,96-99]. However the interval can be longer, until several years[93]. Radiation proctitis can include tenesmus, bleeding, low volume diarrhoea, rectal pain. A stricture results in abdominal pain, constipation. The main symptom of ulceration is pain, increasing with defecation. It can leads to abscess or fistulae[93,100,101].

Several classification have been developed[102]; the RTOG defined proctitis as " being characterised by rectal irritation or urgency (tenesmus),

presence of mucous or blood in the stool and in some patients frequent loose bowel actions". More recently the LENT/SOMA scoring has been introduced which lists 6 symptoms for proctitis[103]. Some authors have utilized their own classification[96,99].

2.2 Incidence and risk factors

2.2.1 After radiotherapy for cervical carcinoma

Cervical carcinoma can be treated with the association brachytherapy and surgery. With this technique, the incidence of rectal complication is low, about 1 %[104-106]. Perez[107,108] has compared preoperative radiation followed by surgery with radiation alone in a randomized and in a retrospective trial: major rectal complications were more frequent with radiation alone, but not significantly: 5.7 % versus 0 %, and 3.4 to 6 % according to the tumour stage versus 1 to 4.5%.

Using radiation alone (external beam irradiation and brachytherapy) the incidence of severe rectal complications is variable. Perez[109] in 1456 patients found respectively 4.1 %, 3%, and 3 % of major rectal, bladder and small intestinal complications. The most frequent grade 2 sequelae were proctitis (3%) and cystitis (0.7%) (Table 2.2.8-1).

Several studies have shown the superiority of concomitant chemo-radiotherapy versus radiotherapy alone, or concomitant chemo-radiotherapy more surgery versus radiotherapy more surgery for locally advanced or high-risk disease[112-117]. Whitney[116] found the same incidence of late intestinal or urinary major complications at 3 years (about 16%) but chemotherapy was given in the 2 arms.

Morris[113] who compared radiotherapy alone and radiotherapy more 5 Fluoro-uracil and cisplatin found no significant difference in "late" effects (occurring or persisting more than 60 days after the completion of the treatment): about 7.5% and 1% of severe rectosigmoideal and bladder complications. Tseng[118] found no difference in late intestinal or urinary complications too. However these studies are recent, with a short follow-up; Grigsby[119] reported higher complication rates in a series of patients treated with concomitant chemoradiotherapy (5 fluorouracil and cisplatin).

Table 2.2.8-1. Major complications at 5 years, using radiation alone

	Number of patients	Colon	Small intestine	Bladder
Komaki[110] 1995	1686	8.7%* (bowel)		5 %*
Pernot[106] 1995	361	2.2% (gastro-intestinal tract)		2 %
Eifel[111] 1995	1784 (Stage IB)	2.3%* (rectum)	3.9 %*	2.6%*
Perez[109] 1999	1456 (Stage IB to IVA)	4.1%	3%	3%

* Actuarial rates

Prior abdominal surgery, stage and diabetes are risk factors for rectal complications[97,111,120]. It's now established that old age is not one[97,99,111,121]. Pignon[121] in a meta analysis including 1619 patients (nine EORTC trials of radical radiotherapy for pelvic cancers) found no difference in late intestinal or urinary complications according to the age (about 9%). Conversely the cumulative risk is greater for patients treated at a young age[97,111] (before 40 years for Lanciano[97]).

The risk of proctitis increased as a function of rectal dose[122-124]. For Montana[122], the rate is 2% for patients receiving less than 50 Gy to the rectum, and 18% for those receiving more than 80 Gy, with a significant relationship between rectal dose and severity of proctitis. For Pourquier[123], when mean and maximal rectal doses do not exceed 60-70 Gy, the percentage of complications remain between 5 to 10%, and are less severe; there is a rapid rise in the number of complications above 75-80 Gy. The paracentral radiation dose is also correlated to the risk of complications and may reflect the dose to bowel and bladder; Lanciano[97] in 1558 patients reported a significant higher risk if paracentral dose is superior to 75 Gy. Perez[109] reported 4% of rectosigmoideal complications with dose lower than 75 Gy and 9% with higher doses. Logsdon[125] found a risk of major complication greater for patients with FIGO III B cervical carcinoma treated with dose superior to 52 Gy of external beam irradiation to the central pelvis, followed by brachytherapy. For Roeske[120], the point A and external beam irradiation doses were the most significant treatment related factors.

Major rectal complications are more frequent when the total rectal dose and the HWT (Height, Width, Thickness) volume (volume enclosed by the 60 Gy isodose for combined irradiation) are higher[96,126-128].

Several authors have studied the role of dose rate. Haie-meder[129] in a prospective randomised trial comparing 0.4 Gy/h and 0.8 Gy/h reported more complications with the higher dose rate. In a randomized trial of preoperative brachytherapy, the patients treated with the higher dose rate (0.73 Gy/h versus 0.38 Gy/h) showed a two fold increase in surgical difficulties[130]. Perez[109] found an increased rectal morbidity with dose rate higher than 0.8 Gy/h too.

2.2.2 After radiotherapy for prostate carcinoma

In recent series, severe late rectal morbidity is inferior to 5 %[93,131-136]. Dose and volume of irradiated rectum are closely connected to late rectal morbidity. Perez[137] showed that conformal versus conventional radiotherapy allows a two third reduction in normal bladder or rectum receiving 70 Gy or more; with this technique proctitis was significantly lower (1.7% vs 9.1%). Dearnaley[138] in a randomised trial confirmed these results: 5% vs 15% superior or equal RTOG grade 2 proctitis with conformal versus conventional radiotherapy (p=0.01). Boersma[131] reported in a dose escalation study the limits above which rectal bleeding was significantly increased: >65Gy to more than 40% of the rectum wall volume, >70 Gy to more than 30%, and >75 Gy to more than 5%. Watcher[139] using dose-volume histograms as predictive factors, showed an actuarial incidence of 31% of late rectal bleeding at 3 years (EORTC/RTOG grade 2) if more than 57% of the rectum volume was included in the 90% isodose (60 Gy), versus 11 % if this volume is lower than 57% ($p<0.03$).

2.3 Treatment

2.3.1 Conventional treatment

Local corticoids have been rarely studied in this indication. A randomised prospective trial (18 patients) has showed the efficiency of rectal steroids, but sucralfate was superior[140].

Two retrospective trials, including 9 patients, conclude that 5-aminosalicylic acid enemas are not effective in the treatment of radiation proctitis[141,142].

Rectal sucralfate has improved diarrhoea and bleeding in 3 patients[143]. In a randomized trial, rectal sucralfate allowed improvement of the symptoms in 94 % of the patients[140]. A retrospective trial, including 26 patients, showed and improvement in 77% and 92% at 4 and 16 weeks; 22% had recurrence of bleeding. All recurrences responded to the same therapy

(20 ml of 10% rectal sucralfate twice a day)[144]. Several authors reported the efficiency of sucralfate (enema or oral administration)[145,146].

Intra rectal application of formalin (formaldehyde) has been used in retrospective trials. The application can be realized under general anaesthesia or sedation. Rectal bleeding is controlled in 75% to 100% of the cases[147-153]. Biswal[147] presented 16 patients, with bleeding not responding to steroid enemas; formalin stopped bleeding in 81 % of them. In another study, bleeding stopped in 22 of 29 patients (after one application in 17 of them)[149]. The technique of application must be strict, because formalin can induce colitis[150]. Formalin seems effective, however randomised trials are necessary.

Local application of short chain fatty acids (SCFA) has been studied[154]. A first non controlled trial showed a clinical improvement in all 7 patients[155]. Two randomised trials are contradictory. In 15 patients, SCFA enemas were not more effective than placebo[156]. In 19 patients, after five weeks, rectal bleeding significantly decreased, and haemoglobin values increased in SCFA treated patients[122]. Larger trials are necessary to conclude.

Laser (Nd-YAG or Argon) can be used to destruct telangiectasia. An important trial included 47 patients with rectal bleeding; after a median of 2 procedures, bleeding was controlled in 37 of them, with a median follow-up of 14 months[157].The efficiency of Nd-Yag laser has been confirmed by retrospective trials[158-161]. Rectal ulceration, stricture, ileus or fistulae may occur[157,158,161]. Argon laser has been studied in non controlled trials. In one of the most important trial, a median of three procedures was performed; bleeding stopped in all 14 patients, but recurrent bleeding occurred in 10 patients, requiring maintenance therapy[162].

Coagulation of telangiectasia can be realized by bipolar electrocoagulation, heater probe or more recently by argon plasma. Heater probe and bipolar coagulation seem to be equivalent; 12 and 9 patients with bleeding resistant to steroid enema were cured, after a median of 4 procedures[163]. Argon plasma obtains same results, in non controlled trials[164-167].

A phase II trial by the RTOG suggests that proctitis could be managed by pentosanpolysulfate (91% of complete and partial response, in 13 patients)[168].

The main indications for surgery are rectovaginal or rectovesical fistula and rectosigmoidal stricture[93,169,170]. The reported mortality in old series varies from 0% to 32%[93,169], seems few actually[96,170], but surgery must be reserved for the more severe cases, resistant to non surgical treatment. In the series reported by Jao[169], 40 of the 62 surgical patients had post operative complications; rectal resection followed by colostomy is correlated with a lower morbidity rate. However coloanal reconstruction with an ileocecal

segment is feasible and allows a better anorectal function, and a good continence[170,171].

2.3.2 Hyperbaric oxygen therapy (HBO)

The first case of hemorrhagic radiation proctitis treated by HBO has been reported in 1991[172]. Others retrospective trials report its efficiency[173-182] (Table 2.2.8-2). Warren[181], in 14 patients, found complete resolution of symptoms in 8, and one had improvement (with a median follow up of 17 months). A trial included 18 patients with radiation proctitis; most of them have been treated for prostate carcinoma. Most had failed previous therapies: steroids[183], formalin[158]. The average number of session was 24 (2 Atmosphere Absolute (ata), 105'/session, 6 days a week). Before HBO 17 patients complained bleeding: in 4 of these it stopped completely, and three had partial improvement. About 50 % of patients improved (bleeding, incontinence, diarrhoea, pain)[182]. The largest study included 36 patients; toxicity was recorded with the SOMA–LENT system. The score was 1 in 1 patient, 2 in 11 patients, 3 and 4 in 16 and 8 patients. Complete response was defined as the disappearance of symptoms and endoscopic lesions, while partial response was defined as a decrease of at least one point to the SOMA LENT score and failure was described as a stagnant or worsened score. The long-term results were able to be evaluated in 32 patients. With a mean follow-up of 52 months, a complete or partial response was observed in 21 patients[176]. HBO has been successfully used in few cases of duodenal and rectal ulceration too[173,184]. Nevertheless, no controlled study was published and the level of evidence of HBO beneficial action is weakly supported.

Table 2.2.8-2. Results of HBO in the treatment of radiogenic late rectal complications

Authors	N	Study design	Symptoms	HBO_2 sessions pressure	Results	Follow up (months)
Bui[174] 2004	18	Retrospective	RTOG grade 14 patients <3 4 patients ≥3	40 (20-60) 2,4 ata	22% with durable improvement	72
Mayer[178] 2001	10	Retrospective	80% failure of previous treatments	27 (18-60) 2,4 ata	Improvement of 1,7 points in RTOG/EORTC scale	14 (2.2-51.6)
Bem[173] 2000	2	Case study	Refractory severe pain, tenesmus, bleeding	60 sessions at 2,4 ata	Patients healed	3 and 48

Table 2.2.8-2. Continued

Authors	N	Study design	Symptoms	HBO_2 sessions pressure	Results	Follow up (months)
Kitta[177] 2000	4	Retrospective	3 patients with moderate to severe bleeding, typical rectoscopy findings, one had severe proctalgia	3 patients had 30 sessions, 1 had 60 at 2,0 ata (only 60' for each session)	Significant improvement in bleeding and rectoscopy findings for all patients, one patient had a bleeding relapse after 3 months, no change with the patient with proctalgia	11-13
Gouëllo[176] 1999	36	Retrospective	All refractory, 9 chronic wounds, 19 rectorrhagia, 9 profuse diarrheas	67 (12-198), 2,5 ata	9 healed, 12 improved, 11 failed.	52 (2-120)
Warren[181] 1997	14	Retrospective	Symptoms were refractory in 11 patients, 11 had rectorrhagia, 5 diarrhea, 5 tenesmus or colic.	40 (20-72), 2,0 ata in monoplace chamber, 2,4 ata in multiplace chamber	9 patients healed, 3 patients improved and relapsed by end of follow up, 2 did not respond at all.	16 (2-35)
Woo[182] 1997	18	Retrospective	All refractory, 17 rectorrhagia, 4 pain, 4 incontinence, 8 diarrhea	24 (12-40) 2,0 ata	7 rectorrhagias, 2 pain, 3 incontinence and 4 diarrhea improved or healed	14 (3-65)
Nakada[180] 1993	1	Case study	Severe rectorrhagia	30, 2,0 ata	Cessation of rectorrhagia and reversal of histological findings	NS

ata = atmosphere absolute
NS = Not Specified

2.4 Bladder

The acute changes in the bladder during radiotherapy include inflammation and mucosal oedema. The proliferation of vascular

endothelium continues several months after the treatment. Obliterative endarteritis with perivascular fibrosis result in ischemia[185]. Telangiectasia can be observed. Smooth muscle fibrosis, with collagen deposition, is responsible for the reduction of bladder capacity (urinary frequency, urgency)[186-188]. Cystitis is a syndrome characterized by irritative symptoms such frequency and dysuria; hematuria may or may not be a part of cystitis (RTOG definition)[98]. The SOMA/LENT score for bladder and urethral complications includes dysuria, frequency, hematuria, incontinence and decreased stream[103].

Bladder complications occur later than rectal complications: around 80% of them are present within 40 months after the end of the treatment; their median time of appearance is 23-30 months[96,97,99].

2.4.1 Incidence and risk factors

After radiotherapy for cervical carcinoma

As for proctitis, the association brachytherapy-surgery induces a low rate of severe genito-urinary complications: around 1 to 5%[104-106]. In 441 patients, Gerbaulet[105] found respectively 2.7% and 4.6% of severe urinary complications for stages I and II. Perez[107,108], comparing preoperative radiation and radiation alone in two trials, reported no significant difference: 4.1% vs 5.7%, and 3% to 10 % according to the stage vs 3%.

Using radiation alone, the rate of severe complications ranges from 2 to 5%[106,109-111,189] (Table 1). For Eifel[111], in 1784 patients with FIGO stage IB cervical carcinoma, the risk of developing major urinary tract complications was approximately 0.7% per year during the first 3 years, and around 0.25% per year for at least 25 years.

As for intestinal complications, old age is not a risk factor for urinary complications[97,99,111,121], whereas prior abdominal surgery is one[96,111]. Stage is a risk factor too[127]. The correlation between radiation dose and bladder complication is well documented[96,98,109,122,124,125]. For Logsdon[125], major pelvic complications significantly increase when the dose of external radiation is superior to 52 Gy. Montana[190] reported 3% of severe cystitis for patients receiving less than 50 Gy to the bladder, versus 12 % for doses superior to 80 Gy, with a significant relationship between bladder dose and severity of complication. Sinistrero[124] found a correlation between bladder dose and severity of cystitis too. Using low dose rate brachytherapy, bladder complications are more frequent with the higher dose rates[109,129,130]. Perez[109] reported 2.9% of grade 2-3 morbidity with dose rate inferior to 0.8 Gy/h, and 6.1% with higher dose rates.

After radiotherapy for prostate carcinoma

Lawton[98] reported 2.6% of grade 3 or higher cystitis, with 0.4% of grade 4 (RTOG scoring). Grade 3 or higher urethral stricture was the most common urinary complication (4.6%); hematuria was present in 3% of the patients. In modern series, severe late bladder morbidity is inferior to 5 %[131-134,136,191].

After radiotherapy for bladder cancer

Bladder complications are more frequent; the volume of bladder irradiated is greater, and the presence of the tumour may make the bladder more sensitive to radiotherapy. The risk of grade 3 or higher complication is ranged from 2 to 30%; using chemotherapy and radiotherapy, concomitant or sequential, the rates seem similar[190].

For Emami, after radiotherapy for pelvic malignancies, the TD5/5 for whole and 2/3 irradiation are 65 and 80 Gy; the TD 50/5 for whole and 2/3 irradiation are estimated at 80 and 85 Gy[126]. These last data are speculative because the entire bladder rarely receives these doses. For Marks[190], these doses are lower: he estimates the complication rate to be 5-10% with doses of 50-65 Gy delivered to 1/3 of the bladder, or with doses of 65-75 Gy to less than 20% of the bladder. Urethral strictures occur in less than 5% with doses between 60-70 Gy without a prior trans urethral resection (TURP); if a TURP was performed before radiotherapy, urethral strictures occur in 5 to 15%[190].

2.4.2 Treatment

2.4.2.1 Conventional treatment

Mild urinary frequency, caused by a minor reduction in the bladder capacity, can be treated with antispasmodics[192]. Hemorrhagic cystitis require bladder irrigation through a transurethral catheter[193].

For intractable hematuria, intravesical formalin instillation has been studied by several authors, with good results[125,186,188,194-199]. A preinstillation cystogram is necessary, to search a vesicoureteral reflux. General or intradural anesthesia is required. Contact time is ranged from 5 to 30 minutes[125,188]; after instillation bladder irrigation is performed. One of the most important published trial included 35 patients; different concentrations have been used: 1, 2 and 4%. Complete response has been observed in 31 patients after a single instillation; complication occurred in 31% of the patients. A 1% solution was as effective as higher concentration, and was associated with less morbidity[194]. Another retrospective study of 25 patients (15 cases of radiation cystitis) obtained the same results[188]. Potential complications include pain, dysuria, incontinence, extravasation, fistula[125,186,188,199]. Ureteral stenosis and or anuria, tubular necrosis, can ever

occur, specially in the cases of vesicoureteral reflux[200]. The incidence of these complications is difficult to establish. Formalin instillation has been studied in several small retrospective trials and seems effective. The morbidity is correlated to the quality of the technique employed and the concentration solution.

Sodium pentosanpolysulfate has been shown to be effective in few non controlled studies[201,202]. Intravesical instillation of alum has been described, with a limited short term success[203,204].

In a randomised trial, including 448 patients with bladder carcinoma (post-operative radiotherapy), superoxide dismutase significantly decreased acute and late cystitis and proctitis[205].

2.4.2.2 Hyperbaric oxygen therapy

Several authors have studied the use of hyperbaric oxygen in patients with radiation cystitis[174,178,206-221] (Table 2.2.8-3). Bevers[206] reported a prospective study of 40 patients; most of them required transfusion. Patients had received unsuccessful treatments: clot evacuation, electrocoagulation, alum, tranexamic acid. They received 20 sessions of 100% oxygen at 3 bar pressure for 90 minutes, 5 or 6 times a week. In 4 patients, 40 sessions were given because of persistence of symptoms. Hematuria stopped in 30 patients; occasional slight hematuria persisted in 7 patients; with a median follow up of 23 months, 9 recurrences occurred. The severity of initial hematuria appeared to influence the response to hyperbaric oxygen; failure of treatment was seen only in patients with a very severe hemorrhagic cystitis (3 patients with a mean blood transfusion need of 26 units). Lee[211] reported a retrospective study of 20 patients. They received an average of 44 sessions (2.5 ata, 100 minutes/session). Bleeding stopped in 16 patients, and markedly decreased in 2, with a mean follow-up of 14 months. However Del Pizzo[209] reported worse results with a long term follow-up. With a median follow-up of 2.5 years, 8 of 11 patients were asymptomatic (3 had required urinary diversion), but with a median follow-up of 5 years only 3 had complete resolution of their symptoms (8 had been treated with surgery).

The majority of these studies do not use a toxicity scale, which renders their comparison difficult. Although there is no randomised study, the results of one prospective study and several retrospective studies suggest that HBO is effective, leads to a high rate of bladder preservation and has few side effects. These conclusions tally with those of a literature review published by Feldmeier[222]. However, these results should be verified with controlled, randomised trials to obtain the highest level of evidence level.

Table 2.2.8-3. Results of HBO in the treatment of radiogenic late bladder complications

Authors	N	Study design	Symptoms	HBO_2 sessions pressure	Results	Follow up (months)
Chong[207] 2005	60	Retrospective	Haemorrhagic cystitis	33 (9-63) 2,4 ata	Hematuria stopped in 96% of cases	12
Bui[174] 2004	6	Retrospective	RTOG grade 3 patients <3 3 patients ≥3	40 (20-60) 2,4 ata	88% with durable improvement	72
Corman[208] 2003	62	Retrospective	Haemorrhagic cystitis	33 (mean) 2.4 ata	Complete response : 21 patients Partial response : 28 patients Failure: 8 patients	NS
Mayer[178] 2001	11	Retrospective	Radiation cystitis (macroscopic hematuria in 8 patients) RTOG grade Grade 2: 2 patients, Grade 3: 6 patients, Grade 4: 2 patients	26 (median) 2.4 ata	Grade 0: 2 patients, Grade 1: 4 patients, Grade 2: 2 patients, Grade 3: 1 patient, Grade 4: 1patient. P=0.004	18 (mean)
Hendricks[210] 2000	20	Retrospective	Cystitis	35 2 ata	Complete response: 14 patients, failure: 6 patients	13
Mathews[212] 1999	17	Retrospective	Haemorrhagic cystitis (blood transfusion in 8 patients)	14 (mean) 2 to 2.5 ata	Complete response : 11 patients, partial response : 2 patients, microscopic haematuria: 2 patients, failure: 2 patients	21 (mean)
Del Pizzo[209] 1998	11	Retrospective	Haemorrhagic cystitis (blood transfusion in all patients)	40 (mean) 2 ata	Complete response: 3 patients, complete response followed by recurrence:	61 (median)

Table 2.2.8-3. Continued

Authors	N	Study design	Symptoms	HBO_2 sessions pressure	Results	Follow up (months)
					5 patients, failure: 3 patients	
Bevers[206] 1995	40	Prospective	Haemorrhagic cystitis (blood transfusion in 30 patients)	20 (40 sessions in 4 patients) 3 ata	Complete or partial response: 37 patients	23 (mean)
Lee[211] 1994	20	Retrospective	Haemorrhagic cystitis in 19 patients, radiation cystitis without haematuria in 1 patient	44 (mean) 2.5 ata	Complete response: 16 patients, partial response: 2 patients, failure: 1 patient, radiation cystitis without haematuria: complete response	14 (mean)
Weiss[219] 1994	13	Retrospective	Haemorrhagic cystitis (blood transfusion in 9 patients)	60 2 ata	Complete response: 12 patients	30 (mean)
Nakada[214] 1992	6	Retrospective	Haemorrhagic cystitis	45 2 ata	Complete response: 5 patients	NS
Rijkmans[216] 1989	10	Retrospective	Haemorrhagic cystitis	20 3 ata	Complete response: 6 patients	7

ata = atmosphere absolute
NS = Not Specified

2.5 Other sites

2.5.1 Larynx

Laryngeal chondronecrosis is a rare complication of radiotherapy: less than 1 % with conventional daily fractions[126,223-225].

The most common presenting symptom is hoarseness[225]; the others accompanying symptoms are pain, dysphagia, odynophagia, dyspnea, induration of neck skin and subcutaneous tissues, fistula formation, fetor[223,225]. As for osteoradionecrosis, a tumor recurrence must be excluded.

Hypofractionation, total radiation dose, large treatment fields and involvement of cartilage by tumor are risk factors[225,226]. In 1979, Chandler[226] proposed a grading system, with a proposition of treatment for each grade. Grades I and II are expected, whereas grades III and IV are complications. The conventional treatment of chondronecrosis includes analgesics, steam, corticosteroids, antibiotics, temporary or permanent tracheostomy, and even laryngectomy. In early stage reactions (grades I and II), humidification and anti reflux regimen are usually effective. Grade III requires the addition of oral steroids, and appropriate antibiotics[223,226]. Chandler[226] reported 13 cases of grade III, treated with humidification and antibiotics, with clinical resolution in all of them. In non responsive grades III and grades IV, the treatment is surgical. If airway obstruction is present, a temporary or permanent tracheostomy is performed. A total laryngectomy is warranted for a necrotic and nonfunctional larynx.

Several investigators have studied the interest of HBO as an adjunct to the treatment. Hart[227] used HBO for five patients; all had cutaneous fistulae. Improvement was present in four of them. Ferguson[228] in eight patients with Chandler grade III and IV (4 grade IV) chondronecrosis found an improvement in seven of them; two patients with grade IV required temporary tracheostomy; one of the four required laryngectomy. Feldmeir[229] in nine patients (eight Chandler grade IV, one Chandler grade III) obtained the following results: the three patients with tracheostomies were able to be decannulated. All nine patients maintained their voice, and seven without hoarseness. None required laryngectomy. In 1998, London[230] published the results of an retrospective study. Five patients have been treated with 15 to 25 HBO sessions at 2.5 ata for 90 minutes; additional dives were given depending on clinical response. All the patients had advanced disease (Chandler grade III or IV) and were tracheostomy dependent; two were decannulated, and none required laryngectomy. Narozny[231] reported major improvement in all six patients. In the largest study published, Filntisis[232] presented 18 patients (two grade III, sixteen grade IV) treated with HBO. They received a mean number of 41 sessions (2 ata, 2 hours, twice a day, 6 days a week). Thirteen patients (72 %) had a major improvement; all of them maintained their voice. Five underwent total laryngectomy.

All these studies suggest that HBO has a beneficial effect in the management of laryngeal necrosis, whereas they are all retrospective studies and the global number of patients is small.

2.5.2 Head and neck soft tissue necrosis

The incidence of soft tissue necrosis is very variable, according to the technique used. Pernot[233], in a series of 1134 patients treated by external

irradiation and/or brachytherapy, found 18 % of small superficial ulceration disappearing within two or three months, 4 % of persisting necrosis and 1 % or deep ulceration requiring usually surgery or repeated hospitalisation. The median duration of these soft tissues necrosis was respectively 3, 8 and 11 months.

Using external beam radiation therapy alone, the risk factors are stage, total dose, shorter treatment; hypofractionation is not a risk factor, unlike osteoradionecrosis[234]. Using external beam radiation therapy combined with brachytherapy, risk factors are total dose superior to 80 Gy, a surface treated superior to 12 cm^2, a volume treated superior to 30 cm^3 and a number of lines superior to 6 for Pernot[233].

With brachytherapy alone, the risk factors are stage, total dose, a dose rate superior to 0.5 Gy/h (0.7 Gy/h for Pernot[233]), a large intersource spacing, a volume treated superior to 30 cm^3 [233,235,236]. The tumour site is also a risk factor: floor of mouth is more often affected than mobile tongue[236].

Current treatment of soft tissue necrosis includes local irrigation, wound debridement, antibiotics, analgesics and often prolonged observation. Surgery is rarely required. Pentoxifylline has been studied but its efficiency is not still confirmed[237,238].

Some cases of successfully treated soft tissue necrosis with HBO have been reported[239-242]. Farmer[240] reported two cases of nose and floor of the mouth necrosis, which were improved with HBO. Davis[239] reported recovery in 15 out of 16 patients following HBO (2.4 ata, 90 min daily, 45 sessions in average) used as an adjunct to surgery and antibiotic treatment. Neovius[242] published the results obtained in 15 patients treated with pre-operative radiotherapy. These patients presented with soft tissue necrosis, some of which also had fistula, free flap necrosis or chronic infections. Patients were treated with 30 or 40 sessions of 75 min, once or twice a day at 2.5 or 2.8 ata. Twelve of 15 patients healed completely, and 2 healed partially within 1–5 months after the introduction of HBO. However, only a few retrospective studies support the use of HBO for this indication, thereby leading to a poor level of efficacy evidence.

2.5.3 Breast and chest wall

HBO has been used in the management of breast and chest wall injury[227,243-245]. Carl[243] prospectively reported outcome in 44 patients presenting with pain, oedema, erythema, fibrosis and telangiectasia after lumpectomy and radiotherapy for early breast cancers. Complications were scored using modified LENT–SOMA criteria. Only patients with at least grade 3 pain or a summed LENT–SOMA score of 8 were studied. Thirty-two patients received a median of 25 sessions with 100% oxygen at 2.4 ata

for 90 min. Patients who received HBO had a significant reduction of pain, erythema and oedema compared to those who refused HBO; however fibrosis and telangiectasia were not significantly reduced. Gothard[245] reported a phase II trial in patients with chronic arm lymphoedema. The twenty-one patients received 30 sessions with 100% oxygen at 2.4 ata for 100 min over a period of 6 weeks. Arm volumes were measured in an operator-independent method. There was a statistically significant but clinically modest reduction in arm volume at 12 months follow-up; a controlled randomised trial is under development.

2.5.4 Nervous system

Using modern techniques, the incidence of neurological complication is very low. In the cases of focal brain necrosis, corticosteroids can allow improvement. Sometimes the evacuation of necrotic focus is necessary. In adults, the use of HBO is reported in some contradictory case reports[246,247]. In children, Chuba[248] reported 10 cases of brain necrosis treated with HBO. Patient age ranged from 4 to 23 years (median 12 years); all of them presented with new or increasing neurological deficits, associated with imaging changes. For 8 patients, necrosis was histologically proved. The 10 patients received 20 to 40 sessions (2-2.4 ata, 90 to 120 minutes). Initial improvement or stabilization occurred in all patients. For the 6 patients still alive (4 died of tumour progression) at follow-up (median 19 months), the benefit of HBO was durable. However the authors were unable to determine the relative effects of steroid therapy used in combination with HBO.

There is no curative treatment of peripheral nerve damage. Narcotics, corticosteroids and physiotherapy are used. Surgical procedures as neurolysis give uncertain results . Some cases reports of successfully treated patients with HBO have been published[235,249]. No randomised trial has shown the efficiency of HBO. A double blind randomised trial (34 patients) showed no evidence that HBO slows or reverses brachial plexopathy (12 months follow-up), in spite of improvements in sensory threshold[250].

No treatment of myelitis has shown to be effective in the long term. The administration of corticosteroids allows a transient improvement of neurological symptoms. In animal, HBO showed no benefit in the treatment[251], but should be interesting for prevention[252]. HBO has been used in case report[253] and retrospective trial[227], but has not shown its interest in controlled trials.

The data from the literature concerning the efficacy of HBO in the treatment of neurological side effects in radiotherapy is scarce. The negative result of a randomised study does not therefore recommend its use in the

treatment of plexopathy[250]. The level of evidence of efficacy in the treatment of complications of the central nervous system is very weak.

2.6 Conclusion

Few controlled trials are available concerning tissues radionecrosis. Complications are often not assessed with either the RTOG/ EORTC or SOMA/LENT scales, the duration of symptom improvement is not specified, and endpoints are not clearly defined. A small number of studies have reported facts about quality of life. It is therefore difficult to draw a guiding principle. Nevertheless, during the European Consensus Conference organised jointly by the European Society for Therapeutic Radiotherapy and Oncology (ESTRO) and the European Committee for Hyperbaric Medicine (ECHM), held in Lisbon, Portugal in October 2001, the international jury came to the conclusion that some indications have a higher evidence level than others due to the presence of prospective studies and the significant number of positive retrospective studies such haemorrhagic cystitis resistant to conventional treatments[254] (table 2.2.8-4). These recommendations are however not supported the highest level of evidence based on several randomised trials. In future, the setting up of multicentre controlled trials to compensate for the scarcity of these complications may bring an answer to these issues. This will require a close collaboration between physicians concerned with hyperbaric medicine and radiation oncologists.

Table 2.2.8-4. Indications of HBO in the treatment of radio-induced lesions in normal tissues[254]

Recommendation grade	Indication
Level 2 – convincing grade	Radionecrosis of the mandible
	Radiation Cystitis of the bladder resistant to conservative measures
	Tooth extraction in irradiated tissues (preventive action)
Level 3 – evidence of beneficial action but weakly supported	Radionecrosis of other bones
	Radiation-induced proctitis and enteritis
	Radiation-induced lesions of soft tissues
	Surgery and implants in heavily irradiated tissues (preventive action)
Level 4 – anecdoctal evidence	Radiation-induced lesions of the larynx
	Radiation-induced lesions of the central nervous system.
No evidence to support	Radiation-induced plexopathy

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Chapter 2.2.9

NON-HEALING WOUNDS

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Abstract: A large body of pathophysiological evidence supports the beneficial role of HBO in reversing a delayed healing process. Daily experience supports its use in the clinical management of patients with non-healing wounds. T_CPO_2 measurement is a valuable and helpful method for patient selection, follow-up and treatment monitoring.
The ECHM, in its 7th European Consensus, has confirmed its recommendation for the use of adjunct HBO in the management of selected patients with delayed healing (diabetic foot lesions; arterial ulcers; compromised skin grafts; and musculocutaneous flaps). However, there is still a need to perform good randomized controlled studies to improve the level of evidence supporting these recommendations

Keywords: Wound healing, ischemic wound, infected wound, fibroblast, collagen, angiogenesis, granulator tissue, remodeling arterial ulcer, diabetic foot lesion, venous stasis ulcer, decubitus ulcer, chronic leg ulcer, transcutaneous oxygen pressure

A chronic (non-healing) wound or the so-called 'problem wound' is defined as any wound that fails to heal within a reasonable period of time by the use of conventional medical or surgical techniques[1].

As defined, this is a common clinical condition that prompts multiple medical visits, prolonged hospitalisation, and fastidious nursing care. Its economic and social costs are is largely unquantified but certainly exorbitant.

In this chapter non-healing wounds of the lower extremity are considered – as these are the most common. However the concepts apply equally to other non-healing wounds, whereas healing problems due to burns, cold, radiation or toxic injury are detailed in others chapters.

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1. PATHOPHYSIOLOGICAL BASES OF HEALING PROCESS IMPAIRMENT

Healing is a highly integrated biological process made up of several distinct but inter-related steps (Table 2.2.9-1). In order to heal, haemostatic and inflammatory mechanisms must be intact; mesenchymal cells must migrate to and proliferate within the wounded area; angiogenesis and epithelialization must occur; and collagen must be synthesized, cross linked and aligned properly to provide strength to the healed area. In open wounds contraction must also take place. All these processes must occur in proper sequence and time for optimal wound healing[2,3].

Table 2.2.9-1. Normal wound healing process

A normal wound healing response (type non closed skin incision) can be divided in different phases		
Day 0	Haemostasis	* vascular contraction
		* platelet aggregation and degranulation
		* fibrin formation (thrombus)
Day 0 – 3	Inflammatory phase	* vascular exudation
		* neutrophil infiltration
		* monocyte conversion to macrophage
		* matrix enrichment in proteoglycans
Day 3 – 6	Proliferative phase	* angiogenesis
		* fibroblast infiltration and proliferation
		* collagen formation
Day 3 – 15	Remodelling phase	* vascular maturation
		* fibroblast conversion to fibrocyte
		* collagen degradation and formation

Non-healing wounds are the result of an impairment of one or more of these processes. Multiple factors may lead to impaired healing. They can be classified as (1) intrinsic, or local, factors that are characteristics of the wound itself, and (2) extrinsic or constitutional factors that are characteristics of the patient (Table 2.2.9-2)[1]. Many of these factors are inter-related and most of the extrinsic factors act through intrinsic effects.

The most common factors resulting in impaired healing are ischemia and infection.

Infection increases the inflammatory process thereby inducing wound hypoxia through high oxygen consumption and local blood flow impairment due to tissue oedema. The inflammatory phase is thereby prolonged, delaying the whole healing process. Collagen deposition, epithelialization and contraction do not occur or only to a limited extent[4,5].

Ischemia is another common factor in non-healing wounds. It causes tissue hypoxia – a key element of healing failure. Oxygen is essential for aerobic metabolism and energy production and, although anaerobic

metabolism is possible in a hypoxic wound environment, it cannot generate the vast quantity of energy required for normal healing[6].

Table 2.2.9-2. Factors that impair healing

Intrinsic Factors	Extrinsic Factors
Infection	Hereditary healing disorders
Foreign bodies	Nutritional deficiencies
Ischemia	Distant malignancies
Cigarette smoking	Old age
Venous insufficiency	Diabetes
Radiation	Jaundice
Mechanical trauma	Alcoholism
Local toxins	Uraemia
Cancer	Glucocorticoid steroids
	Chemotherapeutic agents
	Other medications

Fibroblast proliferation is similarly affected by the oxygen concentration[7]. Oxygen drives the process of hydroxylation of lysine and proline during collagen synthesis[8]. Without adequate hydroxylation, collagen thermal stability is significantly impaired, leading to diminished wound tensile strength. The overall rate of collagen synthesis is also inhibited in vitro by hypoxia[9]. The only aspect of healing that is stimulated by hypoxia is the induction of angiogenesis[10]. However appropriate maturation of new capillary networks requires a normal oxygen tissue pressure.

Hypoxia has been shown to impair healing in several wound models. Niinikoski first demonstrated that the rate of collagen accumulation in cellulose sponges correlates with inspired oxygen tension[7]. Hunt and Pai obtained similar results using a wound cylinder model[11]. Stephens and Hunt showed that the tensile strength of incision wounds varied with inspired oxygen tension[12].

In addition to its direct effect on wound healing biology, hypoxia also impairs the body's defence mechanisms against bacterial invasion. Oxygen is required by neutrophils for the creation of free oxygen radicals that kill bacteria[13]. The susceptibility of wounds to infection is directly related to oxygen concentration as shown in two experimental models[4,14].

2. RATIONALE FOR HYPERBARIC OXYGEN THERAPY IN NON HEALING WOUND MANAGEMENT

2.1 Evidence that HBO may correct tissue hypoxia

If wound hypoxia is the cause of healing failure, then to provide oxygen is a causal therapy. Hyperbaric oxygen is known to increase tissue oxygen pressures by increasing arterial oxygen pressure (PaO_2). Using Krogh's mathematical model[15], oxygen partial pressure in any point of a tissue may be predicted in relation to the distance from a capillary and the oxygen pressure over the whole length of the capillary. Factors that influence capillary oxygen pressure are tissue oxygen consumption, capillary blood flow, inter-capillary distance, and arterial oxygen pressure. If the Krogh's model is applied to the hyperbaric condition, when arterial oxygen pressure is increased from l00 mmHg (with the patient breathing air at atmospheric pressure) to 2000 mmHg (with the patient breathing pure oxygen at 3 ata), there is a corresponding four-fold increase in the oxygen diffusion distance at the capillary arterial end and a twofold increase at the venous end.

These theoretical predictions have been confirmed experimentally by Hunt[16], Hunt and Pai[11], Kivisaari and Niinikoski[17].Niinikoski and Hunt[18] also demonstrated that tissue oxygen pressure is increased from 50 mmHg to more than 400 mmHg during HBO at 2 ata using tonometric pO2 measurements with an implanted silastic tube.

Using the Krogh model, it is possible to predict the ability of HBO to increase tissue oxygen pressure in different forms of hypoxia: (1) where there is an increase in intercapillary distance such as in edema; (2) with vascular destruction such as with infection, diabetes or radionecrosis, and (3) where the vascular flow is reduced such as in vasculitis or arteriosclerosis. However, HBO is only able to increase tissue oxygen pressure if the local circulation is still partially functional. Some circulation is required to transport the increased blood oxygen content into the tissues towards the target area.

2.2 Evidence that HBO may support the healing process

The rationale for using HBO in non-healing wounds has been extensively reviewed[19-22] and may be summarized as follows:

* HBO corrects wound hypoxia by increasing blood oxygen content via dissolved oxygen and then redistributing it to hypoxic areas due to the

hyperoxic vasoconstriction in healthy ones[23]. It also improves microcirculatory blood flow by increasing red blood cell deformability[24].

* HBO enhances cell metabolism[25]; it preserves intracellular ATP[26]; and it reduces oxidative injury to cells[27].

* HBO stimulates fibroblast proliferation[28,29]; it improves extracellular matrix synthesis[30]; it increases collagen formation and deposition[7,28]; and it promotes rapid growth of capillaries and the formation of functional microcirculatory network[31,32].

* HBO reduces oedema formation[33] and increases wound tensile strength[32].

* HBO reduces wound infection by its direct effect on anaerobic bacteria and its indirect effect on aerobic bacteria by enhancing the microbicidal capability of polymorphonuclear leukocytes[5].

However, two points are important to consider:

Effect of oxygen pressure on healing processes varies according to the phase of healing. Hypoxia is a potent stimulus for the initial events i.e., secretion of angiogenetic factors, migration of fibroblasts, and induction of pro-collagen synthesis. On the other hand, a normal oxygen pressure is needed to obtain the formation of a normal capillary network[32]; proliferation and maturation of fibroblasts[7,34]; and the formation of resilient collagen [7,32]. In that respect, alternating hypoxia and hyperoxia, as occurs during HBO therapy, may optimise the healing process by providing the stimulus of hypoxia to drive the process but also providing the oxygen substrate to complete it.

HBO only corrects certain factors of healing impairment. It only improves ischemic wounds and has minimal effects on normal wound healing[35]. It also cannot be provided as stand-alone therapy but should be integrated in the overall management of the patient.

2.3 Evidence that HBO may be clinically effective in the treatment of non-healing wound

HBO has been used in many types of wounds and ulcers[36]. In many of these the effectiveness of HBO is not supported using Evidence Based Medicine principles so that its use cannot be recommended. Accordingly efforts should be made to improve the level of evidence for those conditions where clinical experience shows promise but scientific verification is lacking.

Central to the indication for HBO in wound healing is proof of the presence of tissue hypoxia being a causal or contributing factor in delayed healing with subsequent evidence that this can be reversed using HBO.

2.3.1 Ulcer due to arterial insufficiency

Peripheral vascular disease (PVD) is a common cause of non-healing ulcers. The most common cause of PVD is *arteriosclerosis obliterans*. Usually this becomes apparent between the ages of 50 and 70 years. Smoking, diabetes, hyperlipemia and familial history are the primary risk factors. It produces a segmented narrowing or obstruction of the lumen in arteries supplying the lower limb, leading to tissue hypoxia. Ulcers are the hallmark of the 4th stage in Fontaine's classification and are a urgent indicator for revascularization.

Thrombo-angitis obliterans is a less common cause of PVD. It predominates in 20 to 40 year olds and causes arterial obstruction by segmental inflammatory and proliferative lesions of the medium and small vessels of the lower limb. The aetiology is unknown, but there is a strong association with cigarette smoking.

Some studies have been published reporting favourable results using HBO but good randomised controlled studies are still lacking[37-39].

In our own experience, as long as HBO can increase $TcPO_2$ above 100 mmHg all patients heal with an average number of 46 HBO sessions[40].

As such, HBO may be considered for the treatment of an ischaemic, non-healing ulcer if:

- revascularisation is not possible.
- revascularisation alone does not solve the healing problem such as with a concomitant infection, or
- revascularisation is of uncertain durability and maximised healing shoud be achieved in the window of opportunity it affords.

2.3.2 Diabetic foot ulceration

Diabetic foot ulceration (DFU) is a major complication affecting 4 to 10 % of the diabetic population at large[41,42]. As such, foot problems represent one of the most common reasons for hospital admission amongst diabetic patients. Despite many prevention and treatment protocols introduced over the last two decades, the rate of lower extremity amputation is still 15 times greater in diabetic patients when compared to non-diabetics[43]. In addition, due to increased weight bearing and ongoing vascular degeneration, 50 % of diabetic amputees may end up with an amputation of the contra lateral limb within four years of the initial amputation[44].

Apart from the morbidity economic costs related to diabetic wounds are astronomical. The cost of hospitalisation for amputation in a diabetic patient has been estimated at 18 000 Euros with an average stay of 42 days[45].

2.3.2.1. Pathophysiology of diabetic foot ulceration (DFU)

Sensory neuropathy, ischemia and infection are the principal pathogenic factors in DFU[46].

Peripheral neuropathy has a central role and is present in more than 80 % of diabetic patients with foot lesions[47]. Often ulceration is the result of a loss of protective sensation allowing multiple small injuries to go unnoticed until an infection sets in[48,49]. However, the most common mechanism appears to be the insensate, excessive and repetitive pressure on plantar bony prominences like the metatarsal heads[50]. This explains why non-weight bearing measures are mandatory in the overall treatment of DFU.

Ischemia is the other major factor contributing to DFU. Peripheral vascular disease has a high incidence in diabetic patients and has been shown to be a pathogenic factor in 60 % of diabetic patients with non-healing ulcers and 46 % of those undergoing major amputations[51]. Ischemia weakens local defences against infection because of a reduced supply of oxygen, essential nutrients and growth factors. Transcutaneous oxygen measurement ($TcPO_2$), but not ankle brachial pressure indices, have been shown to be an independent predictor of DFU healing with a value of 30 mmHg in ambient air being a critical threshold[52]. Whenever possible, revascularisation should be considered in the overall treatment of ischemic DFU.

Infection is a frequent complication precipitated by the neuropathy and ischemia. Its severity may range from a mild, localised infection to a limb-threatening necrotizing fasciitis[46]. Beside imminent tissue and limb loss, bone and joint involvement has been shown to be an important factor of delayed healing and eventual amputation even where ischemia has been reversed by revascularisation[53].

2.3.2.2. Clinical studies

Many factors cause impaired oxygenation in the diabetic foot[54-56]. Measurements of tissue oxygen tensions ($TcPO_2$) in non-healing diabetic wounds show values far below those where wound healing could be expected. Even breathing 100 % O_2 does not necessarily raise the $TcPO_2$ enough to achieve healing. HBO has been shown to increase tissue O_2 tension in certain diabetic patients with chronic wounds[57,58]. A direct response to hyperoxygenation and a further response over time were demonstrated. An HBO induced increase in $TcPO_2$ is predictive of healing irrespective of the values on air or breathing normobaric oxygen[59].

The first study on HBO in DFU treatment was done by Hart et al in 1979[60] and was followed by several other anecdotal or retrospective studies. Prospective trials were reported by Doctor[61] and Zamboni[62], but the largest prospective, randomised study so far was published by Faglia et al.[63]. A total

of 70 patients with Wagner grades 2, 3 and 4 were treated; 35 with HBO and 33 without HBO. Variables in demographic and clinical features were not significant. Neuropathy and vasculopathy were similar in both groups. In the HBO group there were 3 major amputations: 1 above knee amputation (AKA) and 2 below knee amputations (BKA) – 8.6 %. In the non-HBO group there were 11 major amputations: 4 AKA and 7 BKA – 33.3 %. The reduction of the amputation relative risk (RR = 0.25) was statistically significant. The significance was highest in the group of patients with a Wagner classification of 4 (2/22 HBO, 11/20 non-HBO).

Considering this evidence, the Jury of the ECHM Consensus Conference on hyperbaric oxygen in the treatment of foot lesion in diabetic patients, held in London, the 4-5th of December, 1998, stated[64]:

"*There is some evidence from a number of trials, each of which suffers from methodological problems, to support the use of HBO in ischaemic limb-threatening problems in diabetic patients. This is Level 2 evidence.*

A result of the meeting is the recognition of urgent need for a collaborative international trial for the application of HBO in diabetic foot lesions. Patients with diabetic foot problems warrant treatment by foot care teams with careful evaluation of metabolic, neuropathic and vascular factors. Potential candidates for HBO may include those with Wagner grade 3 to 5 lesions treated unsuccessfully by standard methods when amputation seems a possibility. Pre-treatment evaluation should include an assessment of the probability of its success which might include: TcPO2 & O2 challenge at pressure, assessment of peripheral circulation by invasive / non-invasive methods".

Such a randomised controlled study is in progress under the auspices of the European Research Program COST Action B14 (information may be found on the web site: www.oxynet.org).

2.3.3 Venous stasis ulcer

Up to 1 % of the general population suffer from a chronic venous ulcer at some point of their lives. Venous stasis ulcers are one of the manifestations of chronic venous insufficiency, i.e., hypertension involving either the superficial or both the superficial and deep venous system. Edema is frequently associated with the condition. Due to the prolonged evolution, this process leads to chronic inflammation and tissue sclerosis. Transcutaneous oxygen measurements and laser Doppler flowmetry has shown a decrease in microcirculatory perfusion and tissue hypoxia.

Conventional treatment is generally effective when correctly applied. It includes physical therapy with leg elevation and compression, ulcer dressings and surgery when indicated.

Role of HBO seems very limited. Some authors have reported favourable results[39,65-67] but it is generally agreed that these ulcers heal without the need for HBO. Nevertheless, a double blind, randomised study has demonstrated a decrease in the size of chronic leg ulcers that showed no response to standard wound care[68]. These included a significant number of venous stasis ulcers.

2.3.4 Decubitus ulcer

The cause of decubitus ulcers is pressure on the skin that interferes with the circulation at the point of contact. Prolonged rest or immobilization in one position, as with hemiplegics and paraplegics, may lead to this complication within a matter of a few hours. Poor skin hygiene, malnutrition, and debilitation are contributing factors. These ulcers are usually located over bony prominences such as the sacrum and the heel. The ulcer results from breakdown of the ischemic skin and subsequent bacterial invasion and inflammatory reaction. Persistence of the latter leads to microvascular thrombosis, which further aggravates ischemia.

Conventional treatment includes pressure limiting measures, infection control, management of secondary contributing factors such as spasticity, skin maceration and malnutrition.

The role of HBO is very limited. Eltorai[69] reported a study of 28 patients with a 65% success rate. However HBO cannot be used in lieu of proper offloading strategies; it may be of use as an adjunct to surgery, either for the preparation of patients with infected pressure ulcer as following a skin graft or flap.

2.3.5 Chronic leg ulcer in sickle-cell anemia

Sickle-cell anemia is the result of high concentrations of hemoglobin S[70]. Clinical manifestations occur mainly in homozygous (SS) patients, and heterozygous patients with another associated abnormal hemoglobin (Hemoglobin C disease, beta-thalassemia). Deoxygenation of this abnormal hemoglobin, acidosis, dehydration, and temperature variations induce the sickling of erythrocytes. Sickling is responsible of chronic hemolytic anemia and of three kinds of acute events: thrombosis, infections, and paroxysmal anemia. Oxygen transport is also impaired because hemoglobin S has a lower affinity for oxygen than hemoglobin A. P_{50} of hemoglobin S is high and the mild hypoxemia found in sickle-cell anemia is related to a low oxygen saturation and a low oxygen arterial content[71].

Sickle-cell anemia is responsible of chronic alteration of various organs: brain, lungs, liver, kidneys, eyes, and skin. Legs ulcers are known to be very

difficult to treat using conventional therapies[71]. Accordingly, HBO has been proposed in order to increase oxygen tissue delivery[71].

Medhaoui[73] reported a study in 15 patients, all homozygous SS, presenting 23 ulcers. The average session number was 11 ± 9. Healing was obtained in all patients but recurrence occurred in 8 patients.

3. MANAGEMENT OF A PATIENT WITH A NON HEALING WOUND

An accurate diagnosis of all the factors impairing healing is a prerequisite for the success of the treatment in a non-healing wound. This means that patient referred to a hyperbaric centre for a non-healing wound has to go under an extensive evaluation, if not made previously.

3.1 Management of Factors Impairing the Healing Process

Once causal and contributory factors have been identified, treatment can be instituted accordingly. Great benefit may be derived from improving the management of contributing factors, even if the primary disease process cannot be reversed. For example, diabetes benefit from careful dietary management and the infection may respond to optimal treatment. Once local conditions have been optimised, some wounds will heal by secondary intention. This emphasizes the need to correctly select patients for HBO after an extensive evaluation and an optimisation of the treatment. HBO alone may be a futile treatment if not integrated in the overall management of the patient.

3.1.1 Local wound management

Optimal local wound management depends on the nature of the wound (Table 2.2.9-3)[74]. Surgical debridement is indicated for wounds containing non-viable tissue or foreign material. For infected wounds, the objective is to decrease the bacterial load without disturbing normal bacterial flora and selecting for multi-resistant strains. It has been shown that systemic antibiotics are not effective in lowering bacterial counts and should not be prescribed unless there is clear invasion of surrounding healthy tissues with cellulitis or bone/join infection.

Table 2.2.9-3. Wound care strategy

Deal with underlying pathology (including infection)
Cleanse and debride wound
Determine wound type, depth and degree of exudation
Absorb exudation by appropriate dressing
Occlude the wound as soon as possible
Appose the wound edges as soon as possible (in healing by primary intention)

Topical agents with antibacterial activity have been utilized for a long time but evidence of efficacy is lacking and some have definite toxicity for normal tissues. Dressing must therefore be carefully chosen in order to provide an optimal healing milieu. This is based principally on the rehydration and elevating oxygen tension within the wound. Because of their high water content and autolytic properties, hydrogels are preferred for wounds with slough or necrosis that cannot be removed surgically. Hydrocolloids are indicated when wounds are non-infected and have a persisting fibrinous exudates. Film or gauze may be considered for clean and well granulating wounds in preparation for grafting.

3.1.2 Patient management

Nutritional status is a key factor for healing. A deficiency in protein intake will impair collagen synthesis and alter cellular functions. Inadequate intake of carbohydrates or fats slows all normal metabolic functions and diverts proteins from cell synthesis to cell energy supplies. Selective deficiencies in vitamins or minerals may also impair various aspects of healing. Correction of nutritional deficiencies must be obtained; simply improving nutritional status may promote healing when malnutrition is a contributory factor.

The importance of smoking and alcohol abuse in healing failure should be emphasized even if compliance is variable. If possible drugs that interfere with normal healing, such as steroids or chemotherapy agents, should be temporarily discontinued to afford a better opportunity for healing.

Metabolic control of diabetes is an important objective. Diabetic patients are at particular risk for wound healing complications and infection may again precipitate poor glycemic control. Uncontrolled diabetes has definite impact on wound healing, so that reinforcement of diet modifications and switching from oral medication to insulin may be required.

Constant effort is required to eliminate or reduce pressure on the wound area. In many cases, undue pressure on insensate areas induces wounds that do not heal until the pressure is relieved (e.g., diabetic patients with neuropathic foot lesion and pressure ulcers in plegic patients). Non weight-bearing measures are mandatory in the management of these patients.

Venous insufficiency has to be taken into account. Persistent venous hypertension is often the cause of non-healing ulcer. Proper evaluation is required to determine possible surgical solutions. Edema control with compression systems is helpful in obtaining healing in this setting.

Arterial insufficiency is a major barrier to healing and should be considered in any patient with a non-healing wound. Patient history, physical and Doppler examinations should be made in view of possible surgical correction. Rest pain, disabling claudication and non-healing wounds are indications for surgery in these patients. An arteriogram is required and will provide necessary information regarding possible surgical or endovascular interventions. Whenever possible, revascularization takes precedent over HBO as the preferred therapeutic option for arterial wounds.

3.2 Selection of patients for HBO therapy

The use of HBO in non-healing wound is based on the assumption that wound tissues are hypoxic and this hypoxia is the major factor impairing healing. The validity of this assumption has been largely confirmed and commonly accepted indications for HBO include diabetic foot lesions, arterial ulcers, skin grafts and flaps and radionecrosis.

However, in all these situations, conventional therapy as detailed above, may some success so that the need for, and differential effect of, HBO is less evident. Therefore, objective criteria are required in selecting appropriate patients where HBO is truly needed.

3.2.1 Rationale for using transcutaneous oxygen pressure measurements for selecting HBO-prescribed cases

Tissue hypoxia is the common denominator for many HBO indications. However, for HBO to be of value, tissue hypoxia should be reversed by its application to have a therapeutic benefit. Such reversal should be demonstrated as part of the selection process.

Although the advantages of measuring oxygen pressure during hyperbaric session are obvious, the invasive (arterial puncture, implanting of electrodes) and complex (radioactive oxygen, magnetic resonance imaging) nature of these measurements been a discouragement to clinicians. Fortunately transcutaneous oxygen measurement is a non-invasive method and represents an opportunity for such assessment with a number of useful applications within the HBO arena.[75].

3.2.2 Transcutaneous oxygen pressure measurements

3.2.2.1. History

In the early 1950's, Baumberger and Goodfriend[76] showed that when a subject immersed his finger in a buffer solution heated to 45°C the partial oxygen pressure of this solution resembled arterial pO_2 within 60 minutes. Some years later, Clark[77,78] developed a polarographic electrode capable of measuring partial oxygen pressure in the blood both in vitro and in vivo. Huch[79,80] adapted Clark's electrode to measure $TcpO_2$ with the aim of evaluating arterial oxygen pressure in a non-invasive way. Monitoring PaO_2 by measuring T_CPO_2 is common in neonatology[81-83], but has not been extended to adult medicine due to the variability of the PaO_2/T_CPO_2 relationship in adult skin. Intensive care units quickly realized that a decrease in T_CPO_2 could either be due to a fall in PaO2 or simply a decrease in skin nutritive blood flow[84]. This largely eliminated T_CPO_2 as a non-invasive method for monitoring PaO_2. However, Shoemaker and Vidyssagar[85] renewed interest of $TcPO_2$ as an indicator of overall blood flow and an early warning of cardiovascular decompensation. Measurement of $TcPO_2$or $TcPO_2/PaO_2$ gradient has been used in evaluating the peripheral circulatory state either in shock[86-88] ; during localized ischemia such as in arterial trauma[89]; for peripheral vascular disease[90-93]; in musculocutaneous flaps and grafts[94,95]; and more recently, in hyperbaric medicine[96-99].

3.2.2.2. Technique

Transcutaneous oximetry uses a Clark's polarographic electrode modified to incorporate a heating element and a thermistor. The principle of the measurement is based on a electrochemical reduction at the cathode.

The current generated by oxygen reduction is proportional to the number of oxygen molecules entering in the chamber between anode and cathode. The heating element maintains a constant temperature between 42°C and 45°C controlled by the thermistor monitoring (Fig. 2.2.9-1). A phosphate-buffered potassium chloride solution ensures contact between the surface of the electrode and the oxygen-pervious membrane.

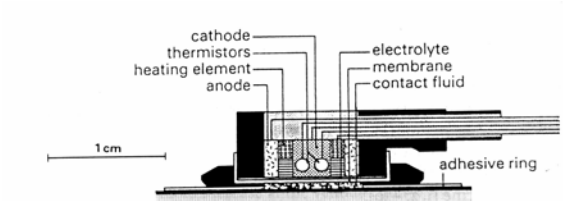

Figure 2.2.9-1. Diagram of a TcPO2 electrode

The electrode is fixed to the skin via an adhesive ring filled with a contact solution (Fig. 2.2.9-2). As the electrode is heated, heat is transferred to the surface of the underlying skin. This has three effects: (1) vasodilatation of arterioles and capillaries located immediately beneath the electrode, (2) increase in the size of cutaneous pores, and (3) better oxygen permeability of the stratum corneum, all these effects reduce the barrier to transcutaneous diffusion of oxygen.

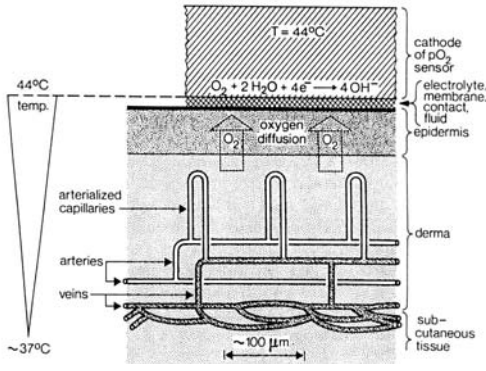

Figure 2.2.9-2. Cross section of skin showing the oxygen diffusion path from dermal capillaries to measurement chamber of $TcPO_2$ electrode

Transcutaneous oxygen pressure measurement has several advantages: It is non-invasive method so that patient compliance is good; it is easy to use; and it can be repeated at several points without problems with bacterial contamination. However, the method has several limitations: Skin properties influence T_CPO_2 measurements because of differences in skin oxygen permeability (localization, thickness) and oxygen consumption. Heating is critical because there is a constant relationship between the electrode temperature and the recorded T_CPO_2. Heating modifies also skin properties

specifically by inducing vasodilatation and increasing oxygen permeability. Temperature profiles created in tissue by heating may be different from site to site and from one subject to another, leading to false differences between T_CPO_2 readings. Mechanical pressure onto the electrode alters T_CPO_2 producing a drop in the recorded value. Anaesthetic gases may also affect T_CPO_2. Finally, electrode response time influences the delay before reliable readings can be made. All theses factors have to be taken into account before interpreting a T_CPO_2 value. Therefore these parameters have to be reported when test results are provided: electrode temperature; site of measurement; T_CPO_2 value at a reference site (usually subclavicular area); and the time allowed before reading.

3.2.2.3. Mesurement in hyperbaric environment

Before taking any measurement, the electrode be carefully calibrated. Conventional one point calibration in the ambient air is usually recommended by manufacturers and – at sea level atmospheric pressure – this is around 150 mmHg pO_2. However this is too crude if accurate measurements are to be made under hyperbaric conditions. Even though electrode response is linear in a range between 0 and 2000 mmHg, errors in calibration are magnified when high pO2 values are achieved in the hyperbaric chamber. The one-point calibration is therefore inadequate as the electrode response line cannot be determined. We recommend a two-point calibration technique: zero adjustment is done using pure nitrogen with the electrode in a calibration chamber. Electrical zero is not sufficient. The second calibration point is determined using a calibration gas with 22 % oxygen. The calibration is checked by measuring the oxygen pressure in a third gas with a known percentage of oxygen.

In our practice this procedure takes approximately 30 min for simultaneous calibration of ten electrodes and is carried out after each new electrode preparation (approximately once a week). On the other days calibration is only checked by measuring the oxygen pressure of the standard gas. If there is any significant discrepancy, the whole calibration process is repeated.

With regard to T_CPO_2 measurement, selected areas are carefully shaven, cleaned, and degreased. A double-sided fixation ring is placed on the chosen spot and the electrode attached after application of an electrolyte contact solution. Electrodes are placed near the wound and at different levels of the limbs. The heating temperature is set to 43.5°C. A reference electrode is placed on the upper front part of the thorax. Simultaneous readings are made after equilibration; the length of time depending on the oxygen inhaled pressure (usually 10-15 min at 2.5 ata). Measurements are performed under three successive conditions: patient breathing normal air; normobaric pure

oxygen by oronasal mask; and 100% oxygen at 2.5 ata in the hyperbaric chamber.

The use of T_CPO_2 measurements in hyperbaric oxygen raises some specific problems. One problem is the electrical safety when the device is brought in the chamber. This is best solved by leaving the electronic device outside the chamber. The electrodes are then passed through the chamber wall using an electrical penetrator. A second problem is that very high T_CPO_2 cannot be recorded, because the display window is limited to three digits or shown as an error message when it exceeds the range of measurement. To obviate this difficulty it is often advised to halve the calibration value (e.g. using 75mmHg instead of 150mmHg) so that readings can then be doubled and are likely to remain within the range of measurement that can be correctly displayed. This does affect accuracy, of course, but this is acceptable due to the linear response of the electrode and the reality of there being no alternative at present.

3.2.2.4. Interpreting transcutaneous oxygen pressure measurement

There are several studies addressing interpretation of T_cPO_2 measurement. In patients with both normal cardiac output and cutaneous circulation, T_cPO_2 gives a reliable indication of PaO_2, but the correlation is reduced with age. The T_cPO_2/PaO_2 ratio is equal to 1 in a newborn child and 0.79 in a young adult. This is why arterial oxygen pressure is effectively measured via T_cPO_2 in neonates[81,83].

In adults, on the other hand, numerous factors interfere in the PaO_2/T_cPO_2 relationship. Local skin properties and blood flow are especially important[100,101]. No direct comparison may therefore be done between absolute values of T_cPO_2 taken in two different sites on the same subject or between two different subjects. However, given that the subject has a normal PaO_2, and that measurements are done in the same site, T_cPO_2 is a reliable index of local blood flow[102].

An unusually low T_cPO_2 may be due to a cutaneous vasoconstriction (hypovolemia, vasoconstricting drugs, cold environment, etc.) or to insufficient heating of the electrode. On the other hand, a too-high heating temperature will cause a blister, which decreases T_cPO_2. An unusually high T_cPO_2 suggests a leak or that a gas bubble has formed during decompression.

3.2.3 Protocol for patient selection

In our center we follow the following protocol for patient selection in cases of problem wounds (Fig. 2.2.9-3):

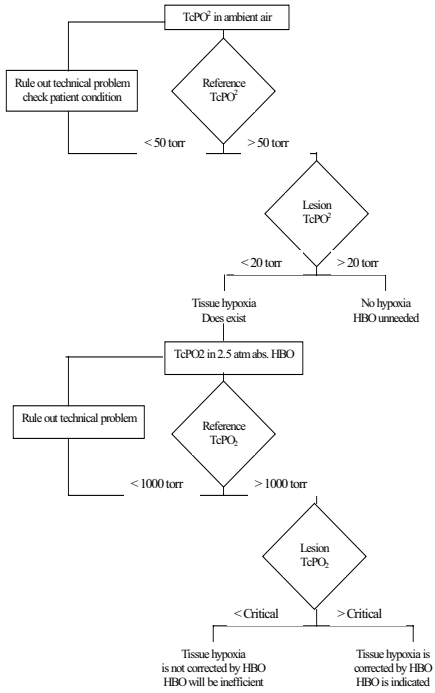

Figure 2.2.9-3. Flow chart for patient selection for HBO using TcPO2 (see text for explanation)

1. Transcutaneous oxygen pressures are first recorded in atmospheric air. Patients lie on their backs, comfortably, in a medium-warm environment (22-24°C). Measurements are done at least at three sites: subclavicular area for reference; close to the wound margin; and contra laterally in a mirror-like fashion. Electrode calibration is checked before each test by measuring the oxygen partial pressure of a standard gas. Probe heating is set to 43.5°C.

(a) T_CPO_2 at the reference site should be greater than 50 mmHg. If not, a technical problem should be excluded (e.g., electrode calibration, skin preparation and electrode fixation, heating, mechanical pressure, etc.). Thereafter the patient's condition has to be checked: previous lung or heart disease, skin vasoconstriction (cold, stress, drug, etc.), hypovolemia (particularly in acute conditions such as crush syndrome or limb ischemia) may cause central hypoxia affecting the reference site. Arterial blood gas determination may be necessary. After careful examination, supplemental oxygen may be needed to get sufficient level of T_CPO_2 at the reference site.

(b) T_CPO_2 at the wound site is recorded after a sufficient time to allow equilibrium (5-10 min in atmospheric air).

i. T_CPO_2 at the wound site is normal or slightly decreased (i.e., $TcPO_2$ > 20 mmHg). Tissue hypoxia is not the main cause of the lesion and HBO is not indicated to reverse hypoxia; it may still be indicated for other reasons (e.g., anaerobic infection).

ii. T_CPO_2 at the wound site is below normal (< 20 mmHg). Tissue hypoxia is present. The patient then undergoes compression to 2.5 ata.

2. Transcutaneous oxygen pressure is then recorded with the patient breathing 100% oxygen at 2.5 ata. Measurement is done in the same three sites. Ideally three different electrodes and devices should be used to avoid any variation in the technical part of the measurement. After compression and oxygen breathing, the patient is allowed some time to be comfortably accustomed to the hyperbaric environment before taking the reading.

(a) T_CPO_2 at the reference site has to be over l000 mmHg. On a theoretical basis $TcPO_2$ should be over 1800 mmHg, but because of hyperoxic vasoconstriction, mean reference values are between l000 and 1200 mmHg with a trend to be lower in elderly patients. If a low T_CPO_2 is obtained, oxygen delivery problems or blister formation should be excluded.

T_CPO_2 at the wound site is recorded after equilibrium has been reached (10-15 min slightly longer than in atmospheric air).

i. T_CPO_2 at the wound site increases and exceeds a critical level depending on the indication. Interpretation: HBO will induce a normalization of tissue oxygen pressure and then will have a therapeutic effect. HBO is indicated.

ii. T_CPO_2 does not increase or insufficiently increase tissue oxygen pressure. Tissue hypoxia will not be corrected by HBO and there is no justification for use of HBO in this case.

3.2.4 Critical TCPO2 Values for HBO Patient Selection

Based on our experience, we have determined critical values of $TcPO_2$ for HBO patient selection in different clinical settings (Table 2.2.9-4). We report here these values together with the clinical background on which they were based.

Table 2.2.9-4. Critical values of TcPO2 in HBO

Arterial trauma:	20 mmHg
Musculocutaneous flap:	50 mmHg
Arterial ulcer:	50 mmHg
Diabetic foot lesion:	100mmHg

Note: Failure of HBO treatment is highly probable if $TCPO_2$ measured in HBO (2.5 ata) near the lesion is lower than these critical values.

3.2.4.1. Refractory arterial skin ulcer [40]

A total of 20 patients with refractory arterial skin ulcers were evaluated. T_CPO_2 was measured close to the ulcer and values did not change in atmospheric air or normobaric oxygen.

A T_CPO_2 of less than 50 mmHg when breathing pure oxygen at 2.5 ata was consistently associated with failure, whereas a T_CPO_2 over l00 mmHg in HBO consistently met with success.

3.2.4.2. Diabetic foot lesion[102]

A total of 38 patients with diabetic foot lesions were evaluated. T_CPO_2 measured close to the wound did not change in atmospheric air or normobaric oxygen. $TcPO_2$ in HBO (2.5 ata) was significantly higher in patients who healed when compared to those who did not. Unlike arterial ulcers, values less than 100mmHg met with failure. This illustrates that local ischemia is not the only factor causing wound healing failure in diabetic foot lesions.

3.2.4.3. Musculocutaneous skin flap[103]

A total of 15 patients with pedicled musculocutaneous flaps were evaluated by clinical examination and $TcPO_2$ measurements. Twelve had clinical evidence of total flap ischemia and 3 of partial flap ischemia. In ambient air neither absolute values of T_CPO_2 (2.6 ± 3.6 vs 11.7 ± 12.6 mmHg, n. s.) nor the difference in the ratio between T_CPO_2 of the flap and the subclavicular reference showed any significant difference in terms of the final outcome (i.e., failure vs. success). Normobaric oxygen measurements were the same. During HBO there were significant differences in $TcPO_2$ between the two groups (12 ± 12 vs 378 ± 385 mmHg; $p < 0.02$).

A T_CPO_2 higher than 50 mmHg in hyperbaric oxygen (2.5 ata) was the best cut-off value to discriminate between success and failure.

3.2.5 Transcutaneous Oxygen Pressures in Monitoring of Evolution

After the first T_CPO_2 evaluation for patient selection, repetition of T_CPO_2 measurement may be useful to follow recovery. It allows early detection of any vascular complication occurring during treatment that might require medical or surgical intervention.

It also allows an estimation of the angiogenetic progression by comparing the $TcPO_2$ at fixed intervals[75].

3.2.6 Transcutaneous Oxygen Pressure and HBO Treatment Quality

The goal in hyperbaric oxygen therapy is essentially to increase tissue oxygen pressure by increasing the peri-capillary diffusion gradient. Numerous factors may influence the oxygen concentration delivered to the patient: incorrect mask application, poor patient compliance, or pre-existing pulmonary pathology[58]. Measurement throughout the HBO session of transcutaneous oxygen pressure in a reference zone may detect insufficient oxygen pressure increases. The effectiveness of oxygen administration should be confirmed the personnel (i.e, flow rates; activation and release of demand valves; mask fit; etc.). If problems persist, pulmonary function should be evaluated (e.g., looking for arteriovenous shunting, alveolar capillary block, etc.).

4. CONCLUSION

A large body of pathophysiological evidence supports the beneficial role of HBO in delayed healing when the cause is wound hypoxia and this can be shown to reverse during HBO administration. Experience supports its use in such wounds but, following the Evidence Based Medicine principles, there is a need for affirmative randomised controlled studies before a strong recommendation can be made.

The 2004 European Committee for Hyperbaric Medicine 7th Consensus Conference[104] the previous recommendations were confirmed[105]. HBO might be a valuable adjunct to conventional management in patients with ischemic lesions (ulcers or gangrene) in the absence of a surgically treatable arterial lesion or in the presence of persistent healing failure after vascular surgery:

- In diabetic patients the use of HBO is recommended in the presence of reversible chronic 'critical' ischemia as defined by the European Consensus Conference on reversible Critical Ischemia, i.e., if transcutaneous oxygen pressure readings under hyperbaric conditions (2.5 ata, 100 % Oxygen) are higher than 100 mmHg (Type 2 recommendation).
- In the arteriosclerotic patient the use of HBO is recommended in the case of a chronic critical ischemia, if transcutaneous oxygen pressure readings under hyperbaric conditions (2.5 ata, 100 % Oxygen) are higher than 50 mmHg (Type 2 recommendation).
- HBO is recommended in compromised skin grafts and myocutaneous flaps (Type 2 recommendation).
- In all other cases, measurement of transcutaneous oxygen pressure is recommended as an index for the defining both the indication and the effects of treatment (Type 2 recommendation)

Further studies are urgently needed in order to improve the level of evidence of such recommendations.

*Chronic Critical Ischemia: periodical pain, persistent at rest, needing regular analgesic treatment for more than two weeks, or ulceration or gangrene of foot or toes with ankle systolic pressure < 50 mmHg in the non-diabetic or toes systolic pressure < 30 mmHg in the diabetic (Second European Consensus on Critical Ischemia: Circulation 1991, 84, IV, 21-26).

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Chapter 2.2.10

PERSISTENT OSTEOMYELITIS

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Abstract: Chronic persistent osteitis/osteomyelitis is defined as an acute bone infection persisting for more than six weeks despite adequate therapy. Chronic infection may persist for a life-time. Infected tissues with impaired perfusion have been shown to benefit form hyperbaric oxygen (HBO) therapy. Multiple surgical interventions and long-term antibiotic therapy are regularly necessary in osteomyelitis. Limb salvage is not always possible. Therapy of various orthopaedic diseases with HBO is established. Specifically, in chronic osteitis/osteomyelitis, adjunctive HBO therapy is an effective modality within the multidisciplinary treatment concept

Keywords: persistent osteomyelitis; osteitis; adjunctive hyperbaric oxygen; bone infection

1. INTRODUCTION

Hyperbaric oxygenation (HBO) therapy is an innovative and promising adjunctive therapy for treatment of chronic inflammation and infection of soft tissues and bone[1]. Infected tissues with impaired perfusion have been shown to benefit from HBO therapy. Indications for HBO therapy in chronic infections, according to reports in the literature and our own experience, include treatment of:

- Myositis
- Impaired wound healing in problem wounds
- Diabetic foot ulcer
- Intracranial abscess
- Spondylodiscitis
- Necrotizing fasciitis
- Chronic osteitis and osteomyelitis

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Patients suffering from both chronic osteitis/osteomyelitis and diabetic foot ulcer are the predominant group of such patients suffering from chronic infection.

1.1 Chronic Osteitis/Osteomyelitis

1.1.1 Background

Chronic osteitis/osteomyelitis is defined, depending on the literature, as an acute bone infection persisting for more than six to twelve weeks. The term refractory osteomyelitis is applied to chronic osteitis/osteomyelitis which fails to respond despite adequate surgical and antibiotic therapy. Chronic infection may persist for a life-time. Consequences can be severe. Multiple surgical interventions and long-term antibiotic therapy are regularly necessary. Limb salvage is not always possible. Hospitalisation for weeks and months is often necessary. The infection may spread into adjacent tissues and organ systems. Infection of the vertebral body may cause abdominal or retroperitoneal abscess formation, and can exacerbate into generalized sepsis syndrome ultimately resulting in multiple organ failure and death.

Chronic osteitis contributes significantly to health care costs. The average cost of treatment is an estimated 800 000 Euros per patient. All treatment options warrant critical consideration in order successfully to treat and control refractory osteomyelitis, and not only from an economic point of view. In recent years, HBO therapy has been demonstrated to have therapeutic value as an adjuvant therapy[2]. In a review, Strauss demonstrated a five-fold advantage in cost-effectiveness on using HBO as adjuvant therapy for refractory osteomyelitis[3].

1.1.2 Pathogenesis

In the English literature differentiation between osteitis and osteomyelitis is not common. In the German literature the two pathological entities are clearly distinguished. The indication for successful application of HBO therapy depends on the pathogenesis of the disease. Thus, distinction between osteomyelitis caused by bacterial seeding from the blood and osteitis caused by direct contact of the tissue with bacteria during trauma or surgery is necessary.

1.1.3 Osteomyelitis

Osteomyelitis is an acute or chronic inflammatory process of bone and its structures, secondary to infection with pyogenic organisms. Haematogenous osteomyelitis is caused by the seeding of the bacteria within the bone from a remote source. Sources of infection include otitis media, tonsillitis, sinusitis or dental disease, or may be of unknown origin. The infection may be localized, or it may spread through the periosteum, cortex, marrow and cancellous tissue.

The most common site is the rapidly growing and highly vascular metaphysis of growing bones, and thus osteomyelitis occurs primarily in children. The apparent sludging of blood flow in vessels with angled configuration at the distal metaphysis predisposes the vessels to thrombosis and the bone itself to localized necrosis and bacterial seeding, causing infection of bone marrow (myelitis) and cortex (osteomyelitis)[4].

In adults bone marrow is gradually substituted by fat tissue with reduction of vascularization. Thus, localized osteomyelitis in adults is rare. In contrast, vertebral bodies are the predominant localization. Additional potential sites include the sternum, pubic rami, and the clavicle. Osteomyelitis of the skull typically originates from sinusitis or a urinary tract infection.

Children and teenagers with immune impairment caused by underlying disease, malnutrition or hormonal imbalance are predisposed to osteomyelitis. In adults, immune insufficiency is regularly present, and is often caused by diabetes, renal dialysis, and drug and alcohol abuse.

1.1.4 Osteitis

In contrast to haematogenous osteomyelitis, osteitis is secondary to contiguous foci of infection and accounts for at least one half of all bone infection cases, with increasing incidence. The organisms may be directly inoculated into the bone at the time of trauma, spread by nosocomial contamination during perioperative or intraoperative procedures, or extend from an adjacent soft tissue infection. Osteitis is characterized by a imbalance between the humoral host defences (mainly caused by tissue hypoxia) and the infecting agents, ie bacteria or fungi. Typically, infection has persisted over several weeks in an area which was compromised by trauma, radiation, malignancy or other injury. Hypoxia plays a major role in this process.

Following fracture of the bone, perfusion of fragments is significantly impaired. Haematoma, edema and soft tissue necrosis present ideal conditions for bacterial growth. Spreading of the infection along Haversian

and Volkmann's canals as well as along the osteosynthetic apparatus may result in necrosis of vital bone. Manifestation of chronic osteitis may be delayed for several years following the infection. These patients demonstrate unremarkable local and systemic infectious parameters, but suffer from chronic sinus tracts and abscess formation.

The most common cause of vascular insufficiency in patients with osteitis is diabetes mellitus. The small bones of the feet (the talus, calcaneus and distal fibula, and the tibia) are commonly involved. The patients in this group are aged 35-70 years. The infection frequently is initiated through a portal of entry for organisms, such as infected nail beds, cellulitis, or atrophic skin ulceration.

Additional pathways of infection resulting in osteitis include open fractures, open reduction and internal fixation of closed fractures, penetrating trauma, and reconstructive surgery of non-traumatized bone or joints. In orthopaedic joint replacements, infection of the prosthesis originates predominately from bacterial contamination during the surgical procedure.

In adults, bone marrow is gradually substituted by fat tissue and its perfusion decreases. Therefore, infection is limited to cortical bone. Due to the rigid structure of the bone, infection causes increased intramedullary pressure with additional reduction in perfusion, ischemia, intravascular thrombus and necrosis. Fragments of devitalized bone are called sequester. The infection spreads through the cortex, forms subperiostal abscess, transmigrates through the periosteum and forms soft tissue abscesses and fistulae which communicate with the skin.

1.2 Clinical Presentation

Children suffering from acute haematogenous osteomyelitis present with fever and pain over the affected bone. Sometimes there is a past medical history involving trauma or injury. Fever may precede pain symptoms. Increased erythrocyte sedimentation rate (ESR), leukocytosis and elevated C-reactive protein (CRP) are characteristic[5]. Post-traumatic osteitis and contiguous-focus osteitis cause localized pain, formation of sinus tracts with skin fistulae, soft tissue infection and abscess formation adjacent to the bone. In early stages of osteitis, body temperature and leukocyte count remain normal whereas ESR and C-reactive protein are moderately elevated.

In contrast to acute osteitis (which causes causes persistent pain), the chronic form of osteitis is characterized by episodic pain, intermittent or persistent formation of sinus tract and soft tissue inflammation in close proximity to the affected bone. Acute exacerbation of pain and subcutaneous abscess formation is provoked by spontaneous closure of the sinus tracts.

Vertebral osteomyelitis is characterized by insidious onset, with back pain being the most common symptom. Usually, neurological signs are not present until late in the disease course when there can be destruction and collapse of the vertebral body. Blood tests typically demonstrate normal leukocyte count whereas ESR and CRP are elevated. These elevated parameters are indicative for vertebral osteomyelitis in contrast to various other causes of back pain. Paraspinal abscess formation causes severe pain and local tissue destruction. If abscess formation and granulation tissue affect the spinal cord, intestinal paralysis, bladder dysfunction or even abrupt and irreversible paraplegia can occur. HBO therapy can be helpful to reduce the risk of these complications.

1.3 Diagnostics – Therapy

1.3.1 Imaging Studies

Commonly, 3-phase bone scan with technetium 99m is positive even in early stages of the infection. On conventional radiographs boney changes are not evident for 14-21 days and initially manifest as periosteal elevation followed by cortical or medullary lucencies. By 28 days, 90% of patients demonstrate some abnormality.

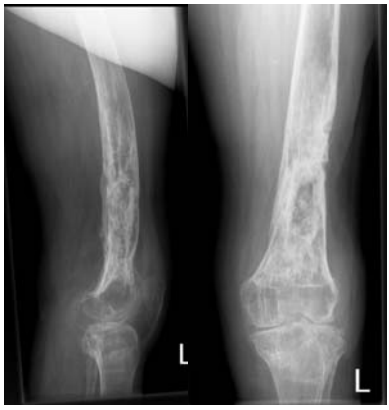

Figure 2.2.10-1. Female 69 years old patient with persistent Osteomyelitis of the distal femur for 60 years, now reaching the knee and proximal Tibia

MRI is effective in the early detection and surgical localization of osteomyelitis. Studies have shown its superiority compared with plain radiography, CT and radionuclide scanning, in selected anatomical locations.

Sensitivity ranges from 90-100%[6]. Short-term therapeutic success cannot be detected by these radiological methods. Additional diagnostic imaging techniques include Positron Emission Tomography (PET) scanning preferably combined with a CT scan (PET-CT).

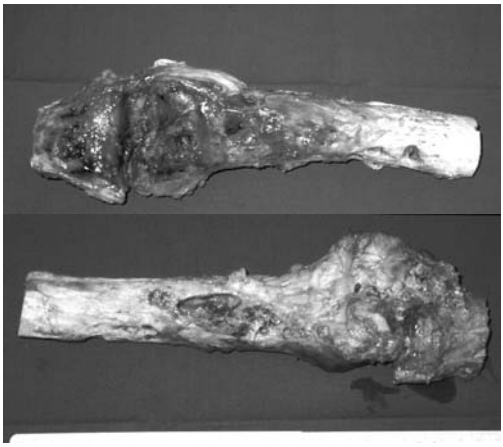

Figure 2.2.10-2. Ca 25 cm resection of the distal femur, knee and proximal tibia

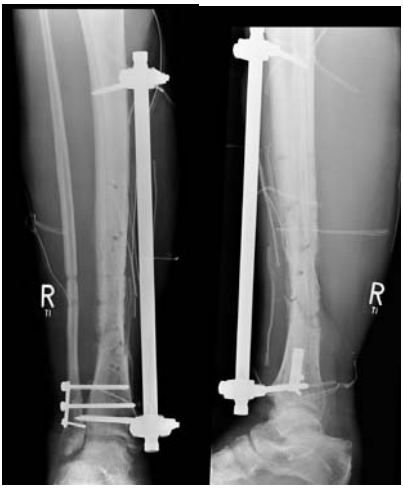

Figure 2.2.10-3. 42 years old man with persistent osteitis of the distal tibia after III° open fracture, 4 month after injury, x-ray shows signs of bone destruction

At an early stage of infection the bone scan is positive. However, tumours, fractures, and various metabolic diseases also cause positive scan results. To increase specificity in diagnosing osteomyelitis further scanning with leukocytes labelled with gallium 67 and/or indium 111 is performed: this demonstrates positive results only in osteomyelitis[7].

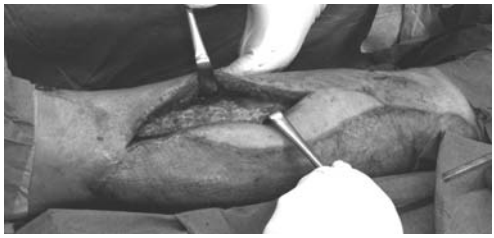

Figure 2.2.10-4. Typical destruction of the bone by microorganism

1.3.2 Microbiological findings

Accurate diagnosis necessitates isolation of the microorganism. In children with acute haematogenous osteomyelitis blood cultures may be positive, whereas in the chronic form isolation of bacteria in the blood is rare[8]. It is mandatory to perform multiple swabs from all accessible sources that present with pus, abscess and soft tissue infection. If test results remain negative treatment is started with antibiotics appropriate for *Staphylococcus aureus* which is usually the causative bacterial agent. If initial treatment with application of intravenous antibiotic is successful, antibiotic therapy is continued with oral antibiotics for a further four to six weeks. In juvenile osteomyelitis, early and continuous antibiotic therapy may avoid the need for surgical therapy. In patients presenting with structural defects of bone or joints, or with periosteal or subcutaneous abscesses, surgical debridement is mandatory[9].

In osteomyelitis of the vertebral body, the adult form of osteomyelitis, blood cultures may be positive. However, for precise diagnosis tissue biopsy of the vertebral body or the intervertebral space is harvested using a needle technique or open surgical biopsy. A single pathogenic organism is almost always recovered from the bone. The most common bone isolates are *Staphylococcus* species, the most common gram-negative organism is *Pseudomonas aeruginosa,* and the most common anaerobes are *Peptostreptococcus* species. However, in immune compromised patients, other organisms, including fungi and mycobacteria, also must be considered.

Treatment includes bed rest, application of appropriate intravenous antibiotics over a course of six to eight weeks, and HBO therapy. Surgery is indicated in cases with paravertebral or epidural abscess formation or unstable vertebral segments requiring osteosynthesis.

In patients with chronic post-traumatic or post-operative osteitis, or chronic osteitis mediated by an infectious focus in close proximity to the bone, diagnosis is dependent on microbiologic cultures from the affected bone or adjacent abscess. Typically these infections are polymicrobial. Therefore superficial swabs, or swabs from suction tubes, are limited in capturing skin microorganisms but are not sufficient to identify deep bacterial seeding.

1.3.3 Therapy

Treatment of chronic osteitis requires surgical debridement, antibiotics, and in persistent cases HBO therapy. During surgery radical debridement of affected bone and soft tissue is performed. Radical resection may require segmental resection of bone, resection or disarticulation of joints, or even amputation of the affected extremity. For adequate microbiological work up it is critical to harvest samples from both soft tissue and bone. Surgical debridement is followed by copious irrigation with Ringer's lactate and antiseptic solution. Irrigation of the bone is performed by additional pulsating lavage. Application of topical antibiotics is indicated when osteosynthetic implants are present. Osteomyelitis becomes refractory when the patient does not respond to both surgical debridement and a six week course of appropriate antibiotics.

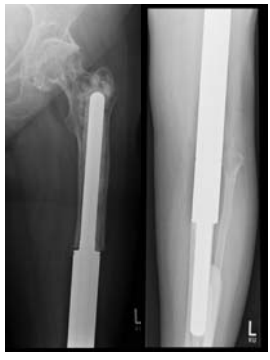

Figure 2.2.10-5. Arthrodesis of the 69y old lady, cemented, painless fully mobilized after 4 weeks

If multiple revision surgical procedures with irrigation and debridement are necessary, temporary wound closure is performed with wound tamponade using polyvenylalcohol (PVA) or polyurethane sponges, continuous or intermittent suction, and vacuum sealing. Suction is maintained using a vacuum pump or a standard suction bottle with high or low pressure. Only HBO-tested systems may be used during hyperbaric therapy.

If the patient is free of infection, reconstructive surgery with stabilization and internal fixation, implantation of an endoprosthesis, or soft tissue reconstruction, is planned. In these patients, addition of a second course of HBO therapy is to be considered and can be of therapeutic value.

2. HYPERBARIC OXYGENATION THERAPY

Bone infections are well accepted indications for adjuvant HBO therapy. Success of HBO therapy will largely depend on the pathology of the underlying disease. The pathophysiology of osteomyelitis with local edema, increased internal bone pressure and necrosis, suggests a decrease in blood flow[10]. Hypoperfusion is the direct consequence of increased intramedullary pressure in bone. Increased pressure results when pus and other debris block the Haversian system and medullary canal. The resulting hypoxia has been shown to be a regular problem in osteomyelitic bone[11].

The first report on the efficacy of HBO treatment in chronic osteomyelitis of human comes from Slack in 1965[12]. Since then, HBO has been described as an adjunctive therapy for refractory osteomyelitis by many authors.

2.1 Classification of osteomyelitis

To identify patients who will benefit from adjunctive HBO, systemic classifications like the Cierny-Mader classification[8] of osteomyelitis can be helpful[13]. This classification categorizes patients using anatomical and physiological parameters regarding both disease and patient (table 2.2.10-1). Patients with diffuse osteomyelitis include those with structurally unstable bone either before or after surgical debridement. Adjunctive HBO is used to treat the most difficult stages of chronic osteomyelitis, ie localized and especially diffuse osteomyelitis in a Type B host. Patients suffering from refractory osteomyelitis in stages 3B and 4B respectively are ideal candidates for HBO therapy, and will benefit from this adjunctive treatment modality in combination with surgical and antibiotic therapy. The decision to use HBO should be made regardless of the duration of chronic

osteomyelitis, as the time from first diagnosis seems to have little influence on the clinical outcome. Each patient, regardless of the history, should therefore be considered as if he were presenting de novo; and standard therapy including optimizing of host status, debridement, sampling of bacterial cultures, adequate antibiotic therapy, and adjuvant HBO therapy as clinically indicated, should be applied.

Table 2.2.10-1. Cierny-Mader classification of chronic osteomyelitis[8]

	Anatomical Type
Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis
	Physiological Classification
A Host	Normal host
B_S Host	Systemic compromise
B_L	Local compromise
C Host	Treatment worse than disease

2.2 Therapeutic principles and pathology

The factors leading to chronic refractory bone infection are well known: open wounds, crush injury with vascular damage, osteosynthetic apparatus, specific microorganisms, local bone ischemia, and host factors such as diabetes mellitus or angiopathy. Impairment of the immune response following trauma or infection contributes to the increased risk for osteitis. Most of these factors provoke hypoxia in the area of the lesion, enabling phagocytic antibacterial activity to take place. Hypoxia is the major reason why infections become chronic. In patients with chronic osteitis, impaired chemotaxis of neutrophilic granulocyte and phagocytic activity caused by low oxygen tensions have been shown.

The hypoxia of osteomyelitic bone is explained by the imbalance of oxygen demand and oxygen supply caused by compromised local microcirculation (vessel damage, edema formation, vascular stasis due to thrombosis)[10].

In addition to enhanced leukocyte and macrophage activation and direct bactericidal properties of hyperbaric tissue oxygenation, further beneficial effects have been demonstrated. Bone is characterized by a high rate of metabolism and rich perfusion. Nutrition is predominantly provided by endosteal perfusion, and to a lesser degree by periosteal vascularization. Matrix-forming peripheral osteoblasts are located further from the perfusing vessel than resorption-active centrally located osteoclasts. Reduction in perfusion will therefore down-regulate the activity of osteoblasts more than that of osteoclasts. Osteoblast-mediated osteoid formation is dependent on

oxygen supply in the periphery. HBO therapy promotes angiogenesis with consequent increase of blood flow into tissue, organs and bone, allowing the antibiotic to penetrate closer to bacterium-rich areas. Increased oxygen tension and blood flow also have beneficial effect in reducing soft tissue swelling.

However, surgical debridement remains critical to eliminate areas of necrosis and sequester, and to reduce local hypoxia and bacterial contamination.

Following successful infection control HBO therapy may help salvage local or microvascular soft tissue flaps during the phase of soft tissue reconstruction (*see chapter 2.2.7*).

In general, the efficacy of HBO therapy is more evident with increasing impairment of tissue perfusion. This has been clearly demonstrated in infection of the foot or distal lower limb in patients with diabetic or arteriosclerotic angiopathy. In our own practice the rate of limb amputation following chronic disturbance of microcirculation has dropped significantly.

2.3 Experimental studies

As clinical studies during the 1960's showed some benefit from HBO treatment in severe cases of osteomyelitis, a series of controlled animal studies confirmed the perceived clinical effect[14-16].

Esterhai et al.[16] showed in an animal model that pO_2 under atmospheric conditions in osteomyelitic bone reached only 17 mmHg whereas pO_2 was 32mm Hg in normal bone of the contralateral side. On breathing 100% oxygen, readings were 99mm Hg for normal bone but only 18mm Hg for infected bone. Using HBO at 200kPa, both infected and uninfected bone reached pO_2 values of almost 200mm Hg (table 2.2.10-2).

Table 2.2.10-2. Oxygen tensions (mm Hg) in normal and osteomyelitic tibia of the rabbit (according to Esterhai et al.[16])

Treatment gas	Normal bone	Osteomyelitic bone
Atmospheric air	31.9 ± 4.60	16.7 ± 3.8
Normobaric oxygen	98.8 ± 22.0	17.5 ± 2.7
HBO at 200kPa	191.5 ± 47.9	198.4± 2.7
HBO at 300kPa	309.3 ± 29.6	234.1± 116.3

Niinikowski[10] and Hunt found oxygen tensions in osteomyelitic bone to be 10-20mm Hg. Several later studies[10,17] demonstrated furthermore that these decreased oxygen tensions typically associated with bone infections can be elevated to normal or supra-normal by using HBO.

The importance of these elevations for the hypoxic milieu of osteomyelitic tissue is made clear by the work of Hohn et al.[18]. They were

able to show that phagocytic killing of *Staphylococcus aureus* was reduced when oxygen tensions in the area of bacterial invasion fell to below 30mm Hg. If oxygen tensions were around 0mm Hg the microbicidal power of polymorphonuclear leukocytes (PMN) fell to 50%. The reduction of phagocytic killing ability at oxygen tensions near zero was similar to individuals suffering from chronic granulomatosis, a disease caused by a defect of NADPH oxidase. This defect leads to a diminished production of oxygen free radicals in the phagocytes, and thus to a reduced bacterial killing ability of phagocytes. This effect was reversible by reversing hypoxia only in non-granulomatous animals. Hohn concluded that hypoxia was responsible for the diminished production of lysosomal oxygen free radicals, causing a disturbed phagocytic killing mechanism.

These findings were confirmed by several other authors[19-21], and extended to other bacteria such as *Escherichia coli*, Proteus species and *Pseudomonas aeruginosa.*

Indeed, HBO has been shown to be effective as adjunctive therapy in several animal models of chronic *Staphylococcus aureus* and *Pseudomonas aeruginosa* osteomyelitis[13,22,23].

2.3.1 Acute osteomyelitis

The therapeutic effect of HBO in well-perfused tissue may not, at first glance, be apparent. Anaerobic microorganisms make up approximately. 10-15% of the isolates in chronic non-haematogenous osteomyelitis, with some isolates being mixed aerobic/anaerobic. Therefore the well validated direct toxic and lethal effect on anaerobes will eradicate these organisms. Anaerobic microorganisms lack the ability to produce superoxide dismutase and catalase, enzymatic mechanisms used by aerobic bacteria to degrade toxic oxygen radicals. HBO therapy leads to elevated oxygen free radical levels both intracellularly and extracellularly in the infected area. In clostridial and non-clostridial anaerobic infections this effect is well validated (see chapter 1.6).

2.3.2 Chronic osteomyelitis

The indication for HBO therapy is even more conclusive in patients with chronic osteitis, especially because most of the principles of action are conclusive for both acute and chronic osteomyelitis. In the pathogenesis, post-traumatic osteitis occurs following open fracture, or following open reduction and internal fixation of fractures. The severity of trauma is a critical factor. Open fractures and extensive soft tissue injury favour the development of infection. A second factor is the additional trauma caused by

surgery and osteosynthesis. Surgical technique and operative stabilization may compromise perfusion, and therefore adversely affect bone healing and immune response. In patients with impaired host defences adjuvant HBO can be helpful to prevent secondary damage by surgical procedures.

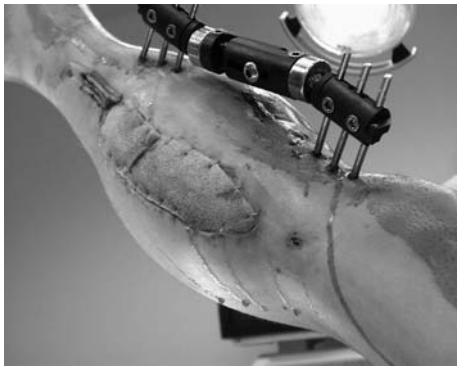

Figure 2.2.10-6. Acute osteomyelitis after crush injury, stabilisation with external fixation

Stabilization techniques which protect the soft tissue envelope around the fracture such as external fixators or intramedullary nails are associated with a reduced risk of post-operative infection, whereas open reduction and internal fixation in combination with extensive exposure of fragments renders the bone more susceptible to the acquisition of infection. Additional factors include the bacterial load, type, and virulence. Up to 80 % of patients suffer from *Staphylococcus aureus* infection. HBO therapy has been shown to be as effective as cephalothin against osteomyelitis due to *Staphylococcus aureus* in the rabbit[14].

In addition to the bactericidal effect of oxygen on anaerobic bacteria, HBO mainly increases the phagocytic activity of leukocytes and macrophages and potentates the effect of some antibiotics. There is emerging evidence that certain antibiotics such as aminoglycosides, cephalosporins and quinolones may be more readily incorporated into the cell wall of the bacterium itself in the presence of high oxygen tension. The transport process across the cell wall is highly oxygen depending and ceases in hypoxic conditions when tissue oxygen tensions fall below 20-30mm Hg[24]. HBO therapy was shown to augment the antibiotic efficacy of aminoglycosides[25]. Using cephalosporins in combination with HBO, a 100-fold reduction in bacterial counts was found compared with either a cephalosporin or HBO alone[26].

An important factor in the healing process of osteomyelitis is the removal of necrotic bone by osteoclasts. Their high metabolic activity makes

osteoclasts sensitive to hypoxia. At low oxygen tension osteoclasts will not remove necrotic bone; and thus bone healing will be impaired. Interestingly, bone healing not only requires a minimum level of oxygen tension, but also the duration of elevated oxygen tension is important.

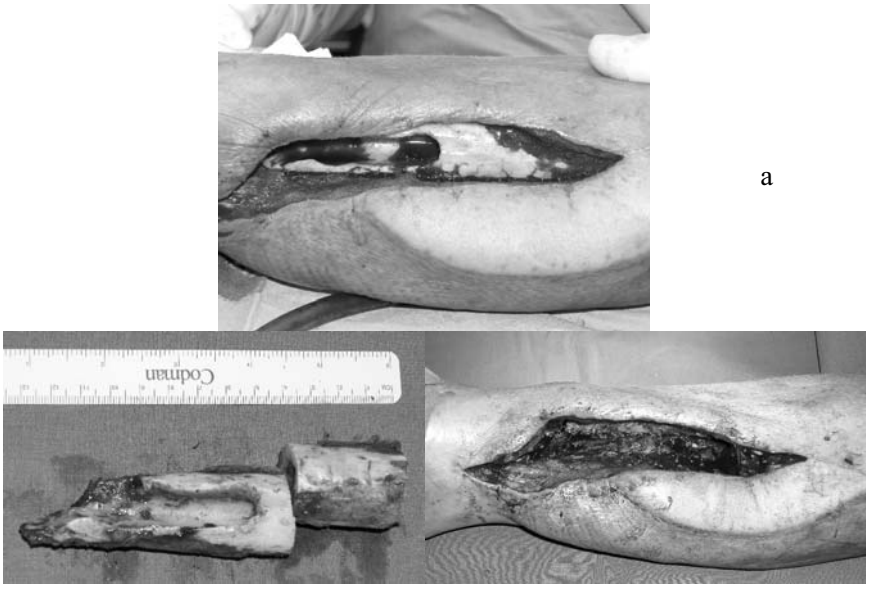

Figure 2.2.10-7a. Avital tibia of a 42y. old man;
7b. Resection 13cm of the tibia;
7c. After resection of the segment.

Barth[27] found that, if HBO at 200kPa for 90 minutes once daily was administered in rats, femoral fractures healed by primary ossification. If treatment was given twice daily, fractures healed through endochondral ossification, leading to structural weakness. Bone repair rate and neovascularization were retarded and osteoclastic activity was increased. Bone healing seems to be impaired quantitatively and qualitatively if HBO is administered above or below[28] the conventional once daily treatment at 200-280kPa for 90-120 minutes.

2.3.3 Conclusion

On the base of experimental work we can conclude:

- osteomyelitic bone and the surrounding area has a decreased blood flow and is hypoxic;

- hypoxia reduces host defence mechanisms by impairing the oxygen-dependent killing of bacteria by polymorphonuclear leukocytes;
- hypoxia diminishes fibroblast proliferation and collagen production, the basis of bone repair;
- decreased oxygen tension in osteomyelitic bone and surrounding tissue can be elevated to normal or above normal by HBO;
- HBO has a synergistic effect with certain antibiotics;
- experimental treatment of osteomyelitis caused by *Staphylococcus aureus* was equally effective when using HBO as when giving antibiotics.

2.4 Clinical studies

Even if there are precise and well founded physiological and pathophysiological conditions for the use of HBO in chronic osteomyelitis, the complex nature and the number of clinical variables involved in osteomyelitis[29] make evidence-based clinical studies difficult. Individual variations in the extent and location of infected bone, the status of surrounding tissue, the identity and quantity of microorganisms, the use of antibiotics, the presence of various coexisting diseases, the timing and form of surgical intervention and, last but not least, the unpredictable time course of the disease over years, all render the development of randomized controlled patient studies impracticable. Thus it is easily understandable that there are no randomised prospective, double blind studies of HBO therapy in patients with chronic refractory osteomyelitis.

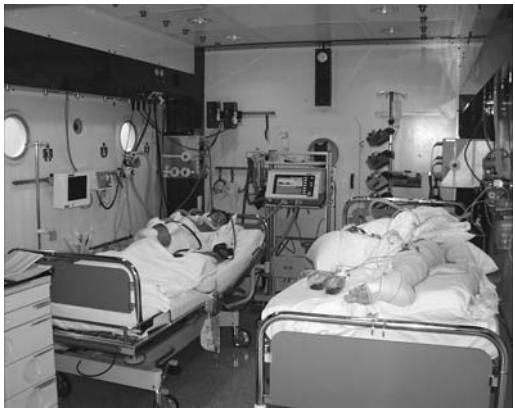

Figure 2.2.10-8. Treatment of severe bone infection under intensive care conditions in a hyperbaric chamber

Regardless of this, most of the published clinical studies which used common protocols (surgical and hyperbaric) for the adjuvant treatment of chronic refractory osteomyelitis have confirmed the previously reported experimental data. In patient series of refractory osteomyelitis HBO therapy, success rates range from 60-85%[30-34].

Few of these published clinical series explain their inclusion criteria or therapeutic protocol. Long-term follow up of the patients is rarely recorded. Patient compliance was poor, leading to a number of treatment failures which were related to the patient's refusal to have additional surgery[35].

The first clinical report on patients with refractory osteomyelitis described success in five patients treated with a combination of surgery, antibiotics and HBO[11].

More recently, a success rate of 86% in 15 patients with adjuvant HBO treatment of previously refractory osteomyelitis was reported by Chen[36]. In this study patients were followed up for an average of 17.2 months after completing HBO therapy. There are quite a number of interesting reports in the Chinese literature on HBO treatment of osteomyelitis; unfortunately, they are not easily accessible.

One of the best clinical studies so far comes from Morrey et al. In a prospective study they report on 40 patients with a treatment protocol including repeated surgical interventions (average 3.1 interventions, range 1-7), parenteral antibiotics, HBO therapy and muscle flap transplantation if necessary. 34 patients (85%) showed no signs of infection after a follow-up of two years, and could be observed for an average of 8.4 years (7.5-10.5 years) in total. In 30 patients (75% of the initial group) a sustained resolution of symptoms was demonstrated, four patients (12%) showing treatment failure with recurrent infection.

Malerba[37] reports a success rate of 66.5% in 430 retrospectively examined cases, in 28% of whom an improvement of bone infection was found. The average number of treatments was 67.

In our own experience, 54 patients (68%) of 79 patients with chronic osteomyelitis of the extremities and with a follow up of more than 24 months (24-60 months) showed sustained resolution of refractory chronic osteomyelitis. Most of these patients had undergone multiple unsuccessful treatments over more than three years (some up to 20 years) in other clinics. The drop-off rate in patients with chronic osteomyelitis, due to the patient's refusal to have additional surgery or to continue HBO therapy beyond about 15 treatments in our institution, is around 20%. This reflects the problematic nature of patients with chronic osteomyelitis.

Davis demonstrated sustained resolution of osteomyelitis in 89% of 38 patients. A similar success rate was reported by Aitasalo[38] with osteomyelitis of the mandible.

An overview of the main papers on HBO therapy in refractory osteomyelitis is given in table 2.2.10-3.

Table 2.2.10-3. Main papers on HBO therapy in osteomyelitis

Author	Year	Success rate
Slack[12]	1965	5/5
Depenbush[31]	1972	35/50 (71%)
Bingham[39]	1973	66/88 (75%)
Davis[33]	1977	63/89 (64%)
Morrey[30]	1979	34/40 (85%) after 24 months
		30/40 (70%) after ~8.4 years
Davis[32]	1986	34/48 (89%)
Chen[36]	1998	13/15 (86%)
Aitasalo[38]	1998	26/33 (79%)
Waisman[40]	1998	5/5
Maynor	1998	21/26 (86%) after 24 months
		12/15 (80%) after 60 months
Jamil	2000	26/28 (93%)

2.5 Practice of HBO therapy

HBO therapy should be seen as a part of the management plan for acute or chronic infection of the bone combined with a specific surgical protocol of sequential revision procedures involving irrigation and debridement. Depending on the severity, localization and joint involvement of the infection, surgical revisions are carried out at defined time intervals of two to seven days. Treatment should also include targeted administration of systemic and local antibiotics. During surgical intervals, wound closure is performed by vacuum sealing using polyurethane or polyalcohol sponges. Complete vacuum sealing is guaranteed by application of drapes or by surgical skin closure. Vacuum sealing is secured by external pads or suction drainage. Drainage tubes are connected to suction bottles if soft tissue conditions have improved and bleeding has subsided. In critical wound conditions, application of continuous suction by a low pressure pump is recommended.

HBO therapy can be administered to patients with vacuum sealed wounds. However, vacuum sealing has to be controlled to prevent a valve mechanism. Drainage bottles and low pressure bottles that resist hyperbaric pressure can be left in place. Vacuum pumps are not compatible with a hyperbaric atmosphere and need to be disconnected. Wound drains are connected to a suction device within the HBO chamber. Attention must be directed to leaks in the wound seal.

For reasons of patient monitoring and safety we prefer to administer HBO therapy on days of surgery prior to the surgical procedure. This

excludes patients who are still drowsy from anaesthesia, and who are unable to cooperate with ear clearing techniques, which would place them at risk of developing haemotympanum.

Figure 2.2.10-9. HBO Treatment of patients with osteomyelitis in a multiplace chamber

2.6 Treatment protocols

Usually treatment pressures of 200-250kPa are recommended, with treatment times varying from 120 minutes at 200kPa to 90 minutes at 240kPa. Since there is some experimental evidence suggesting that more than one treatment per day or higher pressures in the long term might interfere with bone healing, at our institution we use 240kPa for 90 minutes of oxygen therapy at pressure, once daily. Utilisation review is recommended after 40 hyperbaric treatments.

2.7 Recommendation

Agreement exists between the major Hyperbaric Medicine societies world-wide regarding the use of adjuvant HBO in chronic refractory osteomyelitis. Considering the difficulties (if not the impossibility) of performing a randomised controlled clinical study on this disease, and based on the evidence gained from both clinical experience and experimental studies, HBO is recommended as adjuvant therapy in cases of persistent osteomyelitis when previous appropriate antimicrobial therapy for six weeks, together with at least one surgical therapy, has failed.

Treatment protocols should use treatment pressures of 200-250kPa with treatment times from 90-120 minutes depending on the clinical situation.

Continued prospective clinical evaluation of HBO therapy in persistent osteomyelitis is recommended.

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Chapter 2.2.11

SUDDEN DEAFNESS

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Abstract: Idiopathic sudden sensorineural hearing loss (ISSHL) or "sudden deafness" (SD) is a sudden or rapidly progressive hypoacusis in which no known cause of sensorineural hearing loss can be identified. The hearing loss is due to pure damage of the cochlea; and four main theories are proposed to explain this disturbance: vascular, viral, round window rupture and auto-immune disorders. Although these hypotheses are controversial, the most likely cause involves impaired oxygen delivery to the organ of Corti. Cochlear activity is dependent on energy supply which is itself directed by the oxygen metabolism; and it has been well demonstrated that perilymphatic oxygen tension decreases significantly in patients with SD. According to these pathophysiological data, various therapeutic agents (steroids, vasodilators, hemodilution, among others) supposed to enhance rheology and oxidative metabolism have been proposed. In the same way, and due to its general and specific effects, hyperbaric oxygen therapy (HBO) is able to increase perilymphatic oxygen pressure, by restoring the oxidative metabolism in the stria vascularis and by protecting neurosensory cells. All these drugs and techniques have been tried singly or in combination for many years. Despite the results of retrospective and prospective studies, their therapeutic efficacy is difficult to establish due partly to the high rate of spontaneous recovery. Conventional therapies and HBO are extensively discussed in this chapter, together with evidence from the literature

Keywords: sensorineural hearing loss – organ of Corti – inner ear oxygen tension – steroids - hyperbaric oxygen therapy

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1. DEFINITION

Idiopathic sudden sensorineural hearing loss (ISSHL) or "sudden deafness" (SD) is defined as a sudden or rapidly progressive hypoacusis, more often unilateral, and in rare cases immediate cophosis[1,2]. The term "idiopathic" means that after performing clinical and laboratory (including radiological) investigations, no known cause of sensorineural hearing loss can be identified.

It is an otological emergency with an equal sex distribution and a peak morbidity in the fourth or fifth decade of life. The incidence of 5 to 20 patients per 100,000 per year[3,4,5] is certainly increasing and also underestimated because of an high rate of spontaneous remission or recovery[6].

2. PATHOPHYSIOLOGY

The hearing loss is due to pure damage of the cochlea.

Only in approximately 20% of cases can a causal factor be identified. (trauma, Ménière's disease, acoustic neurinoma, ototoxic medication, multiple sclerosis, etc.). In the remaining 80% no clear cause can be found. Four main theories are proposed to explain the mechanism of SD.

- Vascular: the most popular evoked etiology[4,7,8]. Since the arteria labyrinthi is a terminal artery, any thrombosis or embolus of this artery would lead to a profound deafness with a poor prognosis[9]. In the case of a mainly rheological disturbance, red blood cell sludge and a slowing of blood flow cause a reduction of the partial pressure of oxygen in the inner ear[7,10]. This reduction would cause the sensory cells to stop functioning, however, cell death would not occur until a critically low oxygen partial pressure was attained[11,12].

- Viral: many viral infections (mumps, cytomegalovirus, rubeola, varicella, etc.) can cause SD[13-15]. Viremia itself leads to a disturbance in the circulation and the formation of edema in the intima of the inner ear blood vessels[16,17]. Several papers report the association of SD with an active viral upper respiratory illness[18-20]; in some patients, SD is associated with antibody titres to several viruses[21,22].

- Round window rupture: in some cases, the clinical history can give evidence for a rupture of the round window (trauma to the inner ear, heavy weight lifting, intracranial pressure rise) [23,24].

- Auto-immune disorders: cochlear inflammation may also be secondary to autoimmune etiologies such as Cogan's syndrome, lupus erythematosus, polyarteritis nodosa, Buerger's disease[5,13,25,26].

Although these hypotheses are controversial, the most likely cause involves impaired oxygen delivery to the organ of Corti.

Oxygen and cochlear metabolism:

It is well known that the cochlear activity is dependent on energy supply which is itself directed by oxygen metabolism. The stria vascularis and the organ of Corti, as well as organs with high metabolic activity, have a high oxygen consumption[27].

It has been demonstrated that perilymphatic oxygen tension decreases significantly in patients with SD[10]. The consequences of these disorders are damage to the sensory neuroepithelium whether directly by blood deprivation and anoxia, or indirectly by the edema which increases labyrinthine fluid pressure. So, oxygen supply could be seen as key to the dysfunction of inner ear dysfunction. Some authors have been demonstrated the potential of oxygen administration to improve cochlear metabolism. Oxygen inhalation clearly raises the intra-cochlear tension of oxygen[28]. Oxygen therapy, in increasing the output of the pentose pathway, could play an important role in the preservation of intra-cochlear metabolic activity[29].

So, the use of hyperbaric oxygen therapy (HBO) has long been proposed[30] as a good way of increasing perilymphatic oxygen pressure; its rationale in treating SD is not only based on its general effects (massive increase in dissolved oxygen, vasoconstriction leading to edema reduction, restoration of blood flow, deformability of red blood cells) but also on the potential for specific local effects.

According to Matchinsky[31,32], the cochlea is very likely dependent on two distinct types of metabolism: aerobic oxidative for the stria vascularis, and glycolytic anaerobic for the organ of Corti. Thus HBO may have a twofold effect:

i). To restore oxidative metabolism in the stria vascularis.

ii). To protect neurosensory cells whose metabolism has slowed down but has not stopped; in this case, HBO could secondarily initiate the recovery of physiological energy metabolism.

In improving oxygenation in the inner ear, HBO increases transmembrane potential and ATP synthesis, and activates cell metabolism and the Na^+/K^+ pump, leading to a restoration of ionic balance and of electrophysiological function in the labyrinth[27]. Furthermore, oxygen diffusion through the round window exerts its rheological effects in the cochlear region by decreasing haematocrit and blood viscosity[33].

Cavallazzi[27] in measuring evoked autoacoustic emmissions, suggested that the increase of the electrical signal after HBO corresponds to better oxygenation of the cochlear organ.

Recently, Lamm et al.[34] have reported that under hyperbaric conditions, oxygen inhalation increases the oxygen tension of the perilymphatic fluid by 450% of its initial value, and that this state persists for one hour after termination of HBO. Arterial oxygen diffuses from the capillary into the

inner ear fluid; and increased partial oxygen saturation influences the oxygen tension of the inner ear.

Finally, during HBO, the high partial oxygen pressure infuses hypoxic areas of the cochlea and accelerates the biological mechanisms involved in functional recovery.

3. DIAGNOSIS

Hearing loss is generally unilateral; tinnitus and aural fullness are frequently associated; and in a variable proportion, vertigo is reported[35]. Tinnitus is a real disturbance which can lead to insomnia. The medical interrogation should include the following:

Date and circumstances of the occurrence of hearing loss: its suddenness and possible provocative factors such as strenuous exercise, diving, trauma (acoustic trauma), viral illness, emotional stress.

Previous medication and current treatment.

History of vascular diseases such as diabetes, dyslipidemia, hypertension, arteriosclerosis.

The physical examination comprises neurological, vestibular, and otoscopic examinations, and will be completed by tuning fork tests which are an initial method of excluding conductive hypoacusis.

Audiometric tests are essential; tonal audiometry, speech discrimination, and tympanometry with stapedius reflex will be performed as soon as possible to confirm the perceptive origin of the hearing loss and to quantify its threshold.

Additional testing (vestibulometry, brainstem auditory evoked potentials) may be obtained according to the clinical data. In case of suspicion of a retrocochlear pathology such acoustic neuroma, magnetic resonance imaging of the posterior fossa with gadolinium contrast is indicated.

A complete evaluation will include standard blood tests, and titres of auto-antibodies and viral antibodies.

4. TREATMENT

Treatment of ISSHL remains a challenge for the otologist. When the cause of the disease is clear, treatment can be specific. However, as a cause cannot often be found in this specific situation, treatment is much more controversial.

According to the different theories trying to explain the pathophysiology of ISSHL, various therapeutic agents have been proposed over the years including the following: steroids, hemodilution, carbogen inhalation,

vasodilators, metabolic activators, vitamins, anti-viral drugs, and HBO. These treatments have been tried singly or in combination therapies, and their empirical use is mainly based on improving the blood circulation and restoring the oxygen tension of the inner ear[36].

Their efficacy is difficult to establish. It seems that the therapeutic outcome is very often in the same range as the spontaneous recovery rate (25% to 65%), which itself is still the subject of controversy[23,37-41]. Nevertheless, some reservation is required about the highest percentages. Scientifically, a 'valid' overview[42] of the many studies into ISSHL-aetiology and the efficacy of various treatment is near impossible because of the diversity not only in treatments, endpoints and outcomes, but also in the study populations[43]. On one hand, criteria used to evaluate the recovery as 'good' vary according to the authors: some set a final mean loss inferior or equal to 20dB[41,44], while others consider it to be less than 40dB[40]. On the other hand, the heterogeneous follow-up cannot lead to unambiguous assessment of the duration of any improvement.

4.1 Conventional treatments

For many years, the results of conventional medical treatments have been reported widely in the literature, in both retrospective studies [26,44-52], and prospective studies as listed below:

Wilson et al. (1980) in a double blind prospective trial found a statistical superiority of steroids versus placebo[38].

Moskowitz et al.[54] (1984) confirmed the findings of the Wilson study[53].

Edamatsu et al. (1985) reported the same hearing improvement with carbogen inhalation versus "standard treatment".

Kronenberg (1992) et al. in a double-blind clinical study showed no statistically significant difference between procaine and low molecular dextran versus placebo[55].

Probst et al. (1992) in a prospective, randomised, double blind trial found no relevant differences between pentoxifylline, placebo and hypervolemic hemodilution[56].

Rahko (1997) found no statistically significant difference between carbogen inhalation and heparin infusion[57].

Kallinen et al. (1997) concluded that anticoagulation therapy is more effective for patients with hearing loss in low tones, while carbogen is more effective for hearing loss in neutral and high-pitched tones[58].

Based on a systemic review of current eligible randomised controlled trials, from 1966 to 2002 (13 studies, 1155 patients), according to the findings of Gong et al.[59], vasodilator therapy is not more effective than placebo or other therapies.

Kanzaki et al.[60], studying the effect of single-drug treatment on ISSHL in a multicentre study could not find any statistically significant difference in the recovery rate among drugs studied (ATP, alprostadil, hydrocortisone, amidotrizoate, beroprost sodium and betamethasone).

Previous measurements with laser doppler micro-flowmeter technique, showed that drugs usually used to improve the microcirculation are ineffective if parenterally injected, while they develop a stronger action when locally administered[27]. Animal studies, published by Parnes et al.[61] which established cochlear fluid pharmacokinetic profiles of hydrocortisone, methylprednisolone and dexamethasone in the guinea pig following oral, intravenous and topical administration, demonstrated a much higher penetration following topical application, methylprednisolone showing the best profile According to these animal studies, Ho et al.[62] and Gouveris et al.[63] published two prospective randomised controlled studies testing the intratympanic administration of dexamethasone in patients refractory to intravenous steroid and vasoactive therapy, with good results.

A certain homogeneity can be seen in these trials. Age (over 50-60 years), therapeutic delay after the onset of SD (7-14 days) and profound deafness (60-70dB) are negative prognostic factors. Prognosis is influenced by the shape of the audiogram curve: best results are obtained in flat and upward slopes.

4.2 Hyperbaric oxygen therapy

HBO has been proposed for many years with the intention of increasing the partial pressure of oxygen and oxygen concentration in the inner ear and of improving the microcirculation and blood profile[6]. HBO may restore oxidative metabolism in the stria vascularis, and protect the neurosensory cells, by increasing the intra-cochlear O_2 tension even in conditions of poor blood supply as described above (see Pathophysiology).

This therapy could be initiated as an early or a secondary treatment with two different philosophies. Early treatment - alone or more often associated with other therapy - is started within ten days of the onset of SD, while secondary therapy is started when conventional therapy has failed.

4.2.1 HBO as an early treatment

Goto at al. (1979) pointed to the superiority of HBO plus stellate ganglion block versus steroids plus vasodilators in patients treated more than two weeks after the onset[64].

Dauman et al. (1985) compared HBO/vasodilator/corticosteroids with vasodilator/corticosteroids alone and with hemodilution therapy. Although the HBO group scored better, the results were not significant[1].

Pilgramm et al.(1985) showed a similar improvement with HBO compared to hemodilution[65].

Miyake (1988) reported a beneficial effect of HBO if started within ten days after the onset of SD[66].

Zennaro et al. (1993), in treating 87 patients with HBO associated with normovolemic hemodilution found a good improvement in 60% of patients[67].

On the other hand, a prospective study led by Dauman et al. showed no benefit in hearing improvement between two schedules of HBO administration: two sessions per day versus one session per day[68].

The First European Consensus Conference on Hyperbaric Medicine[69], held in 1994, using some of the studies mentioned above as a basis for the discussion recommended: *"HBO, together with other treatment measures, such as hemodilution, is recommended in sudden deafness (Type 2 recommendation). However, the respective efficacy of the two treatment modalities is not known at the moment".*

Since these first conclusions, ENT and hyperbarists specialists have continued to treat many patients with variable success rates. So, it seemed interesting to see whether scientific knowledge had moved in the field of HBO. To this end, we carried out a literature survey from 1994 to the present; the search including all patients with acute sudden sensorineural hearing loss.

The intervention of interest was hyperbaric oxygen therapy and the ideal publication would be a controlled and randomised trial. The search included the terms 'sudden deafness', 'hearing loss', 'sensorineural', 'acute', 'hyperbaric oxygen', 'treatment', 'therapy' and was performed with online databases: Medline, Cochrane Library, Best Evidence, Current Contents, Centre for Clinical Effectiveness Monash University.

The results of this review identified papers which reported retrospective trials with their own limitations, or prospective studies either with concurrent or historical controls. Even though some of them have not been published in English (except in abstract form only), or have been presented only as communications at HBO congresses, we report their outcome.

Flunkert et al.[70] compared hemodilution and HBO as an initial treatment in the early stages of the disease in a prospective controlled trial and observed equal outcomes with insignificant advantages for HBO.

Kestler et al.[71], in 49 patients compared HBO up to three weeks after onset of SD to standard infusion therapy. He concluded that the results of the two treatments do not surpass the rate of complete spontaneous remission.

Meazza et al.[72] in a retrospective report, pointed to the benefit of performing at least two cycles of 15 HBO sessions started eight days after the onset of SD.

More recently, three retrospective studies reported the following data:

Aslan et al.[36] evaluated the medical records of 50 patients who all presented within two weeks of the onset of SD. A first group of 25 patients

was "usually treated" with betahistidine hydrochloride, 1 mg/kg/day of prednisone and daily stellate ganglion block with lidocaine. The second group of 25 patients received the same treatment with the addition of HBO at 2.4ata for 90 minutes with a total of 20 sessions (14 twice daily followed by six once daily). The mean hearing gain of 37.9±24.0dB in group 2 was statistically higher than 20.0±19.6dB in group 1 ($p<0.05$). According to age, a significant difference was found in group 2 in which the mean gains in five frequencies were 51.4±19dB and 23.3±20.3dB respectively for patients younger and older than 50 years ($p<0.05$). Even though patients older than 50 years in group 2 scored better (23.3±20.3dB) than those of same age in group 1 (15.1±14.0dB) ($p<0.05$), there was no benefit in patients older than 60 years in either group.

The study by Racic et al.[73], is one of the few reports about HBO used alone. One hundred and fifteen patients presenting after a mean delay of seven days after the onset of ISSHL were studied. They were divided in two groups according to the mode of treatment. A group of 51 patients, receiving HBO alone at 2.8ata for 60 minutes twice daily was compared with a group of 64 patients receiving intravenous pentoxifylline. The mean gain in the HBO group was 46.35±18.58dB as compared with 21.48±13.50dB in the pentoxifylline group ($p<0.001$); and recovery to physiological values was 47.1% of patients in the HBO group as opposed to 6.25% patients in the pentoxifylline group. Moreover, follow-up nine months later confirmed the persistence of benefit in both groups.

Barthelemy at al.[74] reported a therapeutic evaluation of 229 patients simultaneously treated with HBO (1 session/day at 2.5ata for 90 minutes, for at least ten consecutive days), methylprednisolone (1mg/kg) and vasodilators (pentoxifylline, nicergoline). The mean hearing loss before treatment was 52.5±30.0dB versus 26.6±30.4dB after therapy. Good improvement (gain>50%) was noted in 56.3% of patients. The best results were correlated to therapy initiated within seven days ($p=0.01$); and the best gain was obtained in flat and downward audiometric sloping curves.

Other authors have performed prospective trials (Figure 2.2.11-1). Cavallazzi et al.[75] showed a better global improvement in the HBO group in comparison with a group of patients managed with various conventional treatments. With respect to the grade of hypoacusia, the gain decreased according to the severity of the hearing loss, but remained always superior in the HBO group. In addition, HBO was more efficient in SD with downward audiometric slopes.

Fattori et al.[76] compared two groups of patients both treated in the early stage of the disease (within 48 hours of onset). He observed a large statistical difference in favour of HBO compared with vasodilators in the mean global hearing gain. According to the author's improvement criteria, the patients in

the HBO group experienced a significant improvement as compared with the vasodilator-treated group.

Authors	Goal	Patients	Methods, protocol	Improvement criteria	Results
Cavallazzi 1996	Medical TRT vs HBO+medical TRT	62	Group 1 (30): heparine dextran betamethasone antiviral Group 2 (32): idem+ HBO 15 sessions over 3 weeks	3 groups / final gain: good: ¡ Ã0 50%<moderate> 25% poor: <25%	Good results (gain ¡ Ã0% mild losses: 88% group 2 vs 63% group 1 media losses: 60% group 2 vs 50% group 1 severe losses: 57% group 2 vs 43% group 1 Both treatments: improvement in upward and downward slopes HBO: > in downward slope (80% vs 33%)
Fattori 2001	HBO vs Buflomedil	50	All treated within 48h of SD onset Group 1 (30): 10 sessions (1/day) Group 2 (20): 10 day-course Buflomedil	3 groups / final gain: good: ¡ Ã0 50%<significant> 25% insignificant: <25%	Mean global gain: 61,3% (group 1) vs 24% (group 2) p=0,005 Clinical results: Group 1: 56,7% of patients good recovery and 16,7% insignificant Group 2: 25% of patients with good recovery and 45% insignificant In both groups: Significant improvement in severe loss >70 dB compared to mild (<40 dB) p<0,05 No prognosis difference / shape of curve Recovery independant of age
Topuz 2004	Medical TRT vs HBO+medical TRT	51	Group 1 (21) steroids dextran pentoxifylline Group 2 (30): idem+ HBO	mean gain in each group (five frequencies)	HBO: significant improvement in all frequencies except 2000Hz HBO group: mean gain>in patients with initial loss up to 60 dB HBO: more effective in patients<50 years (p=0,044)

Figure 2.2.11-1. Prospective studies

Topuz et al.[77] recently reported a fairly comparable study to that of Cavallazzi. A significant improvement was detected in all frequencies in the HBO group except at 2000Hz. The mean hearing gain in HBO-treated patients was significantly higher in patients with initial hearing levels up to 60dB. Moreover, HBO was found to be more effective in patients younger than 50 years.

4.2.2 HBO as a secondary treatment

Some studies have reported the effect of HBO administration when conventional therapy has failed:

Lamm et al.[6] performed a meta-analysis from 1968 to 1997; fifty selected studies on 4109 patients with acute cochlear disorders and tinnitus who underwent HBO after unsuccessful conventional treatment drew the following conclusions: the previous data regarding the equal effectiveness of placebo therapy and all non steroidal drugs, and in a majority of cases compared with spontaneous recoveries, were confirmed. If HBO was administered between two weeks and six weeks after failure of conventional therapy, 54.3% of patients experienced a significant hearing gain of more than 20dB, and 33% a moderate improvement. If HBO was administered at between six weeks and three months, 13% of patients showed a definite improvement and 25% a moderate improvement.

Thereby, Almeling et al.[78], in treating a cohort of 650 patients after failure of conventional treatment, reported a fairly good improvement if HBO was applied up to three months after the first symptoms of SD.

In a similar study, Nakashima et al.[79] administered HBO to 550 patients after unsuccessful conventional treatment and noted an increase in hearing level in some patients.

Shiraishi et al.[80] treated 119 patients with HBO, stellate ganglion block and vasodilators versus 107 patients with various other therapies. A better score was obtained in the HBO group in the presence of resistance to other treatments and more than two weeks after the onset of the disease. These results are in accordance with Goto et al.[65], who have already demonstrated the same result.

5. CONSIDERATIONS AND FUTURE PROSPECTS

Though a majority of authors report a fairly good improvement when using HBO, it is well known that comparisons between the results of different studies is not a scientific process and can lead to a biased assessment.

In general, it must be stated that the large variability of methodologies, nature and duration of therapies administered prior to or in combination to HBO, as well as heterogeneity in evaluation criteria, are the main problems in the interpretation of conclusions. For example, some results are obscured by including patients with hearing losses due to causes other than SD. Furthermore, the differences in initial hearing level and initiation time of the treatment between HBO-treated and non-HBO-treated groups has impeded comparisons of the outcomes between the separate groups.

Therefore, we are currently faced with many retrospective trials but a paucity of randomised, controlled studies about HBO and SD. Although the results of recent prospective trials[75-77] show strong evidence that primary HBO is more effective than conventional therapy, more large randomised and prospective studies are needed.

Research in different databases according to Evidence-Based Medicine methodology has failed to find any trial appraisal regarding HBO and SD. In the field of other medical treatments of SD, only the results of five studies already quoted to above[38,53,54,57,58] have been evaluated and considered with only level 3 evidence[81, 82]. This small number of analysed articles shows a general lack of research interest in any treatment for SD.

On one hand, there is no true consensus about the medical treatment; however, steroid administration, alone or combined with other treatment[83], has been widely recognized as effective since two prospective randomised studies[38,53] demonstrated that this therapy was superior to placebo or

spontaneous recovery, almost 20 years ago. Corticosteroids may have a stabilizing effect on the cell surface membrane, and could influence phospholipid metabolism, sodium and potassium plasma membrane transport and eicosanoid metabolism, in addition to having a non-specific effect on GABA receptors. Some animal studies[84] have demonstrated that pre- or post-ischemic intravenous administration of glucocorticoids significantly ameliorates the post-ischemic compound action potential threshold shifts in guinea pigs subjected to transient cochlear ischemia of 30 minutes' duration.

On the other hand, based on previous results, it appears that HBO as a secondary treatment for SD could lead to improvement for patients after unsuccessful conventional therapy as reported in many retrospective studies in the last 15 years, and only in weak prospective randomised studies. In fact, a residual percentage of patients not responsive to the classical treatment (ranging from 30 to 50%) could be enhanced by HBO.

Bennett et al.[85], on behalf of the Cochrane database of systematic reviews, tried to conduct a meta-analysis with all the randomised and pseudo-randomised controlled trials comparing the effect of treatment for either acute or chronic idiopathic sensorineural hearing loss where hyperbaric oxygen administration was included, with the effect of comparable treatment in the absence of hyperbaric oxygen.

They affirmed that study quality was generally assessed as low[86] because of the absence of clear randomisation procedures, variability and poor reporting of entry criteria, variable nature and timing of outcomes, and the absence of a formal power (or sample size calculation reaching a very low power) to detect clinically significant differences in the main outcome of interest.

Many authors stress the need for more randomised, prospective clinical trials to confirm the efficacy of HBO in SD. This concept was strengthened during the 1st Consensus Conference on Hyperbaric Medicine in 1994, when the Jury proposed: "*It is strongly recommended that quality research protocols are put in place to assure and reinforce the credibility of hyperbaric oxygen therapy (Type 1 recommendation)".*

Since 2002, a trial entitled "Hyperbaric oxygen in the acute treatment of sudden idiopathic sensorineural hearing loss. Randomised, prospective study of HBO after failure of previous medical treatment" has been underway. This multicentre study including the participation of hyperbaric centres in Belgium, Denmark, Germany, Italy and France has been launched within the scope of COST Action B14: European Cooperation On Science and Technology[7].

The aim of the protocol is to study HBO in patients with SD where previous conventional treatment for at least seven days (involving at least 1mg/kg of corticosteroids) failed. The protocol predicts a correct sample size after randomisation of 400 patients (200 patients HBO-treated compared with 200 control patients without any extra treatment) in order to achieve the

primary endpoint which is at least a 30% rate of "good" recovery with secondary HBO (Chi square test <0.005). The hearing recovery scores are considered: 'excellent' (return to within –10dB or less), 'good' (return to within –20dB), 'poor' (all other cases). This trial is currently still in progress[88].

6. CONCLUSION

Management of SD remains controversial. There are few other disease for which such a variety of treatments have been proposed; and still today, many different treatment regimens are propagated. For more than 35 years, hyperbaric specialists have gained experience in the treatment of SD.

Pertinent prospective and/or retrospective articles have been published; although their value is undoubted, they cannot provide any additional evidence in favour of HBO for SD treatment. It has been reported that non-randomised trials can produce much larger estimates of treatment effects than randomised trials because of potential bias[89]. Nevertheless, hard evidence can only be obtained based on prospective, randomised trials. The last recommendations of the 7th Consensus Conference of Lille[90] were pronounced with the identical level of type II as ten years before because of the current absence of any stronger evidence.

Persistent hearing loss frequently leads to psychological and social handicaps and the aim of physicians should be to propose maximally effective therapies for these patients. Within this framework, HBO represents an excellent alternative; and it is logical to continue to treat sudden sensorineural hearing loss with this technique while waiting for data sufficient to clarify its exact place.

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Chapter 2.2.12

NEUROBLASTOMA

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Abstract: Hypoxia is recognized as a major cause of failure of radiotherapy. In clinical oncology, several treatment modalities have been applied to overcome tumour hypoxia either by increasing the oxygen delivery to tumour cells (ie carbogen and hyperbaric oxygen) or by combined treatment with oxygen mimicking agents to sensitize hypoxic cells (ie misonidazole). Radiation enhancement by HBO in the treatment of patients with recurrent Neuroblastoma stage IV in a setting of unsealed source radionuclide brachytherapy seems to be the most promising indication of that approach

Keywords: Tumour hypoxia, oxygen free radicals, neuroblastoma, oxygen sensitizer

1. NEUROBLASTOMA

The vast majority of neuroblastoma tumours arise from postganglionic sympathetic neuroblasts but a small percentage can arise from parasympathetic neuroblasts[1]. Collectively these tumours comprise between 8 and 10% of all childhood cancers. There is an incidence in the UK and USA of approximately 1 in 8,000 live births. This disease is predominantly a disease of the first decade with about 80% of the patients occurring in the first 4 years of life.

There are several prognostic variables. Stage appears to be the most important prognostic variable. Stages 1 and 2 disease (see table 2.2.12-1) and that of stage 4s, particularly in young infants, have a 75 to 90% curability rate. For Stage 3 and 4, most series report survival at 5 years at a maximum between 10 and 30%. (30% for Stage 3 and 10% for Stage 4). The

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second important variable is age. Those under 1 year have an improved survival, even with more extensive disease. Primary site seems to influence outcome, maybe because of the nature of the disease or maybe because of the extent of infiltration prior to diagnosis with adrenal primaries having a worse prognosis than other primary sites. A number of other biochemical and biological markers have been shown to have some significance.

Table 2.2.12-1. INSS International Staging System for neuroblastoma (from Brodeur et al[2], 1993)

Stage 1	Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral and contralateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
Stage 2a	Localized tumour with complete or incomplete gross excision; representative ipsilateral non-adherent lymph nodes positive for tumour microscopically
Stage 2b	Localized tumour with complete or incomplete gross excision; with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumour infiltrating across the midline with or without regional lymph node involvement; or, localized unilateral tumour with contralateral regional lymph node involvement; or mid-line tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone marrow, liver, skin and/or other organs (except as defined in Stage 4S).
Stage 4s	Localized primary tumour (as defined for Stage 1, 2a, or 2b) with dissemination limited to skin, liver and/or bone marrow[3] (Limited to infants < 1 year).

[1] Multifocal primary tumours (e.g. adrenal primary tumours) should be staged according to the greatest extent of the disease, as defined above, and followed by m, e.g. 3m.

[2] The mid-line is defined as the vertebral column. Tumours originating on one side and and 'crossing the mid-line' must infiltrate to or beyond the opposite side of the vertebral column.

[3] Marrow involvement of stage 4S should be minimal; i.e. less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirates. More extensive marrow involvement will be considered to be Stage 4. The MIBG scan (if done) should be negative in marrow.

2. MANAGEMENT OF NEUROBLASTOMA

The present consensus is that stage 1 and 2 should be resected with no longstanding sequelae. Major attempts at surgical resection are not indicated at presentation for neuroblastoma, except in exceptional circumstances, (those being e.g. a primary tumour in the neck where total surgical resectability may be possible). Damage should not be done to important

tissue including nerves in order to obtain total resection. There is some evidence that surgical removal of residual masses post chemotherapy; particularly abdominal masses may be beneficial. It is recommended that stage 3 tumours, after surgery, careful observation with measurement of urinary catecholamine concentrations and radiological imaging is required. Stage 4 diseases over the age of one year is initially treated with chemotherapy, followed by surgical resection of the primary tumour and consolidation with myeloablative therapy with haempoetic stem-cell support.

Radioactive MIBG is used for three groups of patients:

- Unresectable localized tumours
- Initial treatment of unresectable tumours stage 3 and 4
- Patients with recurrent tumours
- This report concerns patients with recurrent neuroblastoma.

3. OXYGEN FREE RADICALS, MIBG AND NEUROBLASTOMA

Generally two defense mechanisms to free radicals have been identified:

- Low molecular weight substance free radical scavengers (e.g. uric acid, reduced glutathione, N-acetylcysteine, thioredoxin).
- Enzyme systems.

A neuroblastoma cell has two defective endogenous defense enzyme systems against oxygen-derived free radicals: first a reduced catalase activity, causing an intracellular accumulation of hydrogen peroxide, secondly, a two to three times elevated ferritine content. Exposure to an environment with increased amounts of available molecular oxygen (Hyperbaric oxygen) leads to an increased production of oxygen-derived free radicals and consequently to a higher efficacy of radiation therapy.

4. MIBG

Meta-lodo-Benzyl-Guanidine (MIBG), a functional analogue of epinephrine. Radioactive M-^{131}IBG has acquired a definite place in diagnostic scintigraphy and tumour targeted therapy in a range of neural crest tumours. The metabolism of MIBG is characterized by a single active uptake - one mechanism at the cell membrane followed by storage in cytoplasmatic neurosecretory granules. MIBG in itself is an inhibitor of complex-1, which is part of the enzyme system situated in the mitochondrial respiratory chain. Inhibition of Complex-1 by MIBG leads to the leakage of some impaired electrons out of the respiratory chain, which causes an

increased production of the superoxide radical. This superoxide radical is normally converted into H_2O_2 by the enzyme superoxide dismutase and subsequently the H_2O_2 is converted into the harmless H_20 and 0_2 in a reaction catalyzed by catalase. However, when the catalase activity is reduced, as in neuroblastoma cells, the H_2O_2 will partly be converted into the very reactive hydroxyl radical, which contributes to elevated contents of the free radicals: superoxide and hydroxyl. Therefore, utilizing MIBG for neuroblastoma treatment is an important factor in damaging the tumour cells.

5. THE OXYGEN EFFECT

Oxygen is the most electron-affinic molecule in the cell and reacts extremely rapidly with the free electron of the free radical making the damage permanent. In the absence of oxygen, much of the radical damage can be restored to its undamaged form by hydrogen donation from nonprotein sulfhydryls in the cells. Gray[3] and colleagues proved already in 1953 this concept by extensive in vivo and in vitro studies that the amount of molecular oxygen available to tumour cells at the time of irradiation has a direct influence on the effect of irradiation. The oxygen phenomenon has an effect on enzymes in solution; on bacteria; on yeast; and on plant and mammalian cells irrespective of their genetic background. Furthermore, most solid tumours contain nutrient and oxygen deprived compartments, and hypoxic cells are known to be resistant to irradiation. For sterilization of hypoxic cells, a three times higher radiation dose is required than for cells at normal oxygen tension. The ratio of radiation doses given under hypoxic vs. aerated conditions to achieve the same biological effect is called the oxygen enhancement ratio (OER). A typical radiation cell survival curve for mammalian cells under aerobic and hypoxic conditions is shown in Figure 2.2.12-1. Several treatment modalities have been applied in clinical oncology to overcome tumour hypoxia for example hyperthermia, chemical modifiers of tumour blood flow, hypervolemic blood transfusion, hypoxic cell sensitizers (e.g. misonidasole), and hyperbaric oxygen (HBO). The efficacy of HBO as radiosensitizer in tumour therapy has been shown in experimental studies[4] as well as in clinical trials[5]. Controlled trials[6] with HBO have shown a sixty percent overall benefit, whereas in trials with misonidasole only a twenty-one percent benefit has been established. Also in targeted radiotherapy with M-^{131}IBG, the oxygen effect is probably the most important additional factor for radiation enhancement in patients with recurrent neuroblastoma stage IV.

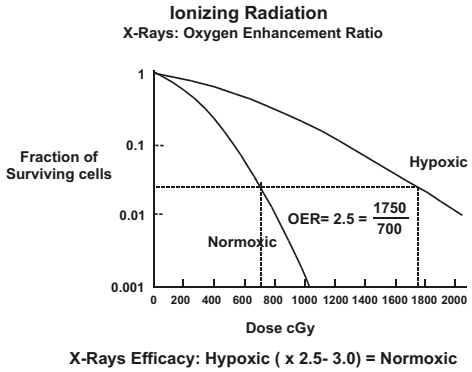

Figure 2.2.12-1. Fraction of surviving cells as a function of radiation dose for cells that are treated under oxygenated conditions vs. hypoxic conditions

6. CLINICAL STUDY RECURRENT NEUROBLASTOMA STAGE IV AND HBO

With M-^{131}IBG treatment, specific radiation protection measures have to be taken. Thyroid protection is necessary. The patients used potassium iodide orally for two weeks (e.g. oral administration of lugol's iodine 0.2 ml three times daily, or potassium iodine 250-500 mg m^{-2} per day) starting 48 hours prior to therapy. The M-^{131}IBG was administered through a Hickman-line or cannula. 200 milliCu M-^{131}IBG were given for the first treatment and 100 milliCu M-^{131}IBG for all further treatments. One hyperbaric session involves, pressurizing the chamber from 1 ata to 3 ata in twelve minutes, followed up by seventy-five minutes at 3 ata. The decompression profile was derived from the Canadian Forces Decompression tables. Radiation enhancement by HBO started two to four days after the initial treatment with M-^{131}IBG, for a consecutive period of four to five days. All patients tolerated the hyperbaric oxygen therapy without additional discomfort. Toxicity from combined treatment was not any greater then with M-^{131}IBG treatment alone. To date, 27 patients with recurrent stage IV neuroblastoma have entered this protocol. Their ages ranged from 1.8 to 15.3 years with a mean age of 7.1 years. From this group, a cumulative survival curve was constructed. Of 27 patients, 8 patients are alive. The 5-year survival is 22% (figure 2.2.12-2).

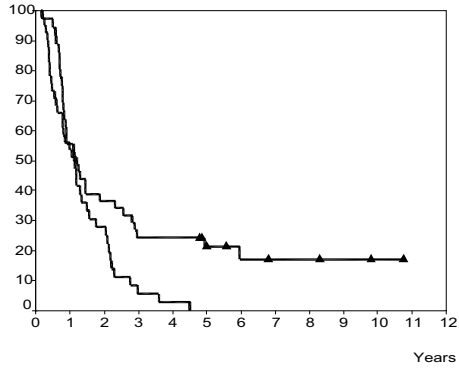

Figure 2.2.12-2. Cumulative survival curves of the two studies. The triangles represent the patients who are alive in the treatment group HBO and radioactive MIBG

7. CONCLUSION

From these studies, it may be concluded that "unsealed source" radiation enhancement by hyperbaric oxygen is feasible and successful provided that a large hyperbaric chamber is available and a pediatric department with all facilities needed for this complicated treatment. Since all patients treated with M-^{131}IBG and HBO had recurrent stage IV neuroblastoma after conventional therapy including bone marrow transplants, these results are promising, when compared with the results of the first phase II study on the use of M-^{131}IBG without HBO in patients with recurrent neuroblastoma stage IV.

Our hypothesis is that radiation enhancement by hyperbaric oxygen in children treated for recurrent neuroblastoma stage IV with M-^{131}IBG is endorsed by the impaired free radical defense mechanisms of neuroblastoma cells, together with the biochemical properties of MIBG in an environment with a high availability of molecular oxygen, all these being potentially damaging to tumour cells.

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2.3 Optional Indications

Chapter 2.3.1

BURNS

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Abstract: The use of hyperbaric oxygen therapy as part of the treatment of thermal burns is far from being universally accepted. Although there appears to be substantial experimental animal evidence of the positive effects of hyperbaric oxygen in many aspects of the pathophysiology of the severe burn, the clinical human studies confirming these effects are lacking. Reasons for this are mostly related to practical and logistic difficulties in organising such studies. In view of the current available knowledge, hyperbaric oxygen therapy should only be administered according to strict protocols of utilisation, optimising the possible benefits while avoiding any extra risk

Keywords: Thermal burns, inflammation, secondary ischemia, oxygen free radicals, ischemia-reperfusion, skin graft, leukocyte activation, cytokines

1. INTRODUCTION

The cutaneous burn wound represents a particular injury to the human body. As the skin is, in surface, the largest of all bodily organs, any alteration of its integrity may have a direct functional impact on other organ systems. Therapeutic strategies in burn wound management usually imply invasive procedures of a limited aesthetic and functional nature, such as excision and skin grafting.

The duration of hospital stay after a burn injury can be crudely estimated at 1.0 to 1.5 days for each percentage of skin surface area burned. About 20% of this hospital stay consists of acute care. For a burn wound of 30% Total Burned Surface Area (TBSA), an estimated hospital stay of seven weeks will be followed by a total duration of treatment of about one year[1].

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 479–494.

The consequences of a cutaneous burn injury are enormous, on a personal as well as on a financial level; in Belgium, burn care is considered one of the most expensive categories of hospital care.

1.1 Classification and Therapeutic Approach

Traditionally, burn wounds are classified according to three different 'degrees', indicating the depth of the cellular destruction induced by the thermal energy transfer. Although this classification has the advantage of being relatively simple (and largely based on macroscopic indicators such as blisters, exudate, colour and sensitivity), it does not permit an accurate prediction in all cases as to the probability of spontaneous healing of the burn wound.

Certain 'second degree' burns will necessitate, if the tissue destruction is too deep, excision and skin grafting in order to ensure healing. As the duration of the healing and cicatrisation phase is an important factor in the risk of development of hypertrophic scarring, certain burn care centres have adopted a policy of early excision of all skin that appears to be deeply burned, even if it does not classify as 'third degree'[2]. Others advocate waiting one or two weeks before deciding which parts can be left to heal spontaneously and which have to be excised[3].

Another classification, often used in the Anglo-Saxon literature, is based on the microscopic determination of the burn wound depth; it apparently permits a better prediction of the healing prognosis. In this classification, 'superficial partial thickness' burns can heal spontaneously, whereas 'deep partial thickness' and 'full thickness' burns need excision and grafting[4]. Because this classification relies on histological analysis, the reliability and clinical relevance of a few biopsies for the entire burned surface are being questioned[5].

1.2 Evolution

In most developed countries, a seriously burned patient is rapidly transferred to a specialised facility. Here, local wound care is performed; but more importantly, aggressive volume resuscitation is started. This resuscitation is aimed at normalising vascular filling pressures and at restoring intravascular oncotic pressure by substituting proteins and electrolytes lost in the exudate oozing from the burn wound surface. This global approach has led to an important reduction in the mortality of the burn injury – mostly in immediate (<24 hours) mortality.

In burn injury, the cause of death has shifted from a critical systemic organ failure during the initial phases of the burn wound and resuscitation,

towards a more delayed Multi Organ Failure (MOF) where the organism seems incapable of providing an adequate immuno-metabolic response to the local (infection), regional (ARDS, renal insufficiency, splanchnic bacterial translocation, etc.) or systemic (sepsis) injury.

A pronounced hypermetabolism (expressed as oxygen consumption) can be observed, in an almost linear correlation with the surface burned; at approximately 60% TBSA, the metabolism is almost doubled[6]. Moreover, in a complicated burn injury, oxygen consumption becomes directly dependent on peripheral oxygen delivery[7].

Even when the first aid and resuscitation measures are rapid and optimally performed, it is often observed that skin areas that were initially estimated to be burned to the second degree, have transformed to third degree over the first 24 hours.

In Jackson's original work of 1953 (in Jackson, 1969[8]), three distinct zones are described in the burn wound: a coagulation zone, bordered by a zone of capillary stasis, again bordered by a zone of hyperaemia and oedema. Zawacki[9] showed in 1974 that in experimental, controlled burns, the zone of capillary stasis progressively expands during the first 24 hours, up to the hypodermis. This causes the burn, which was initially classified as deep partial thickness, to convert to a full thickness burn.

The appearance and the progression of this capillary stasis can be directly related to the development of an interstitial oedema, and as such it is the direct consequence of the loss of intravascular fluids. In this burn wound model, Zawacki observed a maximum in the oedema formation at about four hours after the burn. The capillary stasis, on the other hand, progressed for more than 16 hours, some time after the oedema had reached its maximum. This stasis results in tissue ischemia and may cause a progressive necrosis of the intermediate zone. In the same series of experiments, however, it could be shown that this capillary stasis was not irreversible. If the burned area could be protected against dessication, a return of patency in the capillaries could be observed over time, often even up to the superficial dermal layers, from the second day on[9,10].

Even though this observation looks promising and encouraging, it seems that 30 years after the publication, modern treatment strategies of extensive burn injury - rightly aimed at preventing this wound dessication, at optimising the vascular filling and at meeting the increased demands for energy supplies (in nutrients and in oxygen)[11] - are capable of preventing neither this capillary stasis nor the progression of tissue necrosis.

1.3 Ischemia-reperfusion

Both phenomena – the delayed morbidity/mortality and the deepening of the burn wound during the first 24 hours after the injury – can be attributed to an inflammatory syndrome, both local and general.

A prolonged vasodilatation (induced by either a neurogenic reflex or a disruption of the endothelium-plasma equilibrium, or both) is accompanied by a markedly increased permeability of the capillary membrane[12]. The opening of inter-endothelial spaces has been demonstrated[13]; the endothelial cells take a more spherical form as a consequence of a reduction of membraneous Na^+-K^+-ATPase.

A large number of inflammatory processes are activated: the coagulation cascade, the complement system, the arachidonic cascade, adherence and activation of circulating leucocytes. Even though the activation of different chemical mediators has been demonstrated, we only barely begin to understand each of their specific roles, the exact sequence of their activation and the intricacies of their interactions[14-16].

The appearance in the serum of complement factor C5a constitutes one of the more potent leukocyte chemotactic stimuli. These show increased adherence (stickiness) between themselves and with the endothelial layer, and form intravascular aggregates before starting their diapedesis towards the perivascular space. This is accompanied by a 20-fold increase in their oxygen consumption (oxidative burst) and a markedly increased production and secretion of oxygen free radicals; thus, a vicious circle of inflammation is started[17].

The resemblance of these phenomena to the ischemia-reperfusion phenomena, observed in other medical/surgical domains, such as cardiac ischemia, transplantation surgery and reconstructive surgery, is striking. Oxygen Free Radicals (OFRs) seem to play a pivotal role in these events. OFRs are produced in three distinct sites: polymorphonuclear white blood cells (PMN), the mitochondrial electron transport chain enzymes, and intracellularly, by ischemia-induced conversion of *xanthine-dehydrogenase* to *xanthine-oxidase*[18].

Using a specific burn wound animal model, allowing selective blood sampling from the burned body area, Oldham et al.[19] showed that complement activation takes place at the site of the burn injury, and is mediated by a *hydroxyl radical* ($OH^{\cdot}$). This OFR is itself formed, via hydrogen peroxide, out of a *superoxide radical* (O_2^{-}), generated by the *xanthine-oxidase* system. Leukocyte depletion did not have any effect on the complement activation; this indicated that circulating PMN are not the prime source of these OFR.

This increase in *xanthine-oxidase* activity has likewise been demonstrated in human vascular beds after tourniquet-mediated ischemia of the upper limbs[20]; *xanthine-dehydrogenase* activity was completely absent in the effluent blood. Pre-ischemic administration of allopurinol (a potent *xanthine-oxidase* inhibitor) prevented ischemia-reperfusion lesions in these tissues, and no measurable *xanthine-oxidase* activity could be observed. These observations lead to the hypothesis that in these models, the endothelial cells are the source of the *xanthine-oxidase* activity.

Indeed, significant quantities of *xanthine-dehydrogenase* have been measured in endothelial cell cultures from rat pulmonary artery. Simulation of ischemia and reperfusion in these cell cultures leads to a burst of *superoxide radical* generation, provoking lysis of the endothelial cells. This *superoxide radical* production could be completely blocked by the administration of allopurinol, superoxide dismutase or catalase at the time of re-oxygenation[21].

2. OVERVIEW OF THE POSSIBLE ROLES OF HYPERBARIC OXYGENATION IN THE TREATMENT OF BURNS

As the morbidity and the mortality of burn injury is still, in large part, related to the relation depth/surface of the burned tissue, any measure or treatment that would reduce the surface of deep burn or that would promote rapid spontaneous healing of the burn wound, would logically reduce the occurrence of local or systemic complications.

If one considers the important role of the initial ischemia in the genesis of the inflammatory syndrome secondary to the burn injury, a major role of hyperbaric oxygenation (HBO) could be hypothesised.

2.1 Early utilisation

There are many known physiological effects of HBO that can positively influence early events after the burn injury. The pre-capillary vaso-constriction induced by hyperbaric oxygenation can reduce the plasma loss by reducing the inflow of liquids into the injured capillary bed, while still maintaining a sufficient oxygenation to ensure the survival of (epi)dermal cellular elements. An ‘anti-sludge’ effect could contribute to the limitation of capillary stasis. A (seemingly paradoxical) reduction of OFR production after ischemia-reperfusion has been shown when HBO is applied early after reperfusion.

In the case of concomitant carbon monoxide or cyanide intoxication, often observed after smoke inhalation, the benefits of HBO would be obvious.

In order to have a maximal effect, HBO would, however, have to be administered early (ideally within six hours, earlier if possible), which implies the necessity for the optimal integration of HBO and burn centres within the same hospital building[22].

2.2 Delayed utilisation

In the later stages after the burn injury, HBO will have an adjunctive effect, which may prove critical in some patients. It has an anti-bacterial action, both by maintaining adequate oxygenation in the burned areas (protecting from colonisation and infection by anaerobes) and by restoring and optimising the bactericidal capacity of polymorphonuclear white blood cells and of certain antibiotics.

HBO has an angiogenic effect, which helps prepare the wound bed for accepting skin grafts; and following the placement of such a graft, twice-daily HBO will provide sufficient oxygen for the graft to survive the critical first days - as it must survive on the oxygen diffusing from the underlying tissue.

3. EVIDENCE SUPPORTING THE USE OF HBO IN THE TREATMENT OF BURNS

Only very few of the possible effects of HBO have not yet been verified in an experimental cutaneous burn wound model. Most experiments confirm the benefits that HBO can offer in the treatment of burns. Why then has HBO not been long ago accepted in the clinical setting?

3.1 Reduction of plasma loss

In a canine burn model of 40% TBSA, a reduction of plasma loss of about 40% has been observed[23] when HBO was administered in the early phase after injury (3.0ATA, twice daily). A similar effect has been observed in a human - prospective, randomised - study[24], illustrating not only the pre-capillary vasoconstriction induced by HBO but even more importantly, the preservation of the integrity of the capillary vessel wall. In the first 24 hours after the burn, HBO-treated patients needed an average volume resuscitation of 2.2 ml/kg/%TBSA, whereas the control group needed 3.4ml/kg/% TBSA - a reduction of 35%.

A retrospective human study of 21 patients, of whom ten received HBO (2.0ATA, 90 minutes, twice daily) in the acute phase, confirmed this reduction in perfusion volumes required[25]. The initial experience of a major burn centre integrating HBO into the early treatment protocol of its patients illustrates the importance of this effect: the first patients had a high incidence of respiratory insufficiency, which turned out to have been due to pulmonary fluid overload - as the classical 'rules' of calculating the volume of fluid resuscitation were applied[26].

3.2 Preservation of dermal elements

The possibility that HBO might be able to preserve vital elements in the burned skin was first suggested by Korn et al.[27], who described, in a model of 5%TBSA, a faster epithelialisation of the second degree burn wound compared to non-HBO treated animals. The lesser degree of dermal destruction was illustrated by the faster reversal of capillary stasis (Chinese ink technique). From the first day, a return of capillary perfusion up to the middle third of the dermis was observed; and all through the first five days, it was noted that the degree of capillary patency was advanced by about 24 hours compared to the control group.

In an own study in 1996, we demonstrated the same effect in a model of standardised burn injury in the rat[28]. In this study, a deep partial thickness burn of 5%TBSA was created which progressed, in a reproducible way, towards full thickness after 24 hours.

Comparing two groups of animals, one receiving a classic burn treatment (prevention of dessication, local antibiotic dressing with aqueous sulfamylon) and the other receiving the same treatment plus two sessions of HBO (2.0ATA, 60 minutes) per day, a preservation of deep dermal elements was observed, classifying the burn still as second degree at day 5 in the HBO-treated animals. As the animals were sacrificed on the fifth day, any influence on the rate of epithelialisation could not be determined. Very recently, a similar study report was published, confirming the effects of HBO on the preservation of active regenerative follicles ($p=0.009$) and on the rapidity of epithelial regeneration ($p=0.048$)[29].

In an earlier animal study of a deep second degree burn of 10%TBSA however, Shoshani et al.[30] did not observe a faster epithelialisation in the HBO group. All animals were treated with daily wound dressings of silver sulfadiazine. Those animals receiving normobaric oxygen (90 minutes daily) had a more advanced epithelialisation rate at day ten than those who received HBO (2.0ATA, twice daily) or no supplemental oxygen.

This duality - a beneficial effect of HBO on the preservation of deep dermal elements when applied very early after the burn injury, and on the

other hand a possible retarding effect on the epithelialisation rate when applied after the 5th day - had already been noted by Ketchum et al. in 1967[31]. It is only the first indication that in burn injury, HBO may have to be applied according to strict protocols and schedules, rendering difficult the set-up of randomised prospective studies in the human setting. Each burn patient and each burn wound is so specific that it is virtually impossible to find matched control patients.

In a number of retrospective studies with selected matched controls, early application of HBO reduced significantly the number of surgical interventions and the duration of hospitalisation[24,25,32]. A recent larger prospective randomised study could not confirm these findings[33].

3.3 Neo-angiogenesis

In multiple studies, both animal[23,27,34] and human[35,36], the angiogenic effect of HBO has been shown. It is a late effect which does probably not influence the 'acute' parameters (volume of fluid resuscitation needed, number of surgical interventions necessary, duration of hospital stay); however, it can be a useful adjunct in the reconstructive phase, in order to optimise the chances of survival of non-vascularised tissue (skin) grafts.

3.4 Maintenance of adequate oxygenation in burned tissue

In the rat, a preservation of the adenosine triphosphate (ATP) content has been observed in burned areas[37] in those animals treated with HBO within nine hours of a burn injury, providing evidence of appropriate oxygenation of these areas.

The inhibition of sludge and rouleaux formation of red blood cells may be a therapeutic effect of major importance in the burned patient. Vaughan et al.[38] observed a reduction of burn-induced cardiac dysfunction by the administration of pentoxifylline. Kawakami et al.[39] on the other hand showed that optimal vascular filling could only partially reverse the decreased red blood cell membrane deformability in the resuscitation phase after the burn. Mathieu et al.[40] demonstrated as early as 1984 an increase in red blood cell filtrability during and after HBO. Although the exact extent of this observation has not yet been investigated in an experimental burn wound, this 'anti-sludge' effect may well play an important role in maintaining adequate oxygenation in the burned areas.

In a prospective human study using a small standardised burn wound, a reduction in plasma extravasation and an increase of transcutaneous oxygen pressures ($PTcO_2$) immediately adjacent to the burn wound, as well as an

increase in capillary flow, could be observed when applying three HBO sessions during the first 24 hours after the burn (2.4ATA, 60 minutes)[35]. A similar (but this time randomised double-blind prospective) study confirmed these results[36].

3.5 Antibacterial effect

The antibacterial effects of HBO which have been known through its use in other pathologies[41] have been confirmed in an animal burn wound model[42], even though its effect was less than that of silver sulfadiazine. This is not surprising, since molecular oxygen does not have a direct antibacterial effect at the pressures obtained in tissues under HBO[43,44]. However, HBO restores the oxidation-reduction potential in the (burned) tissues, thereby maintaining the leukocyte killing capacity of PMN and preserving the natural resistance against infection[17,45-47].

3.6 Survival / systemic complications

In animal studies, an important increase in survival has been observed after comparable burns when HBO is applied early[48]. This has been confirmed in human reports, comparing patients treated with HBO with their historic counterparts and using statistical mortality data[49-51]. However, the effects of HBO on the total volume of fluids needed, the number of surgical interventions, the duration of hospital stay and the total cost of treatment, as described by Cianci et al. in 1990[52], have not been confirmed in a prospective randomised study published in 1997[33].

The beneficial effects of moderate and early HBO on different mediators of inflammation as well as on the production of oxygen free radicals (OFR) in the context of ischemia-reperfusion injury, have however been well established in a large number of animal studies. On a cellular level, this has been illustrated by a significant reduction of leukocyte activation and infiltration at the burn site[28,29].

In a follow-up study, we have measured plasma inflammatory parameters as well as the levels of OFR-related protein degradation products (malondialdehyde) in a deep partial thickness 40%TBSA rat burn model[53]. After inflicting a standard burn wound by immersion of the depilated back in hot water, and intraperitoneal fluid resuscitation of 10ml of physiological serum), 20 rats received a single session of HBO (2.0ATA, 60 minutes). Forty-five rats were burned and intraperitoneally resuscitated, but did not receive HBO. Twenty-eight control rats received a ‘sham’ burn, by immersion in 37°C instead of 75°C water.

By serial measurements, we were able to show the presence of the two peaks of OFR-related protein degradation products described earlier by Oldham et al.[19], in the burned-only group (a first peak around 60-90 minutes; a second peak around 4-6 hours). In the sham and 'burn+HBO' groups, these peaks were absent ($p<0.05$). There was a slight increase in complement activation (measured as CH_{50}) in the 'burn' group, which was normalised by HBO. HBO induced a slight but significant increase in plasma TNFα, which remained within physiological limits. There was a clear reduction of the mortality in the HBO treated group (although not statistically significant due to the low numbers in each subgroup); and the histological analysis of the lung tissue of the rats after sacrifice at six hours showed a net reduction of leukocyte infiltration in this group (the principal cause of death being acute respiratory insufficiency in the burn group).

This study[53] showed a beneficial effect of HBO on OFR production and its deleterious effects on the body systems. This apparent contradiction (a massive increase in oxygen delivery reduces the production of OFR) has been similarly observed in a number of animal studies on ischemia-reperfusion[54-56]. Recently, the anti-inflammatory and pro-immunogenic effect of HBO has been confirmed in a Chinese report, describing a complete absence of increase of soluble IL-2 Receptor (sIL-2R) and absence of the decrease of fibronectin (Fn) in human burn patients randomised to treatment with HBO, compared to non-HBO treated patients[57]. This confirms an early human report that failed to document any increase in OFR-induced degradation products (MDA, conjugated dienes) in burn patients treated with HBO[58]

Table 2.3.1-1. Malondialdehyde (MDA) and Tumor Necrosis Factor alpha (TNFα) in a rat burn model of 40%TBSA. MDA±SD (standard deviation), *=p<0.05, NS=p>0.05 [53]

MDA (µmol/l)

Group	**30 min**		**120 min**		**240 min**		**360 min**	
	MDA±SD	***p***	***MDA±SD***	***p***	***MDA±SD***	***p***	***MDA±SD***	***p***
No Burn (n=28)	0.67±0.1		0.54±0.3		0.52±0.3		0.51±0.3	
Burn (n=45)	0.92±0.4	*	0.79±0.3	*	0.69±0.3	*	0.47±0.3	*NS*
Burn+HBO (n=20)			0.53±0.2	*NS*	0.51±0.2	*NS*	0.51±0.2	*NS*

TNFα (pg/ml)

Group	30 min		120 min		240 min		360 min	
	TNFα ±SD	***p***	***TNFα ±SD***	***p***	***TNFα ±SD***	***p***	***TNFα ±SD***	***p***
No Burn (n=28)	11.8±0.1		14.0±5.5		21.0±13.7		19.0±6.2	
Burn (n=45)	15.8±0.4	*NS*	19.7±9.7	*NS*	10.0±00	*NS*	10.0±0.0	*NS*
Burn+HBO (n=20)			19.4±17.8	*NS*	26.4±17.0	*NS*	22.2±12.0	*NS*

Coincidently, the authors describe a significantly lower incidence of sepsis in the HBO treated group. In animal studies, it had already been demonstrated that the degree of intestinal bacterial translocation after a severe burn wound is significantly reduced when HBO is administered[59,60].

HBO also prevented perivascular pulmonary PMN infiltration in this mouse burn model[59]. After inhalation injury, HBO has been shown to almost completely prevent the acute respiratory distress syndrome in the rat, independently of the presence or not of concomitant carbon monoxide intoxication[61]. This study confirms the observations of Hart et al. in 1985[62] in human patients. Anecdotal reports and our own experience show indeed a lower incidence of ventilatory support required in HBO-treated smoke inhalation victims. A reduction of local pulmonary inflammation by decreased leukocyte infiltration may be at the origin of this.

4. CONCLUSIONS

The beneficial effects of HBO in the treatment of cutaneous burn injuries seem evident. However, there is only limited consensus formally to accept thermal burn as an indication for HBO[63,64]. The current evidence for HBO in burns apparently does not stand up to scrutiny for Evidence-Based Medicine[65,66]. It is good to review the causes for this lack of evidence:

- Whereas in animal studies, standardised patients and burn wounds can be obtained relatively easily, this is much more difficult in the human setting: lack of uniformity of the burn wound, with areas of second and third degree, presence of other medical or surgical pathology, variable delay before treatment. This makes the design of proper randomised prospective studies virtually impossible.
- The experimental endpoints, as defined in the experimental studies, are not easily transposed to clinical endpoints in the human trials.

- The integration of HBO in the early treatment of burn patients puts a high demand on the availability of the hyperbaric team and on effective integration with the burn care team. Any destabilisation, be it of a thermal, hemodynamic, nutritional or infectious nature, can easily disrupt and counterbalance the advantages obtained by HBO[22]
- For burn wounds of less than 20%TBSA, the advantage of HBO associated to the 'classical' treatment will probably only be marginal. The risk of systemic complications is low, and any excision of third degree burned zones will be easily covered by skin autografts. However, in the case of burns in aesthetically or functionally important zones (face, hands, perineum) or with delicate vascularisation (cartilaginous – ears, nose) HBO might be considered.

As HBO treatment will probably continued to be used only in major specialised burn centres, it is necessary to define as clearly as possible the different categories of patients for whom HBO is necessary. On the basis of current knowledge, only in the following conditions can HBO give a maximum benefit:

- Patient selection: patients who will benefit most from HBO are those with a 20% to 80%TBSA mixed second/third degree
- Early application: the first HBO session should be given within six hours of the burn injury
- Volume resuscitation: the volume of fluids administered should be calculated on the basis of urine output from the 12th hour on, maintaining adequate diuresis, while preventing pulmonary overload and taking into account the trend in the patient's body weight
- HBO protocol: two sessions per day, at a pressure of 2.0 ATA, for the first four to five days only
- Treatment chamber: only in a multiplace chamber with bed-access, equipped for intensive care treatments, preferably with optimal bacteriologic isolation, can a patient be treated with only a minimum risk of haemodynamic destabilisation. In this type of chamber the patient can be treated while on his own intensive care bed (without the need to use a special stretcher), can be mechanically ventilated if necessary, and can receive continuous (invasive) monitoring of haemodynamic parameters. Finally, any necessary perfusion type (pressure pump, free flow device) can be initiated without difficulty, even during the treatment session.

To this day, there is still an unhappy lack of clinical studies that demonstrate unequivocally the benefits of investing in a complex and costly therapy like HBO for the burn patient. At least a few multicentre, randomised prospective studies should be initiated. They should aim at evaluating short-term parameters, such as weight loss, required resuscitation fluid volumes, surface to be grafted, number of surgical interventions

needed, length of hospital stay; and also long-term or indirect parameters: time to complete healing, time to return to normal or functional life,… These studies should only be conducted in burn centres that have a HBO centre either integrated in their infrastructure or functionally linked to it and available in the immediate (same building) neighbourhood – not in more distant HBO centres.

For burns, even more than for any other of its applications, hyperbaric oxygen should be applied optimally, or not at all.

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Chapter 2.3.2

ANOXIC ENCEPHALOPATHY

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Abstract: Although no double blind randomized study has been performed, Hyperbaric oxygen (HBO) has been proposed and used as an adjunctive treatment for anoxic encephalopathy for more than 30 years. More recently, both cell and animal studies have supported this proposal
Post-hanging anoxic encephalopathy has been extensively studied by our team; and, while the neurological outcome depends on the initial severity of the anoxic insult, we have found in a series of 305 patients that 67 % totally recovered, 25 % died and 8 % suffered sequelae. These results should encourage research in this field

Keywords: cerebral anoxia, anoxic encephalopathy, cardiac arrest, cerebral ischemia, cerebral blood flow, ischemia-reperfusion, cerebral edema, hanging, strangulation

Among the various forms of anoxic encephalopathies, two have been studied with regard to the use of hyperbaric oxygen (HBO) therapy: Post-Cardiac Arrest Encephalopathy (PCAE), mainly in peri-operative situations, and post-hanging or strangulation encephalopathy.

No double-blind randomized prospective study has yet been done in order to assess the effectiveness of HBO for either of these pathologies. Therefore HBO may only be used as an adjunct to other well-defined conventional therapies. These other protocols were described by P. Safar's Resuscitation Research Center (Pittsburgh, USA) and by the Brain Resuscitation Clinical I Study Group [1,2].

Extensive work has been carried out on the pathophysiology of anoxic encephalopathy. From this perspective, post-hanging cerebral anoxia appears to be a particularly good clinical model for studying the effects of HBO on cerebral anoxia because the mechanism of this type of anoxia is clearly identified, involving carotid blood flow interruption with no hypoxia prior to

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the cerebral injury. This is why we extensive used this particular model to assess the potentially beneficial effects of HBO for anoxic encephalopathies.

Hanging, like strangulation, causes cerebral anoxia by stopping the blood flow at the cephalic extremity. This is totally different from judicial hanging where the death is immediate and results from a direct injury of the brain stem. Apart from such cases, hanging occurs in a suicidal or accidental context, and strangulation in an accidental or criminal context. These are serious situations in which the patient dies immediately in two thirds of cases. However if the patient can be rescued in time, the clinical picture is one of cerebral anoxia. HBO was advocated over 20 years ago in these situations [3].

1. CIRCUMSTANCES OF OCCURENCE

1.1 Hanging

This is mostly related to suicides in particular contexts: in detention, where they involve mostly men aged 20 to 40 years, in psychiatric units, where they involve both men and women; or in a free environment where this method of suicide is chosen more frequently by men than women, in the country more than in towns, and predominantly by persons over the age of fifty. It can be combined with intoxication (medication, alcohol, gas). Accidental hanging is much more unusual and involves infants in the vast majority of cases - babies tangled in their cots.

1.2 Strangulation

Less frequent than hanging, strangulation can be of criminal or accidental origin. In the latter cases, they can involve children (playing games with ties around their neck), or adults in their professional environment (wearing floating garments such as scarves in the vicinity of machines with a rotating axis).

2. PATHOPHYSIOLOGY

2.1 Cervical constriction and occlusion of the cervical vessels

The cerebral damage of hanging and strangulation is not caused by the airway obstruction but by obstruction of blood flow to the cerebral extremity caused by cervical constriction. It has been shown that in adults, a 2.5kg force is enough to obstruct the jugular veins and cause an arrest in cerebral venous drainage. A 5.0kg force is required to stop blood flow in the carotid arteries, and a 15-20kg force for the vertebral arteries. A 25-30kg force is necessary to obstruct the airways. Thus a 20kg force causes a total obstruction in blood flow leading to cerebral anoxia. This explains how quickly irreversible injuries can occur but also how some unexpected successes can be seen where, depending on how constriction has been applied, vascular obstruction is incomplete. Hanging and strangulation induce specific associated injuries. Cervical trauma causes cutaneous lesions[4] (traces of the tie - usually not severe but sometimes the seat of a deep wound requiring surgical care), osteo-cartilaginous lesions (cervical dislocation or fractures making careful manipulation of the patient a necessity until the control radiographs can be carried out; or crushed laryngeal cartilage which can cause obstruction of the upper airways which has to be checked by endoscopy) and finally neuronal lesions (stretching or compressing of the brachial plexus, and phrenic paralysis).

2.2 Cerebral injuries

Cerebral injuries are the same whatever the cause of the cerebral blood flow arrest[5]. Experimental research performed over the last 25 years has clearly confirmed that brain cells can survive oxygen deprivation. Short term recovery of the brain's complex functionalities can be obtained after a period of ischemia as long as 60 minutes. Long term recovery of brain functions is possible after a 14 to 17 minute period of ischemia induced by cervical tourniquet in monkeys[6]. There are large differences between neurones regarding their sensitivity to anoxia and the time span from the onset of the attack: the occurrence of irreversible injury caused by the ischemia/hypoxia varies with the severity of the attack and the degree of ischemia/hypoxia.

Global ischemia – whether complete or not – causes two types of brain injury. In some cases only neurones are destroyed and neuroglia and vascular cells are unaffected. In these cases, neuronal necrosis usually only affects vulnerable areas (putamen, central nucleus, thalamus and other sub-cortical

nuclei). In more severe cases, extensive laminar necrosis and infarction affect glial and vascular cells.

When the cerebral injury occurs, it can cause alterations to cell functions and blood flow. Both mechanisms involved are related to a decrease in the production of adenosine triphosphate (ATP).

When O_2 delivery is completely stopped, the EEG becomes isoelectric after approximately 20 seconds, tissue concentration of phosphocreatine is nearly nil after one minute, and tissue concentration of ATP is nil after about six minutes[7]. In respect of neurones are concerned[8], the collapse in glucose and ATP reserves causes an alteration of ATP-dependent Na^+/K^+ pumps, causing a massive output of K^+, an input of Na^+ and membrane depolarization. The increase in extracellular concentration in K^+ stimulates the input of Na^+, Cl^- and water into the glial cells, causing astrocyte edema. When extracellular concentration in K^+ increases to around 12-15µmol/ml, there are enough alterations in membrane potential to open up the calcium channels, causing an uncontrolled inflow of Ca^{++}. Cytoplasmic concentration of Ca^{++} increases, causing a number of functional alterations: phospholipase A_1, A_2 and C are activated, membrane phospholipids are hydrolyzed, cellular and mitochondrial membranes are destroyed and free fatty acids (especially arachidonic acid) are produced.

2.2.1 The three successive phases of cerebral anoxia

- Compensation phase:

Unlike other tissue, the nervous system has only limited metabolic reserves. When oxygen delivery to the brain is reduced, compensating mechanisms are brought into play to maintain oxygenation. The speed with which the lack of oxygen delivery overcomes the effectiveness of these compensating mechanisms depends on the origin of the anoxia. Where circulatory arrest is caused by hanging, there is both an arrest in cerebral blood flow and a drop in the oxygen content of the blood – no compensating mechanisms can be triggered. Thus, anoxia appears very rapidly.

- Anoxic phase :

Experimental research on primates has identified two critical levels: where neurotransmission shuts down, and where neural membrane activity is stopped[11]. These concepts have been confirmed in man by studies using positron emission tomography.

Ischemic threshold for synaptic transmission: loss of consciousness takes place within ten seconds, the electroencephalogram becomes flat and evoked potentials cease. At this stage, the absence of cerebral activity is only the sign of a shutdown in neurotransmission. The blood flow which corresponds to this shutdown is approximately 20-25ml per100g of brain tissue per minute (threshold of neurotransmission shutdown). This is only a mean value, and does not apply to all parts of the brain in the same way. It is to be

compared with the normal values of cerebral blood output, i.e. 55-75ml per 100g of brain tissue per minute. At this stage, electric cerebral activity shuts down in order to save energy. Neurotransmission uses up 50% of cerebral energy expenditure - so shutdown enables neurones to keep all available resources for survival. Cellular depletion in energy is not yet severe: concentration in phosphocreatine is low, that of lactate being high; adenosine diphosphate and monophosphate are increased whereas adenosine triphosphate remains at a normal level. Restoring a normal oxygen supply at this stage ensures a complete recovery.

Ischemic threshold for membrane failure: if anoxia persists, cellular injuries occur. This second threshold of cerebral blood flow under which the membrane activity stops, is approximately 8-11ml per 100g per minute, ie 15-20% of the normal output. The cells are no longer able to retain potassium ions, stored energy levels decline, and lactate concentration increases and becomes toxic. Calcium is no longer held in storage within the cells (in the cytoplasmic reticulum) and the concentration within the cytosol increases, causing an uncoupling of oxidative phosphorylation and an activation of membrane phospholipases. These phospholipases have an effect on the membrane phospholipids, producing free fatty acids, which in conditions of anoxia can produce free radicals, such as thromboxane and leukotrienes. Cells cannot survive these effects for very long. The duration of anoxia is crucial both for the reversibility of injuries and for their initial extent.

- Post-anoxic phase:

Cellular stress does not necessarily cease when a satisfactory level of oxygen delivery is restored. Two events can hinder neurological recovery: reperfusion-induced microcirculatory failure and stress caused by re-oxygenation during reperfusion. After complete cerebral ischemia of more than five minutes, the brain undergoes a transitory phase of global hyperemia lasting 15-30 minutes, and then suffers microcirculatory perfusion failure causing the death of the brain cells which survived the initial ischemia, leading to irreversible neurological damage. Three phenomena explain the secondary intensification of anoxic injuries[12].

Free-radical activity: the decline in energy reserves causes a depletion of antioxidant systems in the cells, and particularly in reduced glutathione. During the reperfusion phase the respiratory chains are unable to handle the high oxygen inflow because of injuries to the mitochondria. This leads to an increase in the production of oxygenated free radicals. These are not detoxified by antioxidant systems and attack the membrane lipids - particularly the unsaturated fatty acids in the vicinity of double bonds and cholesterol, producing residues which have their own peroxidizing effects, causing a chain reaction. This is the re-oxygenation damage.

Micro-circulatory disorders: when blood flow is restored, circulation distribution is heterogeneous due to arteriolar spasm, the occurrence of

microthrombosis and alterations in erythrocyte deformability. On a cellular level, endothelial edema and swelling of the peri-capillary astrocytes caused by the decreased activity of the membrane pumps lead to an alteration of the local blood flow ('no reflow' phenomenon).

Cerebral edema: this occurs especially rapidly and severely in hanging and strangulation cases. It plays a major part in the clinical picture by causing acute intracranial hypertension. Its importance accounts for the reversibility of injuries, particularly under the influence of HBO. It is caused by three components:

- obstruction of cerebral venous drainage: this induces extensive plasma exudation which causes an early vasogenic effect. This effect is all the more extensive when arterial blood circulation continues during hanging;
- cerebral anoxia: the decrease in activity of membrane ATP-ase causes potassium outflow and sodium inflow. Cellular (cytotoxic) edema then occurs;
- reperfusion phase: as soon as blood flow is restored, a new vasogenic element is added by the alteration of the blood brain barrier membrane and fluid transudation from the intravascular compartment into the interstitial spaces in the brain.

2.2.2 Alterations in blood flow

When ischemia occurs, cerebral blood flow (CBF) is no longer autoregulated and becomes passively dependent on arterial blood pressure. On restoring circulation to the brain after cerebral anoxia, CBF increases over a 5-10 minute period, and then a secondary prolonged phase of global hypoperfusion begins. The duration of hypoperfusion seems to be related to the duration of ischemia. However the decrease in CBF is not necessarily homogeneous: normally perfused areas can be combined with unperfused areas or even with hyperperfused areas[13]. A number of reasons have been put forward to account for hypoperfusion: the main ones are coagulation or rheological disorders, endothelial oedema, accumulated vasoactive peptides or prostaglandins, vascular spasm caused by extensive variations in K^+ outflow and Ca^{++} inflow. When O_2 supply is insufficient as is the case in a period of post-ischemic hypoperfusion, endothelial cells can be damaged. This can upset the normal balance between prostacyclin and thromboxane A_2 (TXA_2), leading to an excess in TXA_2 and causing thrombocytic sludging and thrombus. An increase in intracellular Ca^{++} in vascular smooth muscle cells causes an increase in the actin-myosin relation which makes the smooth muscle cells contract, leading to vasoconstriction. Vanhoutte[14] considered that this was most liable to account for post-ischemic hypoperfusion. Also the hypoxia decreases the deformability of the red cells, thus causing an increase in blood viscosity and a decrease in blood flow. All this also contributes to decreasing O_2 delivery to the tissues.

2.2.3 Consequences for therapy

The above phenomena, related to the reperfusion phase, add their own effects to those produced by the anoxia itself. Of course everything must be done to shorten the anoxic phase as much as possible; however, its occurrence and duration are not a matter of choice for physicians, who can only try to suppress or at least reduce the deleterious effects of the reperfusion phase.

3. CLINICAL STUDY

Successful intensive care is only possible for hangings and strangulations of a short duration or when some brain perfusion has persisted.

3.1 On site

As soon as the patient is discovered it is essential to remove the constriction on the neck and place the patient in supine position. A brief clinical examination must be carried out to check the persistence of circulation and breathing. In case of cardiac or respiratory arrest, immediate resuscitation must be begun. In our experience, this often occurs. After rescue, 57 of our 135 patients (42.0%) were in cardiac arrest and 123 patients (92.5%) required ventilatory support[15]. Assessing the Glasgow coma score at this stage is useful for subsequent evaluation of patient's condition. As soon as circulation is restored, and once the neck is immobilized, the patient can be transferred by emergency aid teams. Unless a convulsive seizure occurs, requiring immediate treatment (benzodiazepines), no sedatives or hypnotics should be administered; otherwise the initial examination will not provide an accurate picture of the severity of the patient's condition and therapy will not be adjusted accordingly.

3.2 On hospital admission

On hospital admission, a neurological evaluation is immediately performed. The classification we use for the various degrees of altered consciousness observed on admission is as follows: stage I is a light coma, stage II a moderate coma with adequate reactivity and often some agitation. In stage III, the coma is deeper, and reactivity to nociceptive stimuli inadequate; extrapyramidal hypertonia and pyramidal signs often occur. Stage IV is a deep coma with hypertonia, generalized seizures and signs of brain-stem injury. Stage V is a stage of irreversible coma and cerebral death.

The occurrence of convulsions is an important element requiring immediate anticonvulsive therapy.

In our experience[15,16] (Table 2.3.2-1), on admission to the HBO and Intensive Care Unit, 13.2% out of 170 patients (1971-1981) and 7.0% out of 135 patients (1990-1994) were mildly confused. Respectively 11.5% and 9.0% were in stage I coma; 28.5% and 12.0% in stage II coma ; 19.0% and 25.0% in stage III coma; 20.0% and 32.0% in stage IV coma; 7.0% and 15.0% in stage V coma.

Table 2.3.2-1. Level of consciousness on admission[16]

	Mild confusion	Coma stage				
	0	I	II	III	IV	V
170 cases (1971-1981)	22 (13.2%)	20 (11.5%)	49 (28.5%)	32 (19%)	35 (20.8%)	12 (7%)
135 cases (1990-1994)	10 (7%)	12 (9%)	16 (12%)	34 (25%)	43 (32%)	20 (15%)

Admission evaluation is completed by:

- an examination of the neck to check for associated lesions;
- a general examination, not only to check major functions but to look for any associated trauma or intoxication (gastric suction to be carried out on the slightest doubt);
- further investigations in addition to routine tests such as thorax radiography, electrocardiogram, blood tests including arterial blood gas estimations, and an electroencephalogram which in most cases shows depressed electrogenesis. If an electrical epileptic seizure is present, rapid anticonvulsant treatment must be provided and its efficacy in suppressing this epileptic activity checked and monitored.

3.3 Evolution

As in all cases of coma, clinical surveillance must be carried out at least once an hour during the first three days, and then at longer intervals in the following days. Electroencephalograms must be performed every 24 hours during the first five days, and then once a week. A CT scan of the brain is hardly useful until the third week, by which time it will enable an assessment of neurological prognosis after prolonged disorders of consciousness.

Different evolutions are possible: recovery without sequelae, deterioration and cerebral death, or persisting disorder of consciousness, the chances of recovery from which decrease with time.

A number of points are worth noting: the variability of neurological signs during the first few hours - although the level of consciousness remains the same; the impossibility of making a firm prognosis in the first two or three days; the possible occurrence of complications, including pulmonary complications such as edema or other pathology; total amnesia regarding the

suicide or accident in a vast majority of cases, causing psychological difficulties on awakening; and the necessity of a psychiatric consultation before discharge.

3.4 Clinical parameters useful for prognosis

3.4.1 Cardiac arrest on unhanging

Circulatory arrest is the worst prognostic sign, 79% of the 57 patients (out of our total of 135) who suffered circulatory arrest did not survive[15].

3.4.2 Stage of coma

The deeper the coma, the worse it is for recovery. All patients in coma stages I and II on admission out of 170 patients (and 96% of patients in the second series) recovered. 65.5% of the 135 in coma stages III and IV on admission showed no improvement with treatment, including HBO.

3.4.3 On-site Glasgow coma score

When the Glasgow coma score on rescue was above 4, 93% of 135 of the patients improved; when the score was 3 or under, 92% of these patients deteriorated. In another study, comparing Glasgow coma scores on-site and on admission in intensive care (ΔGCS) proved useful for prognosis: where there was an increase, the patients usually improved. Furthermore, a significant difference was observed between the ΔGCS of the patients who recovered and that of the patients who died [15].

3.4.4 Prognostic relevance of the combination of certain signs

Cardiac and circulatory arrest on rescue combined with absent pupillary reaction to light, or stage III or IV coma on admission combined with absent pupillary reaction to light and blood glucose ≥2.3g/l both predict 100% mortality[15].

Table 2.3.2-2. Usefulness for prognosis of clinical parameters[15]

No significant value	
Age	NS
Gender	NS
Associated intoxication	NS
Abnormal movements	NS
Of significant value	
Corneal reflex absent	<0.05
Cardiac arrest on rescue	<0.0001 (Se:0.94; Sp:0.97)
Coma stage >III or GCS ≤3	<0.0001
Absent pupillary reaction to light	<0.0001

4. HYPERBARIC OXYGEN THERAPY

After the emergency care provided at the rescue site and rapid transport to the hospital by medical aid teams, therapy combines general intensive care and therapy deemed to limit the consequences of the cerebral anoxia. HBO is one of these therapies.

4.1 Pathophysiological effects of HBO in post-anoxic encephalopathy

The time that elapses between the initial injury to the brain and the occurrence of irreversible cell lesions due to ischemia and hypoxia varies considerably with the severity of the attack and the extent of hypoxia. Cerebral tissue cannot survive without an adequate supply of oxygen. Beyond its positive effects on reducing cerebral oedema, HBO has a positive effect on limiting the consequences of cerebral anoxia by increasing the quantity of oxygen available to the cells of the injured brain, thus maintaining the aerobic metabolism of intracellular glucose. The potential beneficial effects of HBO can be classified as follows:

-*Effects on oxygen transport and delivery to the tissues.* HBO increases the quantity of oxygen dissolved in the plasma in relation to the absolute pressure. The increased pressure gradient means that dissolved oxygen can reach the hypoxic and ischemic areas in the brain. At 2ATA, the arterial oxygen tension increases to as much as 1000-1250mmHg.

-*Effects on cerebral blood flow.* It has long been proved that at 2ATA, hyperoxia induces a simultaneous decrease in both cerebral blood flow (of approximately 22%[18]) and intracranial pressure[19] (the usual increase of this pressure in the stages of decreasing cerebral ischemia leads to reperfusion circulatory failure). The hyperoxic vasoconstrictor effect is preferable to the vasoconstrictor effect obtainable by the use of cathecholamines because it does not, unlike cathecholamines, cause a drop in peripheral oxygen

delivery, on the contrary maintaining the extra oxygen in the tissue. The decrease in cerebral blood flow causes a decrease in the flow of plasma exudates, and therefore reduces the development of interstitial edema. In post-hanging anoxic encephalopathy, this effect against edema is particularly clear in the rate of improvement of the conscious level during HBO sessions. Determining which partial pressures of oxygen are the most effective has been very controversial. Early experimentation had shown that the vasoconstrictor response was inverted when the partial pressure of oxygen rose above 2.2-2.5ATA[20]. These results were criticized because in these studies, PaCO2 was not monitored; and the inversion of the vasoconstrictor response was more closely related to the increase of $PaCO_2$ than to a direct effect of hyperoxia[19]. When cerebral autoregulation is no longer functional, there is no longer any decrease in cerebral blood flow as a consequence of HBO. From a clinical point of view, this means that the $PaCO_2$ must be kept constant throughout HBO sessions by providing controlled ventilation, and also that it would seem preferable not to use pressures higher that 2.5ATA in these situations.

- *Effects on microcirculation*: microcirculation disorders, including microthrombosis, the sludge effect and increased red cell rigidity as an effect of hypoxia, play an important part in maintaining hypoxia in some areas of the brain at the reperfusion stage ('no-reflow' phenomenon). By its effect on oxygen transport, HBO restores to the whole body partial pressures of oxygen that are compatible with cellular life and repair. This global compensating effect is combined with the beneficial effect on the deformability of the red cells, which can thus make a better contribution to tissue gas exchange.

- *Metabolic effects*: restoring a normal flow of oxygen to the brain restores aerobic metabolism. The beneficial effect of HBO can be assessed by comparing the rate of correction of lactic acidosis in the brain, which is greater in HBO than in ambient air. In the same way, the activity of pentose shunts in the glial cells has been shown to increase in HBO, promoting a faster restoration of cellular energy stores and thus to an increased rate of functional recovery. HBO has been shown to improve glucose metabolism in the injured brain, this improvement being maintained for 24 hours after the last HBO session. Ducassé et al.[21] have reported that one session of HBO (2ATA pure oxygen for 60 minutes) increased the level of oxygen extraction in the brains of dogs without any brain disorder. As a consequence of this, the risk of an increased production of free radicals and of peroxidation of lipids in cell membranes as a consequence of HBO could be a major concern. However, Yasu showed an increase in the production of hydrogen peroxide (indicating an increased production of superoxide radical) in the brains of normal rats as a consequence of HBO, but not for the brains of rats suffering ischemia[22]. Inasmuch as it improves the impaired function of the

membrane ion pumps in ischemic cells, HBO can prevent the production of reactive substances and contribute to the recovery of damaged cells

- *HBO procedures:* HBO is provided in repeated sessions of 90 minutes at a pressure of 2.0-2.5ATA, preferably in a multiplace hyperbaric chamber supplied with every form of monitoring and therapy routinely used in intensive care. Three sessions are provided during the first 24 hours, and two during the next 24 hours. In our experience, continuing HBO beyond these five sessions does not alter the course of the pathology.

4.2 Results

HBO for treating cerebral anoxia is still a controversial subject, mostly because of the heterogeneity of the clinical situations that can cause cerebral anoxia and also because there are no randomized prospective clinical studies providing an objective assessment of the efficacy of HBO - which is never actually used as sole therapy. In a preliminary study on near-hangings, we showed that HBO promoted a faster and better recovery of the brain than normobaric oxygen therapy. A recent study by Bauer et al. confirmed the beneficial effects of HBO as compared with conventional treatment with respect to mortality and sequelae in patients suffering post-hanging anoxic encephalopathy[23]. Unfortunately, this study is neither randomized nor prospective; and both groups (patients treated with HBO and the control group) were small. In a first series of 170 patients observed between 1971 and 1980, we confirmed the efficacy of HBO for this indication. 132 out of the 170 patients recovered without sequelae, 30 (17.5%) died and 2 (5%) suffered neurological sequelae. These results are in agreement with the results of other studies. Ten years later, in a second series of 135 patients observed between 1990 and 1994[15] and using the same protocol for HBO therapy, the results appeared less favourable (Table 2.3.2-3).

Table 2.3.2-3. Near hangings. Evolution with HBO[16]

	Number of cases	Complete recovery	Death	Sequelae
Lille, 1st series (1971 -1980)	170	132 (77.5%)	30 (17.5%)	8 (5.0%)
Lille, 2nd series (1990 -1994)	135	77 (57.0%)	45 (33.0%)	13 (10.0%)

77 out of the 135 patients (57%) recovered without sequelae; 45 (33%) died; 13 (10%) recovered with neurological sequellae. A more detailed analysis showed that the cerebral condition of the patients on admission was more severe in the second series than in the first. However, both series confirmed the fact that the initial neurological condition has a great influence on the response to HBO. Recovery without sequelae was the norm for patients admitted in coma stage I or II or whose Glasgow coma score was

≥6. Their condition mostly returned to normal during or after the first session of HBO, within 24 hours of admission. Recovery was less frequent for patients in coma stage III and IV, but sometimes occurred without sequelae. This is why severe cases such as these must be given a series of five sessions of HBO (three sessions during the first 24 hours, and two during the next 24 hours). A Glasgow coma score ≤4 after HBO is a very bad sign for cerebral prognosis.

The occurrence and duration of a cardiac and circulatory arrest on rescue, and the time required to obtain a positive response to resuscitation procedures, are determining factors for the initial severity of the neurological condition and HBO response. In our second series, the number of patients who were resuscitated after cardiac and circulatory arrest on site was particularly high (57 out of 135 patients). This fact must be attributed to the effectiveness of the preadmission intensive care methods that were developed over 20 years ago in France. However 79% of those 57 patients admitted in coma stage IV died without any improvement under HBO. Similar results have been reported elsewhere[5]. In this type of situation, two prognostic factors have been identified by statistical analysis using logistic regression: the initial Glasgow coma score, and pupillary reaction to light after HBO. When the initial Glasgow coma score is ≤4, and the pupillary reaction to light is not restored after HBO, a 100% mortality rate can be predicted. Furthermore, the association of circulatory arrest and persistent absence of pupillary reaction to light after initial resuscitation is also predictive of a 100% mortality rate.

5. CONCLUSION

The potential beneficial effects of HBO on cerebral anoxia have been described and they apply particularly well to cases of post-hanging anoxic encephalopathy. Clinical studies have shown that HBO provided immediately after rescue is associated with rapid and complete recovery except when there was cardiac/circulatory arrest on rescue. This is why post-hanging anoxic encephalopathy was declared a Type 3 (optional) indication for HBO by the Jury of the 7th European Consensus Conference on Hyperbaric Medicine (Lille, December 2004) until double-blind randomized prospective studies have provided an objectively indisputable assessment of the beneficial effects of high pressure oxygen over normobaric oxygen. Protocols for providing HBO (pressures, duration, number of sessions) also need to be more clearly defined.

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Chapter 2.3.3

PLEUROPULMONARY ANAEROBIC INFECTIONS

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Abstract: Anaerobic bacteria are relatively common pulmonary pathogens and involved particularly often in aspiration pneumonia and its suppurative complications: lung abscess and empyema. Although most patients respond well to antibiotic treatment associated to adequate drainage, 5-10% may experience persistent infection. Based on our experience in 13 patients, we propose to consider hyperbaric oxygen (HBO) as an adjunct treatment in highly selected cases

Keywords: Anaerobic bacteria, lung abscess, empyema, necrotizing pneumonia

Anaerobic bacteria are now generally considered as relatively common pulmonary pathogens. They are involved particularly often in aspiration pneumonia and its suppurative complications: lung abscess and empyema. Although most patients respond well to antibiotic treatment associated to adequate drainage, 5-10% may experience persistent features of infection: chronic low-grade fever, weight loss and fetid purulent sputum. This leads to a reassessment of the initial treatment (antibiotics, closed chest drainage) and in some cases, to a consideration of surgery. In few patients, despite multiple antibiotic regimens and drainage procedures, infection persists and leads to respiratory failure, cachexia and death[1,2].

In these selected cases, we propose to consider hyperbaric oxygen (HBO) based on our experience in 13 patients.

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1. ANAEROBIC PLEUROPULMONARY INFECTIONS

1.1 Incidence

The true incidence of anaerobic pulmonary infections is difficult to assess since specialized techniques are required for the collection of uncontaminated specimens from the upper airways, where anaerobes represent the dominant component of the flora. Complicating this situation are the need to obtain these specimens before antibiotic treatment and the necessity for laboratory expertise in the cultivation of anaerobic bacteria.

Most published reports deal with the role of anaerobic bacteria in aspiration pneumonia or lung abscess, where recovery rates range from 58% to 100%[3-8]. The usual specimen sources in these studies are transtracheal and transthoracic aspiration. The most definitive study is that by Beerens and Tahon-Castel[3], who used transthoracic needle aspiration into lung abscesses and recovered anaerobic bacteria, usually in pure culture, in 22 (85%) of 26 cases. More recently, Gudiol et al.[8] used a similar technique and found anaerobic bacteria in 37 (90%) of 41 cases.

Empyema is obviously more easily studied than pulmonary abscess because of the relative ease of obtaining pleural fluid for anaerobic culture. Recent studies have shown a sharp decline in the frequency of empyema in general, and a marked change in the bacteriology of the remaining cases. *S. pneumoniae* now accounts for only 5%-10% of cases, while anaerobes account for 25%-40%[3,9-11].

There are relatively few studies of the incidence of anaerobic bacteria among unselected cases of community-acquired pneumonia. The best available information comes from the study by Ries et al.[12], who attempted transtracheal aspiration for anaerobic culture in all patients admitted to a Philadelphia hospital with a diagnosis of pneumonia. Anaerobic bacteria were recovered from 29 (33%) of 89 such patients. In an analogous study by Pollock et al.[13], fibreoptic bronchoscopy with a protected catheter was combined with quantitative cultures ; this approach led to the recovery of anaerobes from 16 (22%) of 74 patients. These two reports suggest that anaerobic bacteria are relatively common among patients with community-acquired pneumonia, which is now commonly labeled «atypical pneumonia» and often ascribed to organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella*[1].

1.2 Pathophysiology

The usual source of bacteria in anaerobic lung infections is the oral cavity - presumably the gingival crevice, where anaerobic bacteria are found in concentrations up to $10^{12}/g$[25,26].

A predisposition to aspiration as a result of impaired consciousness or dysphagia (e.g., in alcoholism, general anaesthesia, seizure disorder, drug abuse, esophageal lesions, and neurological disorders) is commonly associated with these infections. The basal segments of the lower lobes of the lung are favoured by gravitational flow in the upright position. Aspiration in the recumbent position favours the posterior segments of the upper lobes or the superior segments of the lower lobes[6,14].

Additional conditions which appear to predispose to anaerobic lung infections include infarction, pulmonary obstruction due to a neoplasm or foreign body, and bronchiectasis. Each of these conditions is associated with stasis, or necrosis of tissue, which presumably accounts for the predisposition.

A striking feature of anaerobic lung infections is the tendency toward necrosis of tissue, resulting in abscess formation and/or a bronchopleural fistula with empyema. If numerous micro-organisms may cause pneumonia, anaerobic bacteria are clearly the most frequent germs associated with pulmonary necrosis and abscess formation.

Long ago, Smith showed that, following aspiration, the natural history of the infection consisted of pneumonia followed by abscess formation about seven days after bacterial challenge. He also demonstrated the importance of bacterial synergy in the pathological process[15,16]. Other virulence factors of anaerobic bacteria that appear to promote abscess formation are the polysaccharide capsule found in some strains of *Bacteroides* species[17,18] and the short-chain volatile fatty acids that cause acid pH-dependent inhibition of phagocytic killing[19,21].

1.3 Bacteriology

The bacteriology of anaerobic pulmonary infections has come about over the years with improved lower tract sampling techniques and constant revision of taxonomic classification. Anaerobes were first discovered to be involved in aspiration syndromes in large autopsy studies in the late nineteenth and early twentieth centuries[6,22]. Anaerobic flora at that time were classified as fusospirochetes.

In recent studies[5,6,23,24], the major anaerobic isolates in patients with aspiration syndromes are: *Fusobacterium nucleatum*, *Peptostreptococcus*, *Prevotella melaninogenica* and *Pr. intermedia*. An assortment of other

anaerobic species occurs in these settings, however, with lesser frequency (Table 2.3.3-1).

Table 2.3.3-1. Anaerobic organisms associated with aspiration syndromes (adapted from Finegold et al[24])

Most Common Isolates	
Fusobacterium nucleatum	
Prevotella melaninogenica	
Prevotella intermedia	
Bacteroides ureolyticus	
Bacteroides fragilis	
Peptostreptococcus	
Less Common Organisms	
Eubacterium	*Clostridium*
Lactobacillus	*Proprionibacterium*
Actinomyces	

Aerobic bacteria associated with aspiration pneumonia tend to be those usually found in the setting in which the aspiration occurs. Hence, the primary aerobic isolates in the community setting are aerobic or microaerophilic streptococci. In half the cases, gram-negative flora are the predominant organisms in nosocomial-acquired illness, with Klebsiella and *Escherichia coli* the most common gram-negative isolates (23% and 14% respectively), whereas Pseudomonas can be expected in fewer than 10%. Pneumococcus and *Staphylococcus aureus* can be expected to be cultured as often as 31% and 26% of the cases, respectively[25].

1.4 Clinical presentation and management

The clinical presentation in patients with anaerobic pulmonary infection can be acute, subacute or chronic.

Patients with aspiration pneumonia generally present with an acute illness. Clinical features are often indistinguishable from those of community-acquired pneumonia, although initial presentation is often delayed compared with pneumococcal pneumonia. Response to adequate antibiotic treatment is usually prompt, with rapid clinical improvement and early defervescence. An average of 50% of patients have strict anaerobic infection where as up to 80% have mixed anaerobic infection. The mortality rate of simple aspiration pneumonia is less than 5%[2].

Patients with necrotizing pneumonia tend to present acutely ill with high fever, leucocytosis, putrid sputum and weight loss. Median length of time to presentation is longer than in patients with aspiration pneumonia (15 vs 3-4 days), in spite of the severity of the illness. Chest X-ray shows extended pulmonary infiltration with multiple small cavitations (< 1cm). Empyema is frequently associated. Antimicrobial therapy in these patients is identical to protocols used for aspiration pneumonia. Chest tube drainage is required if

empyema is associated. Supportive measures as supplemental oxygen therapy or mechanical ventilation may be required. Complications are frequent and total resolution in often not achieved for at least 4 to 5 weeks. Mortality rate is close to 20%[26].

Patients with lung abscess generally present with a sub-acute illness. Fever, weight loss, cough and fetid sputum are the most frequent clinical features. Chest X-ray shows a cavitating lesion in a gravity-dependent section of the lung often surrounded by infiltrate. Presence of an air-fluid level indicates that a bronchopulmonary fistula exists and that the abscess must be drained. Less frequently, empyema may be associated. Treatment is based on prolonged antibiotic therapy adapted to mixed anaerobic-aerobic bacterial flora. Adjunctive measures include abscess drainage - postural or bronchoscopic - and closed chest tube drainage if empyema is present. Response to treatment is usually good, but in 10-15% of patients, this treatment fails and surgical intervention (intra-cavity tube drainage, decortication, lung and/or rib resection) has to be considered. Indications for surgery are massive hemoptysis, failure to respond to chest tube thoracostomy in the presence of empyema, abscess drainage that fails with postural or bronchoscopic drainage and a diagnosis of carcinoma. The overall prognosis for survival is good (mortality between 5% and 10%). Poor prognosis is associated with large abscess formation (> 6cm), severe underlying disease, extreme age, empyema, sepsis, and prolonged time prior to presentation and treatment. Mortality associated with these risk factors may be as high as 75%[2].

2. RATIONALE FOR HYPERBARIC OXYGEN THERAPY

Although anaerobic pleuropulmonary infections carry a relatively low mortality rate under adequate treatment (5 to 10 p. cent), treatment failure may occur. Surgical intervention is reserved to selected indications. In spite of these therapeutic measures, some patients experiment a long disease course with persisting septic state, parenchymal destruction and secondary infection localisation.

In 1984, based on the beneficial action of HBO in anaerobic soft tissue infections, we were asked by our colleagues from the Pulmonary Medicine Department to consider HBO in a patient with an three month history of lung abscess not responding to adequate and prolonged courses of antibiotic therapy and two surgical interventions. As this case turned out to be a success, we began to accept, for adjunctive HBO, patients with anaerobic

pleuropulmonary infection (lung abscess or necrotizing pneumonia) if a three week course of adequate antibiotic treatment and drainage had failed[27].

Considering the well known effect of HBO in anaerobic soft tissue infections and our experience in 13 patients, we propose that some highly selected cases of anaerobic pleuropulmonary infection may be accepted as an indication for adjunctive HBO.

2.1 Effects of HBO in anaerobic infections

Beneficial effects of HBO in anaerobic infections have been extensively reviewed and are well known in the hyperbaric medical community[28]. Therefore, they do not need to be described here in detail.

In brief : HBO

- inhibits toxin production by anaerobes.
- is bacteriostatic and bactericidal for strict and facultative anaerobes.
- improves the host defences against bacteria in increasing the oxygen-dependent microbicidal capability of polymorphonuclear leukocytes by restoring normal pO_2 in ischemic infected tissues.
- potentiates the activity of selected antimicrobial agents.

Beneficial effects have been found in several models of experimental bacterial infection: *Clostridium perfringens* gas gangrene, *S. pyogenes* myositis, Weinstein model of peritonitis, *S. aureus* osteomyelitis, among others.

2.2 Literature review

When first asked to consider adjunctive HBO for anaerobic pleuropulmonary infection, we undertook a literature review. We did not find any study published in the French, English or German medical literature. On the other hand, we found two papers in the Russian language medical literature claiming HBO efficacy in suppurative and destructive lung and pleural diseases[29,30]. A recent literature search found four more Russian references[31-34]. However, differences in reporting data between Western and Eastern countries leads to difficulties in understanding and interpreting these papers and precludes any definite conclusion.

2.3 Our experience

Thirteen patients with anaerobic pleuropulmonary infection have been treated at our Critical Care Unit with adjunctive HBO since 1984. They were eleven males and two females, mean age 45±12 years [34-63 years]. Predisposing condition for anaerobic pleuropulmonary infections existed in

all except one patient: aspiration in five cases, bronchial obstruction in five, bronchiectasis in one, chest trauma in one.

Clinical presentation when referred to our HBO center consisted of fever over 38.5°C in seven patients, leucocytosis over 12 000 / mm^3 in ten, elevated C reactive protein in seven, large quantity of fetid sputum (over 30 mm^3) in eight. Chest X-Ray showed lung abscess in seven patients, necrotizing pneumonia with multiple small cavities in six. Empyema was associated in nine patients (lung abscess: three, necrotizing pneumonia: five).

Bacteriological study was negative in three patients, probably because of the antibiotic therapy received before the sampling. In the ten other patients, 27 germs were isolated, 15 anaerobes and 12 aerobes. Within the anaerobes, Prevotella, Fusobacterium and Peptostreptococcus predominated as in the aerobes, *Pseudomonas aeruginosa* was the most frequent micro-organism.

The indication to consider adjunctive HBO was the persistence of the lung infection process despite adequate antibiotic therapy and drainage. The mean duration of the standard treatment before HBO was 31±23 days.

HBO was simply added to the current treatment. HBO was given in repeated sessions at 2.5ata, 90 minutes pure oxygen, twice a day. The mean number of HBO sessions was 23±11. The clinical response to HBO was impressive. Apyrexia and decreased sputum volume occurs within two to three days in all patients. Radiographic improvement took about ten days. Every patient except one, survived and was discharged from the hospital after the end of the HBO treatment. One patient died from a disseminated Candidosis, three weeks after the end of the HBO treatment, her lung abscess having resolved.

2.4 Risk of HBO in patients with air-filled lung or pleural cavity

Pneumothorax, air-filled parenchymal bulla and emphysema are well known contra-indications to HBO. Patients with anaerobic pleuropulmonary infections have often air-filled lung or pleural cavity; and the risk of barotrauma is real if these cavities are not properly drained and placed in contact with ambient pressure. If an air-fluid level indicates a bronchopulmonary fistula which drains the cavity, any doubt about drainage efficacy must lead to direct drainage of the cavity by a tube.

HBO sessions must be performed in a multiplace chamber, equipped for performing critical care and under the close supervision of a physician trained in Pulmonary Medicine and/or Critical Care and able immediately to perform an additional drainage procedure.

In our thirteen patients, we did not experience any complication during HBO sessions.

3. CONCLUSION

The well-known beneficial effect of hyperbaric oxygen therapy on anaerobic infections and our experience in thirteen highly selected patients lead us to recommend adjunctive HBO to be considered in patients with anaerobic pleuropulmonary infections when a sufficiently long course of adequate antibiotic therapy, and drainage, has failed. However, in those patients at high risk of barotrauma, HBO may only be performed in a Hyperbaric Medicine facility located in the immediate proximity of a Critical Care Department and using a multiplace hyperbaric chamber under the permanent supervision of a trained Pulmonary Medicine and/or Critical Care physician.

Table 2.3.3-2. Clinical and bacteriological features

N°	Age	Sex	Predisposing conditions	Diagnosis	Bacterial isolate
1	36	M	Aspiration due to neurologic disorder	Lung abscess	*Pr. melaninogenica* *F. nucleatum* *Peptostreptococcus* *Pseudomonas aeruginosa*
2	62	M	Obstruction due to bronchogenic carcinoma	Lung abscess	*B. oralis* *P. aeruginosa*
3	45	M	Bronchiectasis	Lung abscess	*P. aeruginosa*
4	39	F	Seizure Splenectomy Hodgkin disease	Lung abscess	*Pr. intermedia* *Acinetobacter baumanii*
5	43	M	Aspiration due to neurologic disorder	Lung abscess	*Pr. loeschii* *Peptostreptococcus as acharolyticus* *Clostridium* sp. *P. aeruginosa* *Enterococcus faecalis* *Streptococcus* sp.
6	53	M	Obstruction due to bronchogenic carcinoma	Lung abscess	-
7	50	M	-	Lung abscess	*Bacteroïdes* sp. *Proteus mirabilis*

N°	Age	Sex	Predisposing conditions	Diagnosis	Bacterial isolate
8	51	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	*Prevotella* sp. *Fusobacterium nucleatum* *Streptococcus anginosus*
9	48	M	Coma from toxic origin	Necrotizing Pneumonia	*Streptococcus milleni*
10	34	F	Chest trauma	Necrotizing Pneumonia	*Fusobacterium nucleatum* *Pr. melaninogenica* *Streptococcus anginosus*
11	36	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	*Peptostreptococcus* *Peptococcus* *Staphylococcus aureus*
12	63	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	-
13	18	M	Tracheo-esophageal fistula	Necrotizing Pneumonia	-

Table 2.3.3-3. Treatment and outcome

N°	Antibiotic treatment	Duration before HBO start (days)	Number of HBO sessions	Hospital stay after HBO stop (days)	Outcome
1	Piperacillin Metronidazole	90	30	15	Cured
2	Ampicillin / Sulbactam Metronidazole Ofloxacin	45	36	8	Cured
3	Piperacillin / Tazobactam Amikacin	16	13	4	Cured
4	Ticarcillin / Sulbactam Amikacin Metronidazole	45	12	21	Lung abscess cured Died from disseminated Candidosis

N°	Antibiotic treatment	Duration before HBO start (days)	Number of HBO sessions	Hospital stay after HBO stop (days)	Outcome
5	Piperacillin Metronidazole	21	10	4	Cured
6	Piperacillin Metronidazole Amikacin	21	15	4	Cured
7	Piperacillin Metronidazole Amikacin	30	40	1	Cured
8	Piperacillin Metronidazole	20	10	3	Cured
9	Piperacillin Metronidazole Cifloxacine	45	20	1	Cured
10	Piperacillin / Tazobactam Amikacin	30	20	1	Cured
11	Ampicillin Metronidazole Amikacin	28	20	1	Cured
12	Piperacillin Metronidazole Amikacin	30	30	15	Cured
13	Piperacillin Metronidazole Amikacin	60	36	21	Cured

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Chapter 2.3.4

POST VASCULAR PROCEDURE REPERFUSION SYNDROME AND LIMB REPLANTATION

From experimental to clinical evidence

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Abstract: There is extensive in vitro and experimental evidence classified at level 1 that indicates Hyperbaric Oxygen (HBO) improves the deleterious effects of reperfusion injury after circulation has been restored. Unfortunately no human trial has addressed this problem in a proper evidence based way. It is the feeling of the author that existing sound experimental evidence should lead to a randomized study in order to help clarify the utility of HBO in this situation

Keywords: Hyperbaric oxygen, reperfusion injury, vascular surgery, limb replantation

1. INTRODUCTION

Reperfusion injury is still a problem of major concern in situations where circulation is restored after a prolonged interruption. It can happen in many clinical situations and in any organ, for instance: myocardial infarction, stroke, decompression sickness, acute CO poisoning, compartment syndrome, traumatic lesion of major vessels, surgical procedure etc.

2. WHAT ARE THE CONSEQUENCES OF REPERFUSION IN ISCHEMIC TISSUE?

Revascularization of a limb after a severe and prolonged period of ischemia may lead to increased mortality and amputation, because of the development of a post-revascularization syndrome, regardless the origin of

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 521–525.

occlusion (ischemia, trauma, iatrogenic) or the ways chosen to restore perfusion (fibrinolysis, stenting, surgery, resuscitation). This "reperfusion" syndrome includes local (explosive swelling of the limb, compartment syndrome and skeletal muscle infarction (rhabdomyolysis) and general complications such as acidosis, hypercalcemia, hypovolaemic shock, up to multi organ failure and cardiac arrest.

3. PHYSIOPATHOLOGY OF REPERFUSION INJURY

Ischemia/Reperfusion (I/R) injury represents a common mechanism of damage that happens in any situation and organ where circulation is reestablished after it has been interrupted for a certain lapse of time. Tissue damage is first created by the hypoxic state due to the interruption or reduction of blood flow. In hypoxic cells, calcium channels are impaired, the cellular energy provider ATP is degraded into hypoxanthine. Cells have first to use all available energy to survive. Specialized and general cell functions fail and finally the cell dies. With regard to circulation, after a certain time of ischemia, microcirculation can be permanently damaged with an impairment of the capillary circulation, so called “no-reflow situation”. We can see lesions of the endothelium walls, erythrocyte sludging, vasospasm, micro thrombi and finally tissue death. Unfortunately, reperfusion which is supposed to solve the problem creates its own damage called reperfusion injury.

It is thought that due to the high intracellular level of calcium, xanthine oxydase activity is boosted when reperfusion returns; this means that hypoxanthine is upgraded to xanthine leading to excess formation of the hyperactive superoxide anion. There is a second source of increased superoxide anion in neutrophils activation through activation of NADPH-oxydase. As soon as reperfusion is restored, neutrophils start to sludge in and around injured vessels and attach to the vascular endothelium. They then migrate to the injured tissue where they initiate the secretion of vasoactive enzymes. This has a vasoconstrictive effect on tissue arterioles which worsens tissue hypoxia with secretion of proteolytic enzymes leading to microscopic and macroscopic tissue edema. Intercellular adhesion molecule-1 (ICAM-1) and nitric oxide (NO) play an important role in the initialization and modulation of neutrophil migration. It has been shown in several experimental and animal models that the inhibition of ICAM-1 function will diminish the

extension of I/R injury. It has also been shown that the ICAM-1 production is modulated by NO production in vascular endothelium cells.

4. CURRENT THERAPY

Current therapies are applied after completed revascularization, when I/R injury has already started. All are directed to correct the problems as they appear: fasciotomy for compartment syndrome, mannitol and diuretics administration for forced diuresis to correct edema, fluid administration to correct hypovolaemia, iloprost[1] to counteract vasoconstriction, oxygen to correct hypoxia, injection of resins, insulin and glucose or haemodialysis, calcium antagonists to correct or counteract hypercalcemia, of buffers (THAM, bicarbonate) to correct acidosis, control of hypercalcaemia with orthophosphates and calcitonin or free oxygen radical scavengers like superoxyde dismutase and HBO.

5. WHY HYPERBARIC OXYGEN ?

All treatment options rely on experimental data and on physiopathological or symptomatic rationale. There are no controlled data in the literature to support one treatment over another so that we are still in search for a better treatment modality.

Paradoxically, several experimental studies have shown that the deleterious effect of Free Oxygen Radicals (FOR) induced by I/R injury, can be treated by supplemental high dose of oxygen. HBO can efficiently and electively prevent the consequences of reperfusion injury. In vivo and in vitro studies have shown that HBO acts at several different levels of I/R process:

- HBO decreases apoptotic fibroblast activity[2]
- HBO increases ATP level in muscle after R/I[3,4]
- HBO decreases neutrophils adhesion to endothelial walls through a down regulation of the endothelial ICAM-1 molecule[5]
- HBO decreases neutrophils adhesion to the vascular endothelium[6]
- HBO acts as a vasodilatator in injured muscular tissues
- Opens new functional capillaries in injured muscle[7]
- Decreases epiphyseal damage in young ischemic bone[8]
- Delays the progression of metabolic acidosis in amputated limb rat model[9]

- Near normal flap survival after intensive HBO in 10 hours of global ischemia[10]
- Reduces post ischemic edema in rat limb tourniquet model[11]
- Improvement in complex ear graft in rabbits[12] and rats[13]

6. CLINICAL EVIDENCE IN FAVOR OF HBO

As seen in Chapter 2.2.6 and 2.2.7, there is good clinical evidence that HBO can help in situation of crush injury and compromised skin grafts. There are only few case reports on the use of HBO in penile[14], ear and nose[15] replantation

7. CONCLUSIONS

There is level 1 experimental in-vitro evidence that HBO is helpful in the treatment of reperfusion injury. There is level 1 evidence that HBO reduces the extent of reperfusion injury in different animal models. There is only clinical level 4 evidence that HBO may be helpful in situations of post vascular surgery or limb replantation. In view of the excellent animal studies and of the high potential benefits for severely damaged patients, it is surprising that a randomized clinical study involving HBO has not yet been performed. Such a study should urgently be performed.

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Chapter 2.3.5

ACUTE ISCHEMIC OPHTHALMOLOGICAL DISORDERS

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Abstract: In the field of ophthalmology, a beneficial effect of hyperbaric oxygenation therapy has been described for retinal artery occlusions, non-arteriitic optic neuropathy and macular edema secondary to retinal vein occlusion or uveitis. Here we describe the pathology of retinal vascular occlusions and discuss the use of HBO in these conditions

Keywords: Hyperbaric oxygenation therapy; central retinal artery occlusion; CRAO; branch retinal vein occlusion; BRVO; central retinal vein occlusion; CRVO; branch retinal vein occlusion (BRVO); anterior optic neuropathy; AION; macular edema; retina; optic disc; optic nerve; ophthalmic artery; ciliary artery; carotid artery; emboli; arteriitic AION; non-arteriitic AION; arteriitic CRAO; non-arteriitic CRAO

1. VASCULAR SYSTEM OF THE EYE

The arterial vascular system of the eye derives from branches of the ophthalmic artery which is fed from the internal carotid artery. Before entering the eye, one branch is following the optic nerve into the eye to feed as the central retinal artery the inner retina. Other branches of the ophthalmic artery penetrate the sclera as short and long ciliary arteries to feed the choroid which is supplying the outer retina. Therefore, the retina has two vascular systems each supplying half of the retina. The venous system drains with its branch retinal veins converging to the central retinal vein the inner retina. The central retinal vein passes through the optic nerve together with the central retinal artery and later drains into the ophthalmic vein. The venous system of the choroid drains through four vortex veins through the

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sclera into the orbital vein. The optic nerve disc receives its blood supply through the short posterior ciliary arteries.

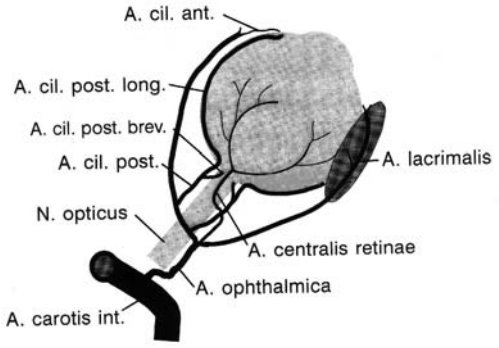

Figure 2.3.5-1. Vascular supply of the eye

2. RETINAL ARTERY OCCLUSION

2.1 Pathomechanisms and clinical picture

Retinal artery occlusion leads to a sudden severe and painless vision loss in the affected eye[1]. Patients with CRAO are rarely younger than 40 years, the mean age is 65 years. Occlusion of the ophthalmic artery is rare, usually the central retinal artery or one of its branches is occluded, leading to a central retinal artery occlusion (CRAO) or a branch retinal artery occlusion (BRAO). The retina is very sensitive to ischemia, experimental data have shown that a total occlusion of the central retinal artery causes irreversible damage to the inner retina if occlusion time exceeds 100 minutes[2]. Clinically, CRAO is seen as incomplete CRAO, subtotal CRAO or total CRAO. Most CRAO observed clinically are subtotal CRAO. Within 48 hours, about 75% of CRAO spontaneously recanalize[3]. However, at that time point irreversible damage at the inner retina has occurred, allowing only ambulatory vision. The leading cause of CRAO are emboli deriving from arteriosclerotic plaques in the aorta or from the carotids. Further sources of emboli are calcified heart valves, thrombi originating from areas of restricted heart movements or in patients with atrial arrhythmia. Rare emboli sources

are bacterial emboli in sepsis cases, air or bone marrow emboli in trauma patients.

Besides embolism, inflammation of the arterial wall in conditions like M. Horton or M. Wegener can cause a CRAO. Arterial hypertension is a major risk factor for CRAO. In this context the anterior ischemic optic neuropathy (AION) has to be mentioned producing a sudden and painless loss of visual acuity due to infarction of the optic nerve disc due to closure of the short posterior ciliary arteries. The risk factors are similar to CRAO, but arteriitis is more frequently (50% of patients) found in AION.

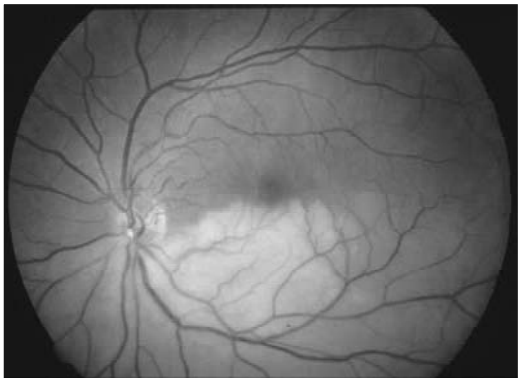

Figure 2.3.5-2. Branch retinal artery occlusion (BRAO). Note the whitish edema in the inferior retina and the white embolus located at the proximal inferior artery on the optic disc

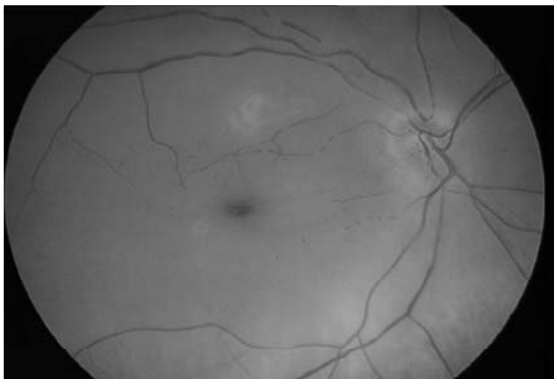

Figure 2.3.5-3. Central retinal artery occlusion (CRAO). Note the whitish edema of the retina and the interrupted blood column with the retinal vessels

2.2 Treatment options

Treatment options in CRAO are limited due to retinal sensitivity to ischemia and late presentation of patients. Massage of the eye ball is being attempted in order to move emboli further distal in the artery. A reduction of perfusion resistance into the eye is achieved by lowering the intraocular pressure either by paracenthesis of the anterior chamber or by administration of anti-glaucoma medication[4]. Hemodilution therapy is attempted to improve rheologic parameters, especially to lower the hematocrit. A systemic lysis therapy has so far been reported in single case reports and considered as to dangerous. Local intravascular fibrinolysis (LIF) using a catheter through the carotid artery to release urokinase (rarely rTPA) into the ophthalmic artery has been described and reported to show better results compared to controls[5]. In AION patients hemodilution therapy, and in some centers, surgical optic sheath fenestration to alleviate compression of swollen nerve axons, is being performed. In arteriitic CRAO, BRAO or AION, immediate systemic steroid therapy is mandatory to protect the fellow eye from vision loss and to limit the damage in the affected eye.

2.3 HBO in retinal artery occlusion

Several reports exist describing a positive effect of HBO therapy on retinal artery occlusion. The aim is to maintain an oxygen supply to the retina through the choroidal vasculature under hyperbaric oxygenation therapy (HBO) until spontaneous recanalisation occurs. The bradytrophic vitreous could serve as an oxygen deposit after HBO therapy, and a local release of tissue plasminogen activator under HBO could further help to accelerate reperfusion. Takahashi[6] described a combination of HBO-therapy with a stellate ganglion block in a small case series of CRAO patients. Beiran and coworkers combined HBO with nifedipine treatment in recent onset CRAO patients[7]. In a study with 8 patients with CRAO and 10 patients with BRAO, a beneficial effect of HBO therapy compared to a control group was described by Aisenbrey and coworkers. In their study, patients were treated with 3x30 min at 240 kPa which was applied 3 times a day on admission, twice daily on day 2 and 3 and once daily for at least another 4 days[8]. In a study at our clinic, 21 patients with CRAO were treated with HBO. We included only patients with an onset of symptoms of less than 12 hours and normal values for ESR and CRP, thus excluding arteriitis. HBO therapy was performed 3 times within 24 hours after admission followed by two treatments daily for up to 2 days at 2.4 ata following the Marx scheme. In our study, about 10 % of our patients regained a visual acuity which allows reading[9]. Meanwhile, we have treated 40 patients with CRAO where

15 % regained reading vision after HBO-treatment (figure 2.3.5-3-2.3.5-4). Meta-analysis with other interventional studies is difficult to perform as inclusion criteria as initial visual acuity and latency of symptoms vary, nevertheless our results have been very good.

In a case report, Bojic and coworkers described improvement in visual acuity in 2 patients with non arteriitic AION[10]. The improvement has been observed 3-5 months after the event. Such developments have been described also in the natural history of AION[11], but it is possibly worth to perform a pilot study with a larger patient number.

A sufficient oxygenation of the retina can be achieved by HBO in retinal artery occlusion. However, the glucose and nutricients transport provided by retinal artery circulation is vital for retinal ganglion cell survival. If retinal artery recanalization does not occur in time, the neuroretinal cells die despite of sufficient oxygenation. Additionally, there is a risk of ischemia-reperfusion injury. It can be discussed if a neuroprotective medication like glutamate antagonists should be given along with HBO to reduce this risk.

Hyperbaric oxygenation leads to vasoconstriction in the autoregulated retinal vascular system[12] which is not welcome in arterial occlusions. In order to minimize this effect some authors performed a stellate ganglion block [6] or applied vasodilatative medication[7]. It is also possible to add 5% of carbon monoxide to the inhalation gas to reduce vasoconstriction[13]. However, the solubility of carbon dioxide compared to oxygen is higher under hyperbaric conditions, and therefore the effect is difficult to predict. In our opinion it is generally not necessary to block autoregulation as in ischemic tissues autoregulation fails. Also, the capability of retinal vessels to constrict declines with age, at the age of 50 the effect is only marginal[14].

CRAO and BRAO could be a symptom of a subtotal carotid artery stenosis. Together with neurologists it should be discussed whether patients with this condition may receive HBO treatment or if generally a carotid artery duplex sonography should be mandatory before starting HBO therapy.

In our clinic we have reserved HBO treatment to non-arteriitic CRAO and BRAO cases as the pathomechanism of ischemia in arteriitic cases is different and requires systemic steroid medication. As we do not have experience with HBO treatment in arteritic retinal occlusion we recommend HBO to be used in early presenting cases of CRAO and BRAO which have not recanalized and have a visual acuity of less than 0.1.

It is also crucial to see patients with retinal artery occlusions as early as possible. We have therefore sensitized our personnel at the hospital admission to send patients complaining of an acute painless vision loss directly to the doctor, bypassing the waiting room.

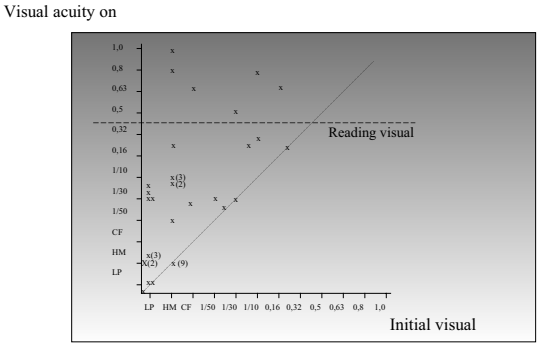

Figure 2.3.5-4. Scattergram Visual acuity after HBO in CRAO.Scattergram showing development of visual acuity before and after HBO therapy in non-arteriitic central retinal artery occlusion. Values above the diagonal line are improvements. The horizontal line represents the visual acuity necessary for reading. Visual acuity values: 1.0 equals 100%, 0.1 equals 10%. CF means counting fingers, HM means hand movements, LP means light perception.

3. RETINAL VEIN OCCLUSION

3.1 Pathomechanisms and clinical picture

Retinal vein occlusions are relatively common condition usually affecting people older than 40 years. In analogy to the retinal artery occlusions, the terminology in retinal vein occlusion is central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), both of which can lead to a severe vision loss. The vision loss is less acute compared to retinal artery occlusions. In some cases the patient did not realize the condition as the visual acuity decreased slowly over weeks in the affected eye. Clinically, ischemic CRVO is discriminated from non-ischemic CRVO. Both forms differ in the extend of retinal hemorrhages and so called “cotton wool spots”, which represent localized ischemia of retinal nerve fibers. Ischemic vein occlusions usually have a visual acuity of 0.1 (10 %) or less on presentation. Both forms of CRVO can convert into the other form. While ischemic CRVO has a poor prognosis, non-ischemic CRVO in some cases can regain full visual acuity. Persistent ischemic CRVO or BRVO require panretinal laser coagulation to avoid complications due to retinal neovascularisation. The final visual acuity also depends on the extend of the cystoid macular edema, a common complication in CRVO and BRVO,

which can develop weeks after the disease's onset. Visual acuity (VA) can improve spontaneously even after several months, however, in general an initial VA of 0.1 or less is an unfavourable prognostic factor. The main risk factor for CRVO and BRVO is arterial hypertension. Further risk factors are glaucoma, smoking, hyperopia, oral contraceptives, increased blood viscosity, a high hematocrit, and phlebitis. Often a retinal vein occlusion is situated at an anatomical narrowing, for example arteriovenous crossings or in the optic nerve head at the level of the lamina cribrosa.

3.2 Treatment options

Current treatments aim at the improvement of risk factors, e.g. reduction of arterial hypertension, isovolemic hemodilution to lower the blood viscosity and the hematocrite. In BRVO it has been attempted to surgically separate retinal veins from arteries in cases where the occlusion site was located at an arteriovenous crossing[15]. In CRVO, incisions into the optic nerve sheath have been performed in order to decompress the swollen nerve fibers. The outcome after these experimental surgical interventions is not satisfactory so far[16].

3.3 HBO in retinal vein occlusions

Hyperbaric oxygenation therapy (HBO) has shown to produce an improvement in visual acuity by reducing macular edema secondary to conditions like uveitis[17]. In a pilot study we treated patients with chronic macular edema secondary to ischemic CRVO with HBO therapy. We used the Marx scheme at 2.4 ata, with one session per day for 15 days followed by one session per week in the following 6 weeks. We observed in some cases dramatic improvement in visual acuity, but also observed a decline in visual acuity back to initial values weeks after HBO treatment was stopped[18]. The effect of HBO on macular edema is not well understood, it can be speculated that vascular constriction within the retina reduces the edema, in these case some autoregulation must be functional. As the observed effect has been temporary, we currently do not perform HBO-treatment in retinal vein occlusion or macular edema secondary to other diseases.

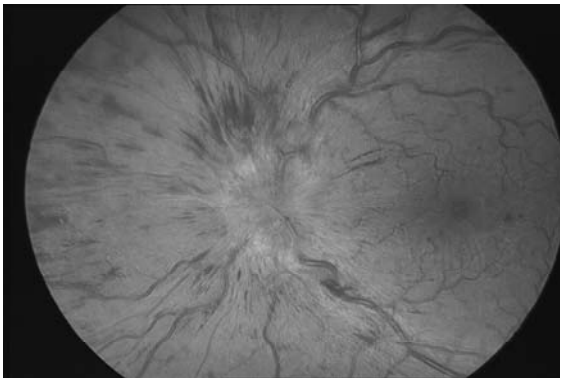

Figure 2.3.5-5. Central retinal vein occlusion (CRVO). Note intraretinal hemorrhage, optic disc swelling and venous congestion

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Chapter 2.3.6

PNEUMATOSIS CYSTOIDES INTESTINALIS

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Abstract: Pneumatosis cystoides intestinalis is characterized by multiple gas cysts in the wall of the gastrointestinal tract. Primary pneumatosis intestinalis is extremely rare. In the more frequent secondary forms small intestine and the right side of the colon are mainly affected, and the underlying pathology can be gastrointestinal, pulmonary or immunological. The cysts are thin walled and break easily. Spontaneous rupture gives rise to pneumoperitoneum. Symptoms are nonspecific, and in pneumatosis associated with other disorders, the symptoms may be those of the associated disease. Complications associated with pneumatosis cystoides intestinalis occur in approximately 3% of cases and include volvulus, intestinal obstruction, hemorrhage, and perforation. Pneumoperitoneum occurs in these patients, usually in association with small bowel rather than large bowel pneumatosis. Pneumatosis cystoides intestinalis represents one of the few cases of sterile pneumoperitoneum and should be considered in the patient with free abdominal air but no evidence of peritonitis. The diagnosis is usually made radiographically by plain abdominal or barium studies. Computed tomography can be used to confirm the diagnosis. Visualization of intestinal cysts has also been described by ultrasound. Most published cases of pneumatosis cystoides intestinalis with radiological finding of pneumoperitoneum have been treated conservatively and should have not been considered as a reason for surgery. Surgical intervention is indicated only in acute complications, such as perforation, peritonitis, bowel necrosis, or tension pneumoperitoneum. Several reports have indicated the advantages of hyperbaric oxygen therapy in the management of pneumatosis cystoides intestinalis. It is stressed that hyperbaric oxygen treatment is effective provided it is continued until cyst resolution has occurred and not just until symptomatic improvement. Disadvantages of normobaric oxygen treatment are that excessive amounts of 100% oxygen are required to be inhaled for prolonged periods and this may produce pulmonary oxygen toxicity

Keywords: pneumatosis cystoides intestinalis; pneumoperitoneum; pathophysiology; diagnosis; surgery; hyperbaric oxygen therapy

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 537–543.

1. INTRODUCTION

Pneumatosis cystoides intestinalis is an uncommon condition presenting as multiple gas-filled cysts of the gastrointestinal tract. The cysts may be located in the subserosa, submucosa, and, rarely, muscularis layer and vary in size from few millimeters to several centimeters in diameter. They can occur anywhere along the gastrointestinal tract, from esophagus to the rectum; however, they are most common in the jejunum, followed by the ileocecal region and the colon. Extraintestinal structures such as mesentery, peritoneum, and the falciform ligament may also be involved. There is an equal incidence among males and females, and this condition most commonly occurs in the fourth to seventh decades of life. Pneumatosis in neonates is usually associated with necrotizing enterocolitis. The cause of pneumatosis intestinalis has not been completely delineated. A number of theories have been proposed, of which the mechanical, mucosal damage, bacterial, and pulmonary theories appear to be the most promising.[1]

Pneumatosis cystoides intestinalis was first described as early as 1730 by Du Vernoy during a cadaver dissection.[2]

The present review is targeted especially on the use of hyperbaric oxygen for the treatment of pneumatosis cystoides intestinalis. The pathophysiology, ethiology and previous treatment reports are discussed, as are the advantages of hyperbaric oxygen therapy over normobaric oxygen therapy or surgery. The use of hyperbaric oxygen appears to represent a significant advance in the treatment of pneumatosis cystoides intestinalis.

2. PATHOPHYSIOLOGY

In a review of 213 cases of pneumatosis cystoides intestinalis Koss reported a 15% incidence of primary pneumatosis cystoides intestinalis compared to 85% of cases that were secondary to other underlying disorders.[3] A great number of diseases and disorders have been associated with it[4]: a) traumatic and mechanical (pyloric stenosis, endoscopy, enteric tube placement volvulus, surgical anastomosis, carcinoma; b) inflammatory and autoimmune disease (Crohn's disease, ulcerative colitis, diverticular disease, necrotizing enterocolitis, poly-dermatomyositis, scleroderma, mixed connective tissue disease, multiple sclerosis; c) infectious diseases (Clostridium difficile, HIV and AIDS, cytomegalovirus, Mycobacterium species; d) pulmonary disorders (chronic obstructive pulmonary disease, asthma, cystic fibrosis; e) drug-induced pneumatosis (cytotoxic agents, immunosuppression, corticosteroids), other conditions such as transplantation, graft versus host disease, leukemia, or intestinal infarction.

St. Peter et al.[4] proposed three possibilities for the source of the gas in the intestinal wall: intraluminal gastrointestinal gas, bacterial production gas and pulmonary gas. The intraluminal gastrointestinal gas alone is not sufficient to explain the pneumatosis cystoides intestinalis. A further mechanism by which the gas enters the intestinal wall could be increased intraluminal pressure, mucosal injury, or combination of them. According to this mechanical theory a lack of mucosal integrity in conjunction with the intraluminal pressure allows the gas to dissect along the bowel wall.[5] Passage of the intraluminal gas into the submucosa requires a damage in the muscularis mucosa which might be possible in the course of an inflammatory process or could be attributed to a defect in the gut immune barrier, common in steroid or cytotoxic medical therapy.[6] Furthermore, mucosal damage or a defect in the gut immune barrier can facilitate the bacterial invasion into intramural compartments. Nevertheless, no evidence of presence of bacteria in pneumocysts in humans exists. The third mechanism explaining the pathophysiology is based on an alveolar rupture theory, which could result in dissection of air along vascular channels in the mediastinum moving to the retroperitoneum and then to mesentery and bowel. Supporters of this theory emphasize the subserosal presence of gas in these cases, which is probably due to gas migration along the vessels rather than to transmural infiltration.[4] It has been suggested that association of chronic obstructive pulmonary disease and pneumatosis intestinalis is related to large fluctuation of the intraluminal bowel pressure during coughing.[7]

3. SYMPTOMS

The symptoms associated with pneumatosis cystoides intestinalis vary from asymptomatic patients to symptoms and signs associated with life threatening complications such as bowel ischemia, perforation and peritonitis. Generally, the symptoms are mild and include abdominal pain, diarrhea or constipation, or weight loss. More serious symptoms such as bleeding or ileus can also occur. The hypothesis that symptoms are due to the mechanical effects of the cysts does not seem to be correct as some large cysts remain asymptomatic or cysts persist despite a successful symptomatic therapy.[7] It is generally accepted that the clinical manifestations of pneumatosis cystoides intestinalis are not necessarily associated with the intramural gas or its location in the gastrointestinal tract but rather with the underlying disorder.[2,4]

4. DIAGNOSIS

The clinical manifestations of pneumatosis cystoides intestinalis are typically not the consequence of intramural gas but due to underlying pathologic conditions. The most common symptoms have been diarrhea, bloody stools, abdominal pain, constipation, weight loss and tenesmus in decreasing order. Physical examination is rarely helpful in diagnosis. It has been shown that the pattern or extent of pneumatosis cystoides intestinalis does not correlate with the severity of the symptoms or the severity of the underlying diseases.[4]

On plain radiography, pneumatosis cystoides intestinalis is characterized by radiolucency within the wall of the gastrointestinal tract. The patterns of the radiolucency may be seen as linear, curvilinear, small bubbles, or collections of larger cysts. Abdominal radiographical findings are detected in approximately two thirds of the patients with pneumatosis cystoides intestinalis.[8] Ultrasonography can be also helpful in obtaining the diagnosis of pneumatosis cystoides intestinalis.[9]

Computed tomography is the best imaging modality for establishing the diagnosis of pneumatosis cystoides intestinalis, as these techniques reveal intramural gas parallel to the bowel wall.[10] It has greater sensitivity in the diagnosis than plain films or ultrasonography.[2] Furthermore, computed tomography can provide the surgeon with an excellent survey of the abdominal cavity for diagnosis of associated pathologic conditions.[11]

Macroscopic elevations of the mucosa make pneumatosis cystoides intestinalis difficult to distinguish from other lesions evaluated by endoscopy.[12] Puncture and complete deflation have been advocated to confirm the diagnosis. However, a high degree of suspicion should be present before undertaking any intervention. Removal of a “polyp” that in fact was a pneumocyst have caused perforation of the bowel.[4]

Some authors suggest that gas cysts present in pneumatosis cystoides intestinalis form inside lymphatic channels. Other researchers, however, disagree with this hypothesis. Multinucleated giant cells, macrophages, and pericystic inflammatory cellular reactions are most common histologic findings.[4]

5. TREATMENT

The focus of treatment is almost entirely on the associated illness inciting pneumatosis cystoides intestinalis. The major dilemma for the surgeon is to identify the patients requiring a surgical intervention. The surgeon should take into account that pneumatosis cystoides intestinalis can be managed

conservatively in most of the cases and that an operation performed without clear indications might worsen even more the general condition of a patient with a serious underlying disease. After careful evaluation of the patient's clinical state and findings of the diagnostics surgery should be kept for patients with signs of bowel perforation, peritonitis or abdominal sepsis.[13]

Conservative treatment including intravenously administered antibiotics in high concentrations has been reported to be effective. Especially, treatment with metronidazole has been recommended.[4,6]

The earlier treatment for pneumatosis cystoides intestinalis was normobaric oxygen therapy. Forgacs et al.[14] proposed aggressive oxygen therapy with partial oxygen pressures as high as 350 mmHg in symptomatic pneumatosis cystoides intestinalis, which may enhance the reabsorption of gas cysts that predominately contain nitrogen and carbon dioxide. The disadvantage of normobaric oxygen therapy is that excessive amounts of oxygen are required to be inhaled for prolonged periods and this may produce lung oxygen toxicity.

Masterson and coworkers (1978)[15] reported the use of hyperbaric oxygen for the treatment of pneumatosis cystoides intestinalis and felt that hyperbaric oxygen therapy represented a significant advance in the treatment of pneumatosis cystoides intestinalis. Grieve and Unsworth (1991)[16] presented 8 patients with pneumatosis cystoides intestinalis who underwent 11 courses of hyperbaric oxygen treatment. All patients responded with a symptomatic relief. This was followed by 7 recurrences and 4 long-term cures. The authors concluded that hyperbaric oxygen therapy is effective for pneumatosis cystoides intestinalis provided it is continued until cyst resolution has occurred and not just until symptomatic improvement. This is the largest reported series of hyperbaric oxygen therapy of pneumatosis cystoides intestinalis. Since then several case reports have been published on the subject.[17,18] The patients have normally received hyperbaric oxygen at 2-2.5 ATA for 1-2 hours per day for five days a week. The total duration of the treatment period has been extended to several weeks until no recurrence of the lesions has been shown.

6. CONCLUSION

Pneumatosis cystoides intestinalis is usually a secondary finding caused by an underlying disease. Mucosal integrity, intraluminal pressure, bacterial flora, and intraluminal gas have an interactive role in the formation of the pneumocysts. The diagnosis is currently best obtained by plain abdominal radiography or ultrasonography and specifically delineated by computer tomography. Results obtained from hyperbaric oxygen therapy of patients

with pneumatosis cystoides intestinalis have been favorable and promising. The challenge facing surgeons asked to evaluate patients with this disorder is to identify those who require surgery. Surgical interventions should be limited only for patients who are not responding to nonoperative management, especially those with signs of gut perforation, peritonitis, or abdominal sepsis.

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2.4 Controversial and Non Indications

Chapter 2.4.1

FEMORAL HEAD NECROSIS

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Abstract: Femoral head necrosis (FHN) is a condition in which the blood supply to the femoral head is compromised. This leads to cell death in the marrow and the bone, and interferes with the normal activity of osteoblasts and osteoclasts, and loss of the structural integrity of the femoral head. The treatment of the FHN is an unresolved orthopedic problem and multiple approaches are used for its management. HBO therapy makes oxygen available to marrow cells and facilitates the bone remodeling processes through edema reduction and angioneogenesis stimulation

Keywords: Hyperbaric Oxygen, Hyperbaric Oxygenation, Femoral Head Necrosis, Avascular Necrosis

1. INTRODUCTION

Femoral Head Necrosis (FHN) also called Avascular Necrosis, Ischemic Necrosis, or Aseptic Necrosis is pathology generated by several causes, which reduce local blood supply so that it compromises the structural integrity of the femoral head. The natural evolution of this pathology leads to the destruction of the femoral head in most of cases (70%)[1] requiring total hip replacement (THR). It affects the younger population (25-55 years) and has an incidence between 10% and 20% of those requiring total hip replacement[2]. The normal lifespan of a hip prosthesis is about 12 years; so considering the young age of the patients with this pathology it is certain that there are going to be several surgical treatments with surgical and anaesthesiological risks; the risk of infection and need for rehabilitation. To all this there are grave social costs as patients are unable to work for extended periods during their lifetime.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 547–552.

2. ETIOLOGY

Trauma is the most frequent etiological factor, but frequently FHN is related to other pathologies: Dietary or Environmental Factors (Dysbaric Conditions, Alcohol Abuse, and Cigarette Smoking); Iatrogenic (Corticosteroids, Radiation Exposure, Hemodialysis, Organ Transplantation, Cytotoxic Therapy, Laser Surgery); Hematologic (Hemoglobinopathies (Sickle-Cells Anemia, Thalassemia, DIC, Polycythemia, Hemophilia) and many others – but these are less common in the genesis of FHN. Sometimes it is not possible to determine a cause so that the term idiopathic FHN applies. At the moment the incidence and relative contributions of different pathophysiological mechanisms are not known; this contributes to the . that contribute to explain the disease are not completely recognized[3-5].

3. PATHOGENESIS

The pathophysiological mechanism that causes osteonecrosis is still unknown, but it causes a progressive destruction of the vascular supply of the femoral head, that halts the oxygen and nutritional supply to the cells. The direct consequence is cellular death with necrosis and ultimately collapse of the trabecular structure with articular pain and dysfunction.

4. DIAGNOSTIC MODALITIES

MRI is at the moment the best technique to diagnose FHN even in its early stages when x-ray examination is negative for bone damage or collapse. Also diagnostic techniques include Bone Scintigraphy, CT and arthroscopy, but their use is limited to those patients where MRI cannot be used.

5. STAGING SYSTEM

In the staging of FHN there are 5 major classifications. Converging or combining the classifications allows for better comparisons between old and new literature using respective systems..

The most commonly used system is that of Ficat and Arlet system[2], but with the MRI scans the Steinberg system is preferred [6-8] (Tab. 2.4.1-1).

Table 2.4.1-1. Classification of Femoral Head Necrosis[2, 6]

STAGE	CRITERIA
	STEINBERG CLASSIFICATION SYSTEM
0	**Normal or non-diagnostic X-Ray, MRI or Bone Scan**
I	**Pain - Normal X-Ray - abnormal MRI or Bone Scan**
	A – Mild (< 15% of head)
	B – Moderate (15% - 30%)
	C – Severe (> 30%)
II	**Sclerotic changes or cystic lesions**
	A – Mild (< 15%)
	B – Moderate (15% - 30%)
	C – Severe (> 30%)
III	**Subchondral collapse without flattening**
	A – Mild (< 15% of articular surface)
	B – Moderate (15% - 30%)
	C – Severe (> 30%)
IV	**Flattening of the femoral head**
	A – Mild (< 15% of surface and < 2 mm depression)
	B – Moderate (15% - 30% of surface or 2-4 mm depression)
	C – Severe (> 30% of surface and > 4 mm depression)
V	**Joint narrowing and/or acetabular involvement**
	A – Mild
	B – Moderate
	C – Severe
VI	**Advanced degenerative changes**

6. RATIONALE FOR THE HBO USE IN THE FHN TREATMENT

The pathogenesis of osteonecrosis is still unclear. Fatty or gaseous emboli, intravascular coagulation, increased intra-medullary pressure, blood hyperviscosity and venous stasis are usually incriminated mechanisms. All of these conclude in the common pathology: interruption of blood supply. This causes bone tissue hypoxia with cell dead. Osteocytes, under normal conditions, use little oxygen and remain viable following up to 12 hours of ischemia; osteoblasts use more oxygen in basal conditions, and they increase this up to 8 times during active repair processes such as fractures. The cells that need the most oxygen are the osteoclasts, which use up to 100 times more oxygen than the ostocytes[9].

Many studies show that HBO is able to modify bone metabolism in a significant way: It induces osteogenesis independent to hemoglobin transported oxygen[1]. For this reason the use of HBO is physiologically and scientifically reasonable: it increases the amounts of available oxygen in ischemic bone – preventing further cell damage.. In addition it has direct and

indirect anti-oedema effects that reduce bone and joint tension, thereby restoring normal conditions of blood supply and reducing pain.

7. THERAPY

The common objective in all surgical and medical strategies at present is to delay the need for a total hip replacement (THR). There is no perfect answer or standard of care. Among the surgical and non-surgical techniques we find many procedures that introduce side-effects and have variable failure rates: (1) Core decompression has the problem of causing a fracture of the femoral neck and carries a 40% failure rate[10]. (2) Vascularized bone grafting requires extended surgery using microvascular techniques. It causes pain and dysfunction at the donor site and has a failure rate of 18% over 24 months[4]. "Vascularized bone grafting" is a viable option for pre-collapse and some post-collapse femoral head lesions"[4]. (3) Non vascularized bone grafting, with or without growth and differentiation factors[11] carries a failure rate of 60%. If used with growth and differentiation factors it leads to bone formation with poor mechanical characteristics due to a high number of blood vessels inside[12]. (4) Osteotomy leads to abnormal femoral head mechanics and has a failure rate of 30% as shown by collapse of the femoral head[4]. (5) Electrical stimulation; (6) magnetic fields; (7) high energy shock wave; (8) pharmacological treatment with osseointegrators and/or prostanoids[13] haven't gained sufficient clinical evidence[4]. In contrast to this, HBO addresses many of the underlying pathophysiological mechanisms. The ironic causal association with avascular necrosis in the context of air or mixed gas diving should not be confused with the beneficial of HBO2 in treating it[1].

8. HYPERBARIC OXYGEN THERAPY

It is possible to obtain very good results when HBO is used in the first stages of FHN before flattening or collapse of the femoral head.

The meta-analysis of Strauss and Dvorak involving 15 papers totals 189 patients with a successful rate of 97% in 12 months and 81 % in 24 months[1]. Among the 15 papers, 3 were case reports and 4 used HBO after surgical treatment. All were retrospective analyses without precise outcome measures. Since then, the only additional reference is by Reis et al who reviewed 12 patients (16 hips) with a Ficat 1 classification. The non-randomised control group consisted of patients that were reasonably matched to those who received HBO. The patients received 100 HBO

treatments and underwent follow-up after 24 months. Within 8 months, 13 hips had recovered completely with HBO therapy[14].

Reis et al performed two more studies on the use of HBO in rats with artificially inducted osteonecrosis of the femoral head[15,16]. The studies are intriguing and encouraging and suggests that HBO is associated with better weight-bearing of the hips.

Other data were obtained in a retrospective analysis performed by Ditri and Montanari involving 227 patients treated for FHN in Ficat stages 1 and 2A stage. These also support the efficacy of HBO in the osteonecrotic pathology (*Vicenza, Italy, unpublished data, 2004*).

In 2005 Vezzani and associates performed a prospective, double-blind, randomized trial evaluating the function of the hips after HBO therapy in a study group (n = 10) and a hyperbaric air control (n=10). The trial was interrupted for ethical reasons after 30 treatments due to the significant improvement observed in the HBO2 group[17].

However, the number of patients treated with HBO for osteonecrotic pathologies are still too few for the treatment to be considered a standard of care. As suggested by Strauss and Dvorak, we need more studies to confirm our observations.

9. CONCLUSIONS

We have many observational studies and one randomized controlled trial demonstrating the efficacy of HBO in the treatment of osteonecrosis of the Femoral Head. However, in an era where medical practice is directed by Evidence Based Medicine (EBD) principles, we need prospective, controlled, randomized and blinded trials with an appropriate number of patients. For this reason we need to complete a study of FHN treated with HBO organized from the Working Group 2 of the Cost Action B14 Project of the European Committee for Hyperbaric Medicine controlled by the European Union.

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Chapter 2.4.2

CEREBROVASCULAR INCIDENTS (STROKE)

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Abstract: Over the past 40 years various experimental and clinical studies have suggested that hyperbaric oxygenation (HBO) may be beneficial in treating acute, sub-acute and chronic stroke. In acute stroke, timing, HBO2 dosage and lack of pathophysiological stratification may be disguising the effectiveness of HBO in a subset of the stroke population. Anecdotally, HBO appears to be most effective in the treatment of small, sub-cortical, non hemorrhagic stroke in which perfusion has recovered early or where the clinical picture undulates – suggesting a functional penumbra. Although feasible and seemingly safe, it is not yet possible to recommend the use of HBO in the treatment of acute and sub-acute stroke based on the scientific evidence available today. In chronic stroke, the cost of HBO would seem prohibitive – given the prevalence of the condition. However, greater independence and productivity in those successfully rehabilitated may affect the equation in favor of treatment. For the time being, however, this cannot be recommended other than as a promising area for further research

Keywords: hyperbaric oxygen; stroke; acute cerebrovascular incidents; rehabilitation

1. INTRODUCTION

Over the past 40 years various experimental and clinical studies have suggested that hyperbaric oxygenation (HBO) may be beneficial in treating acute, sub-acute and chronic stroke [1-3]. Various therapeutic mechanisms have been proposed; these include: hyperoxygenation, vasoconstriction, resolution

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of oedema, preservation of "idling neurons", improving glucose-oxygen utilization, preventing adherence of polymorphonuclear leukocytes to endothelium, attenuation of the inflammatory process, and prevention of cell apoptosis [4-11]. Although the mechanisms of HBO in chronic stroke may be less obvious, it appears almost logical to apply a recognized treatment for arterial gas embolism in the treatment of acute stroke. Nevertheless, its application in such cases remains controversial; experimental and clinical results are often conflicting.

A recent review of the clinical literature on acute stroke concluded that HBO could not be recommended for brain injury or stroke based on research predating 2001 [12]. A subsequent pilot RCT has extended the relevance of this position to the present [13]. Similarly the value of HBO in chronic stroke remains undefined. Large, evidence based studies remain lacking, and the parameters for improvement are difficult to evaluate, particularly in terms of cost-benefit and improved quality of life.

Before excluding a possible role of HBO in the treatment of stroke, it should be realized that many agents in use today, even the use of aspirin as a prophylactic agent in stroke, remain controversial [13-15]. One of the reasons for this are the many confounding factors and variables that complicate any stroke trial which include the:

- time from occlusion to intervention
- site of the lesion and volume of necrosis
- control of haemodynamic parameters – particularly blood pressure, glucose levels and body temperature
- prevention of secondary complications
- duration of the occlusion
- demographics of the subjects (gender; age; co-morbidity; etc.)
- outcome measures (anatomical imaging; functional imaging; functional or clinical measurements; disability scales and scores)
- interval between clinical or functional assessments
- dynamic pathophysiology and the natural history of the disease

In terms of HBO, there are an additional number of variables:

- time from onset of stroke to receiving HBO
- pO2 used
- duration of treatment
- number of treatments
- interval between treatments
- combination with or without rehabilitation

The diversity and the interrelated nature of all these factors deny us a clear picture on the effectiveness of the variety of interventions proposed in the management of stroke, including HBO. The question to ask is therefore not whether HBO is effective in the treatment of stroke, but rather whether

there are pathophysiological processes during the evolution and resolution of stroke that may be amenable to HBO and how to recognize and address these at the appropriate time. This would provide a clearer picture on whether, when and how to apply HBO in the treatment of stroke.

2. THE NATURAL HISTORY OF STROKE

Following an abrupt interruption of circulation to the brain, there is a corresponding loss of neurological function – a stroke. The cause of the occlusion may be thrombosis, embolism, or hemorrhage. Strokes are classified as hemorrhagic or ischemic. Acute ischemic stroke includes thrombosis or embolism and makes up 80% of all strokes. Thrombosis develops in situ whereas embolism may be from a variety of sources and can include fat, thrombus, air, gas or amniotic fluid. Myocardial infarction, atrial fibrillation with dilation of the atria, and valve irregularities are all risk factors for thrombo-embolic stroke. Hemorrhagic strokes may be the result of a ruptured aneurism or arterio-venous malformation, or may occur as a complication of an ischemic stroke or thrombolysis.

With loss of circulation to the brain, cellular changes rapidly appear as the ischemia unleashes a cascade, which – unless reversed – leads to irreversible cell death. Usually there is a central area of virtually immediate tissue loss with surrounding marginal tissue – called the *ischaemic penumbra*. This tissue is believed to be potentially salvageable as long as irreversible cellular changes can be avoided or blocked through reperfusion or neuroprotection respectively. This is the basis for current acute stroke therapy: restore and maintain the circulation (thrombolysis and maintenance of blood pressure) and prevent cellular complications (neuroprotection). Although the ischemic cascade offers various potential opportunities for intervention, all of these are limited by the same factor that caused the original problem: lack of circulation. Also, late restoration of circulation introduces additional hazards rather than benefits – such as hemorrhage and oedema [16]. Even prompt reperfusion can result in the paradoxical progressive destruction of reversibly damaged brain cells apparently due to a multifactorial mechanism involving inflammatory processes and free radical release.

Accordingly, the time to recovery of the circulation (whether spontaneous or therapeutic) and the site of injury are probably the most important determinants of eventual outcome; the role and effectiveness of HBO2 should therefore be contextualized within this setting.

More than 400,000 people have a first-time stroke in the US every year[17-20]. Stroke is also the leading cause of disability and the third leading cause of death in the US. It was the second leading cause of death worldwide in

1990, killing over 4.3 million people [20]. Cerebrovascular disease remains the fifth leading cause of lost productivity. Therefore, the need to actively and diligently explore therapeutic opportunities and modalities is a public health priority and it will remain so for the foreseeable future.

3. HBO IN ACUTE AND SUBACUTE STROKE

3.1 Experimental Evidence

There is a large body of experimental evidence suggesting that HBO may have a positive impact on the evolution of brain necrosis when provided within 6 hours of acute surgical interruption of the cerebral circulation [2]. However, as with many neuroprotective agents, the promise of experimental work has not been realized in the clinical setting. Three recent articles provide some additional clarification and assist in delineating the possible application of HBO [21-23].

In 2004 Schabitz *et al* ligated the middle cerebral artery (MCA) in 34 rats and performed intermittent magnetic resonance imaging from 90 minutes onward [21]. Two hours after the permanent occlusion, the animals were divided into two groups. Seventeen animals received 2 ata oxygen of 1 hour whereas the others remained in normobaric (room) air. At 120 hours the animals were sacrificed and the brains were stained with 2,3,5, triphenyltetrazolium (TTC) to allow calculation of infarct volume. Immunohistochemistry was performed to evaluate oxidative stress. It was found that HBO reduced the infarct size by 38% ($p<0.001$). Neuroprotection was evident 5 hours after ischemia and the effect was sustained over the 5 days of follow up. Relative regional blood flow was no different between the groups after occlusion. The neurological deficit was less in the HBO-treated animals ($p<0.05$), and there was no significant difference between the parameters for oxidative stress in the two groups at 3.5 and 8 hours. As monitored by MRI, HBO treatment reversed ischemic lesion size between 3 and 5 hours after ischemia; it also achieved a long-lasting neuroprotective effect without significant oxidative damage. This study suggests that 2 ata pO2 for 1 hour, when applied within 2 hours of MCA occlusion, is effective and safe in this model.

A second study by Lou *et al* explored the application of a single HBO exposure in rats with either transient and permanent occlusion of the MCA [22]; the objective was to find an optimal therapeutic window for intervention. Using an intraluminal middle cerebral artery occlusion model (MCAO), the effect of a single HBO exposure (3 ata for 1 hour; provided at 3, 6 or 12

hours post occlusion) was evaluated at 24 hours and 7 days. Treatment within 6 hours had a positive effect on transient lesions, whereas treatment beyond 12 hours was detrimental, both histologically and functionally. HBO appeared to have no effect on permanent occlusions, regardless of timing. In this study, HBO appeared to be highly effective in reducing infarct volume and improving neurobehavioral outcome in transient MCA occlusion within the first 6 hours. HBO at later time points was harmful by increasing infarct volume. In permanent MCAO, HBO failed to improve infarct volume and clinical outcome. This study suggests that transient MCA occlusions, if treated within 6 hours at 3 ata pO2 for 1 hour, may have improved functional and histological outcomes. Later treatments seem harmful, whereas permanent occlusions do not seem to respond to HBO at any time.

Finally Yin *et al* tested the hypothesis that HBO reduces brain infarction by preventing apoptotic cell death in an ischemic cerebral cortex [23]. Sprague-Dawley rats were subjected to middle cerebral artery occlusion/reperfusion (MCAO/R) and were exposed subsequently to HBO (2.5 ata for 2 h) at 6 h after reperfusion. Rats were killed and brain samples were collected at 24, 48, 72 h, and 7 days after reperfusion. Neurological deficits, infarction area, and apoptotic changes were evaluated by clinical scores; 2,3,7-triphenyltetrazolium chloride staining; caspase-3 expression; DNA fragmentation assay; and terminal deoxynucleotidyl transferase-mediated 2'-deoxyuridine 5'-triphosphate-biotin nick end labeling, (TUNEL)-hematoxylin and eosin (H&E) co-staining. DNA damage was observed up to 72 hours but not at 7 days following reperfusion. Apoptosis was also observed at 24, 48, and 72 h after reperfusion. HBO abolished DNA fragmentation and reduced the number of TUNEL-positive cells. HBO also reduced infarct area and improved neurological scores at 7 days after reperfusion. This study suggests that HBO may prevent apoptosis in ischemia-reperfusion of the brain.

In summary, experimental data suggest that HBO is of benefit if provided early, in transient ischaemic lesions; its effectiveness beyond 6 hours is uncertain and possibly harmful.

3.2 Clinical Trials

Many studies and case series have appeared since the first publication by Heyman *et al* in 1966 [4]. However few of these have withstood rigorous scientific review due to various design and methodological flaws and the use of non-standardized outcomes. Three randomized pilot studies have appeared since 1995 that require closer scrutiny [13,24,25].

Nighoghossian outlined the practical aspects and the safety of HBO before also evaluating the effect on long-term disability [24]. Over a period of

3 years 34 patients with middle cerebral artery occlusion were enrolled. All patients were seen within 24 hours of onset and then randomized to receive either HBO or sham (air) treatment. The 17 HBO patients were exposed daily to 40 minutes at 1.5 ata for a total of 10 exposures. The Orgogozo scale was used to establish a pretreatment functional level. Changes in the scale score at 6 months and 1 year after therapy were used to assess the effect of HBO. In addition, the Rankin scale and the center's own 10-point scale were used to assess long term-disability at 6 months and 1 year. There was no significant difference at inclusion between groups regarding age, time from stroke onset to randomization, and Orgogozo scale scores. Two sample t-tests and 95% confidence intervals were used to compare the mean differences between the two treatment groups. Student's two-tailed test was used to compare the differences between pre-therapeutic and post-therapeutic scores at 6 months and 1 year in the two treatment groups. Neurological deterioration occurred during the first week in 4 patients in the sham group, 3 of whom died; this worsening was clearly related to the ischemic damage. Treatment was also discontinued for 3 patients in the HBO group who respectively experienced myocardial infarction, a worsening related to the ischemic process, and claustrophobia. Therefore, 27 patients (13 in the sham group and 14 in the HBO group) completed a full course of therapy. The mean score of the HBO group was significantly better on the Orgogozo scale at 1 year ($P < 0.02$). However, the difference at 1 year between pre-therapeutic and post-therapeutic scores was not significantly different in the two groups ($P < 0.16$). No statistically significant improvement was observed in the HBO group at 6 months and 1 year according to Rankin score ($P < 0.78$) and the center's own 10-point scale ($P < 0.5$). Although the small number of patients in each group precludes any conclusion regarding the potential deleterious effect of HBO, no major complications were observed related to HBO. The authors concluded that it could be assumed that HBO might be safe with an outcome trend favoring those receiving it. This paper has been criticized due to a lack of description of the randomization and blinding process [12]. The treatment arm contained patients with greater disability and fewer males. The statistical analysis has also been criticized for having compared the differences in mean scores rather than changes in baseline disability scores between the two groups.

In a second pilot study by Anderson, 39 patients with cerebral infarction received either hyperbaric oxygen or hyperbaric air in a double-blind prospective protocol [25]. Patients were stratified for severity before randomization. The study was interrupted when there appeared to be a trend favoring the air-treated patients, whose neurological deficits were less severe (mean +/- SEM score on graded neurological examination: air, 25.6 +/- 4.9; oxygen, 34.5 +/- 7.5) and whose infarcts were smaller (air, 29.0 +/- 12.2

cm3; oxygen, 49.2 +/- 11.7 cm3) at 4 months. Although probably a randomization artifact, the investigators chose not to resume the trial as they did not observe any significant effects. They also indicated that it had been difficult to administer HBO by schedule and that the treatment protocol was eventually broken in 15 of the 39 patients. Eight patients did not tolerate the treatment and refused to continue. There were also variable treatment times in the hyperbaric chamber.

The most recent clinical study is by Rusyniak[13]. This randomized, prospective, double-blind, sham-controlled pilot study by a group of emergency physicians evaluated effectiveness, safety, and feasibility of using HBO in acute ischemic stroke. Thirty three patients presenting with acute ischemic stroke were randomized into two groups. One group received 2.5 ata pO_2 for 60 minutes, while the other received 1.14 ata pO_2 as a sham control, in a monoplace hyperbaric chamber. None of the patients had received thrombolytics. Primary outcome measures included improvement at 24 hours (National Institutes of Health Stroke Scale [NIHSS]) and 90 days (NIHSS, Barthel Index, modified Rankin Scale, Glasgow Outcome Scale). Secondary measurements included complications of treatment and mortality at 90 days. Baseline demographics were similar in both groups. There were no differences between the groups at 24 hours (p=0.44). At 3 months, however, a larger percentage of the sham patients had a good outcome defined by their stroke scores compared with the HBO group (NIHSS, 80% versus 31.3%; p=0.04; Barthel Index, 81.8% versus 50%; p=0.12; modified Rankin Scale, 81.8% versus 31.3%; p=0.02; Glasgow Outcome Scale, 90.9% versus 37.5%; p=0.01) with loss of statistical significance in a intent-to-treat analysis. The investigators concluded that although the HBO protocol appeared feasible and safe, it did not appear to be beneficial and could even be harmful in patients with acute ischemic stroke. The study can be criticized for the use of the NIHSS to document outcome. For example, a return of speech would not provide a statistical change in score if associated with hemiparesis. The use of 1.14 ata pO2 could also be argued as being therapeutic rather than a sham treatment. The study also lacks power.

The variable results attained in clinical studies remain vexing. Frequently there appears to be a mismatch between clinical severity, the findings of neuro-imaging and ultimate outcome. This has led some investigators to examine variations in HBO dose; provisional findings do suggest that increasing the number of HBO treatments affects outcome [26]. Others have questioned the appropriateness of using clinical stratification when applying a treatment with specific physiological and pharmacological actions. Those who have used HBO in acute stroke recognize the variability in clinical response to it: dramatic recoveries in some cases and disheartening failures in others – often in patients who present with similar disability profiles. In an

attempt to delineate a possible differential effect, Cronje and Duim collected clinical and neuro-imaging material on stroke patients to evaluate the effect of HBO on the dynamic pathology of an evolving stroke[27]**.** Fifteen patients with acute (<24-hours; n=8) and sub-acute stroke (24 hours to 7 days; n=7) were admitted and treated in the Eugene Marais Hospital Stroke Center. In addition to standard stroke management, these patients received HBO exposures of 1 hour at a pressure of 1.5 ata. Exposures were repeated 8-12 hourly in acute stroke patients and 12-24-hourly in sub-acute stroke patients. The number of exposures were based on response and were continued until two subsequent sessions provided no further objective clinical change – with a minimum of 2 and a maximum of 6 exposures. Evaluations included serial clinical assessments, using the National Institutes for Neurological Diseases Stroke Scale (NINDSS); language assessment; brain MRI – with Diffusion Weighted Imaging (DWI) as indicated; and Magnetic Resonance Angiography (MRA). Twelve of the 15 patients improved significantly during HBO exposures, as defined by sustained improvement in language use, or reduction in NINDSS scores. In addition the response to HBO (or the lack thereof) was compared to data obtained from neuro-imaging studies. The greatest changes were observed in 6 aphasic patients with localized cortical infarcts and intact main arterial supply. However, in four patients, MRI imaging (including Fluid Attenuated Inversion Recovery [FLAIR] and Diffusion Weighted Imaging [DWI]) suggested a poor prognosis, whereas the positive response to HBO suggested a better prognosis, which was eventually realized. Three patients showed no HBO response, and in one of these patients, MRI imaging was negative in the presence of neurological deficit, suggesting a lacunar infarct. Again, absence of improvement with HBO correlated with the ultimate lack of clinical improvement at 3 months. This is the first study to correlate stroke type to the effects of HBO. While firm recommendations cannot be made, analysis of these 15 patients does suggest that HBO may have a differential effect depending on stroke type: HBO appears to be of greater value in focal, cortical infarcts, but less so in large infarcts with persistently occluded main arteries, as well as in recurrent and lacunar strokes. Response to HBO corresponded with the clinical outcome at 3 months, whereas the appearance on MRI did not predict clinical outcome reliably. As in a previous study recommending HBO as a predictor of outcome in intra-extracranial bypass[28], the authors also suggest that HBO may provide useful prognostic information in acute and sub-acute stroke.

In summary, clinical studies remain inconclusive in evaluating the effectiveness of HBO in the treatment of acute and sub-acute stroke.

4. HBO IN CHRONIC STROKE

For many years it has been believed that brain injury is irreversible, that regeneration is impossible, and that the only mechanism for recovery is "plasticity" or functional reorganization. These theories are now being challenged as evidence to the contrary continues to emerge [29-32]. There is also support for the possibility that there may be long-term viability of marginally perfused tissues in the brain; these tissues appear to receive enough oxygen to survive but not to ensure proper electrical function [33,34]. In support of this theory, it has been shown that there is some degree of clinical and EEG-detectable improvement of cerebral activity, even with very late intra-extracranial bypass surgery or HBO therapy [3,5,28,35-39]. Functional imaging (i.e., Single Photon Emission Computer Tomography or SPECT scanning) also suggests changes in cerebral bloodflow and brain metabolism attributable to the application of HBO therapy; several authors suggest that these changes correspond to eventual clinical outcome [33,34,40-62]. Measurements of pO2 in cerebrospinal fluid as well as arterio-venous pO2 differences during HBO confirm the increase in brain oxygenation during HBO, in spite of vasoconstriction [5]; this effect is also confirmed indirectly by clinical oxygen toxicity studies in divers [63,64].

A comprehensive review of studies on HBO in chronic stroke has been published recently[2]. In spite of the significant number of favorable case reports and series suggesting clinical benefit, the lack of a large, controlled study continues to undermine confidence. The only controlled study to date is by Marroni [65]: A total of 80 stabilized thrombotic stroke patients (i.e., they no longer experienced any objective benefits from standard treatment and rehabilitation) were enrolled in a controlled study on HBO and in-water rehabilitation. The study had 5 arms: Group A (n = 11) served as untreated controls; Group B (n = 7) received 30 in-water rehabilitation sessions without HBO; Group C (n = 25) received 30 HBO sessions without rehabilitation; Group D (n = 16) underwent a protocol of 30 HBO2 sessions in the afternoon after 30 in-water rehabilitation sessions in the morning; and Group E (n = 21) underwent a protocol of 30 sessions of simultaneous HBO and in-water rehabilitation sessions in a specially built "hyperbaric swimming pool". All patients were evaluated by means of an original neuro-motor disability scale before entering the protocol; then on day 10, 20 and 30 during the protocol; and again on day 60, 90, and 120 after concluding the protocol. The study showed a distinct HBO-related improvement in all the previously stable complete stroke patients, when compared to the non-HBO controls. Among the HBO treated patients, those who underwent simultaneous HBO and in-water rehabilitation showed significantly better improvement with respect to all the other patients and the improvements

appeared to be stable at 120 days. Although this study is perhaps the most encouraging to date, the practical implications of combining rehabilitation and HBO remain challenging and difficult to generalize. It is also known that objective functional improvements can be achieved through appropriate rehabilitation programmes alone; they may even occur spontaneously at times, sometimes long after the original stroke. This variable natural history, combined with the somewhat subjective outcome measures, continues to confound clinical observations attributed to HBO. These will only be adequately resolved by means of a carefully controlled, randomized, large and preferably multicentric study. Sadly, significant polarity exists amongst those in support and those opposed to this application of HBO; this continues to deny us the benefit of such a consolidated effort. Although promising, the application of HBO for chronic stroke cannot be recommended based on current scientific evidence.

5. CONCLUSION

The role for hyperbaric therapy in the treatment of acute, sub-acute and chronic stroke remains controversial.

In acute stroke, timing, HBO dosage and lack of pathophysiological stratification may be disguising the effectiveness of HBO in a subset of the stroke population. Anecdotally, HBO appears to be most effective in the treatment of small, sub-cortical, non hemorrhagic stroke in which perfusion has recovered early or where the clinical picture undulates – suggesting a functional penumbra. Although feasible and seemingly safe, it is not yet possible to recommend the use of HBO in the treatment of acute and sub-acute stroke based on the scientific evidence available today.

In chronic stroke, the cost of HBO would seem prohibitive – given the prevalence of the condition. However, greater independence and productivity in those successfully rehabilitated may affect the equation in favor of treatment. For the time being, however, this cannot be recommended other than as a promising area for further research.

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Chapter 2.4.3

POST-STERNOTOMY MEDIASTINITIS

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Abstract: Post-sternotomy mediastinitis still represent a major complication of open heart surgery. These nosocomial infections lead to an average mortality rate of 15% to 25%, to an increased duration of hospitalisation and consequently to a higher cost of care. According to its efficacy in the treatment of serious infectious diseases, hyperbaric oxygen (HBO) has been proposed as an adjunctive therapy for many years. A review of the literature consistently shows better clinical outcome and less morbidity in HBO-treated patients compared to conventional treatments. HBO may have a preventative action in avoiding the progression of a localised infection into frank mediastinitis. Despite the absence of consensus regarding its use, HBO must retain a place in the treatment of infected sternotomy

Keywords: open heart surgery, infected sternotomy, nosocomial infection, mortality, morbidity, hyperbaric oxygen therapy

Sternal wound infections are a rare but major complication of open heart surgery after median sternotomy. They can remain superficial, or lead to dehiscence, osteomyelitis, and – in the most serious cases – to invasion of the anterior mediastinum. Despite advances in prevention and management of infectious diseases, acute anterior mediastinitis still represents a life-threatening event and a major cause of morbidity.

1. INCIDENCE, PATHOPHYSIOLOGY, RISK FACTORS

The incidence of this disease[1,2] is estimated between 1% and 5%; some[3] report a higher incidence of 12%, with a rate of 0.8-2.4% for osteomyelitis[4].

The incidence of mediastinitis is variably reported, depending on the definition[5]. A widely used definition takes into consideration either the

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necessity for further surgery (without regard to the results of bacteriological cultures) or mediastinitis – confirmed after wound debridement. In these studies[1,5], the incidence ranges from 0.2% to 3.4% with an average mortality rate of 25%.

Other definitions are based on clinical criteria[6,7] according to the local extent of the infectious process: presence of pus beyond the subcutaneous tissue (whatever the depth of spread); bacteriological results; or necessity for further surgery. This definition includes sternal osteomyelitis[5]; the incidence ranges from 0.6% to 7.0%, and the average mortality rate is 15%.

These post-sternotomy infections are nosocomial; mediastinal contamination generally occurs during the intervention. Three sites are identified as reservoirs of bacteria: the endogenous flora of the patient[8] (e.g., nasal carriage of *Staphylococcus aureus*); the flora of the staff during the intervention[5]; and the operating room equipment[9] (i.e., the environmental reservoir).

Some risk factors[1,2,5,10-14] can be identified according to the different stages of hospitalization:

- Preoperative - obesity, diabetes, chronic obstructive lung disease, age over 60 years, duration of hospitalization.
- Intraoperative - duration of surgery, type of procedure (such as coronary bypass with internal mammary artery grafting)[15], use of bone wax.
- Postoperative - surgical re-opening, mechanical ventilation of more than 48 hours, prolonged stay in intensive care unit.

2. DIAGNOSIS, MANAGEMENT AND CONVENTIONAL TREATMENTS

Early diagnosis is essential to reduce both the seriousness of the infection and the morbidity of acute mediastinitis.

The disease generally begins as an infectious syndrome between the first week and the thirtieth post-operative day. It is associated with sternal pain, either spontaneously (i.e., exacerbated by deep inspiration or cough) and/or induced by palpation of the sternum. The clinical picture is completed by pus emanating from the wound and drains with sternal instability. Septic shock is always a possibility in the most serious cases[16].

Radiological imaging is not necessary to make the diagnosis in most cases. Moreover, standard chest radiography and computerized tomography contribute little due to the surgical distortion of the mediastinum. In difficult cases, technetium or iridium labelled leukocyte scans may assist in delineating the extent of the infection[1,17].

Local bacteriological samples and blood cultures must be performed systematically. The major part of the microbial flora is composed of Gram

positive cocci (especially *Staphylococcus aureus* and *Staphylococcus epidermidis*), with Gram negative aerobes appearing less frequently[1,10,13,18-22]. Blood cultures are positive in 15-60% of cases[1].
Conventional treatment is both medical and surgical.

Antibiotics are the main element of the medical treatment which generally includes two agents with (1) good activity against staphylococci and K.E.S. group bacteria, as well as (2) sufficient penetration into bone and soft tissues. Their prescription will be based on the specific bacterial profile of the environment, and will be modified according to sensitivity results[1,22]. Specific management of septic shock in the Intensive Care Unit, including mechanical ventilation and inotropic support, may be necessary.

Surgical treatment varies according to the different teams and with the seriousness of the disease; it requires scar reopening, debridement, open or closed irrigation and open wound packing[23,24]. Closure of the sternal defect by myocutaneous or omental flaps, and – more recently – vacuum-assisted closure, currently give good results[15, 25-28].

3. HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF ACUTE MEDIASTINITIS

The efficacy of hyperbaric oxygen (HBO) therapy on wound healing processes, and in the treatment of serious infectious diseases, is well known (*see chapters 1.6 & 1.8*).

In the management of infected sternotomy, the rationale for its use is based on its efficacy against microorganisms; its promotion of phagocytic function; and its enhancement of the activity of certain antibiotics[29-31]. Because of its positive vascular effects, HBO is efficiently able to combat local ischemia caused by harvesting the internal mammary arteries. Furthermore, it induces angiogenesis, and promotes fibroblast activity and collagen synthesis, leading to the enhancement of tissue and bone repair.

Literature on this topic includes many discussions of surgical techniques and their results[15,23,25,26] together with a complete lack of consensus about them[32]. In contrast, few publications are consider the medical treatment; and the place of HBO is not clearly defined.
With this in mind, we reviewed the records of 23 patients (18 male), mean age 58 years (27-72) with a history of median sternotomy infection after open heart surgery, who were treated in our centre between 1988 and 1999. All underwent initial wound care or re-operation prior to HBO. Cases of mediastinitis were defined according to the Centers of Disease Control (CDC) criteria[7]. Thus, two pictures were identified at the admission:

- Mediastinitis (group 1) - 14 patients presented with sternal pain, purulent discharge through the scar or drains and spontaneous sternal instability. The re-intervention consisted of re-opening the sternotomy, cleaning the anterior mediastinum and open or closed irrigation. The surgical findings were of sternal osteomyelitis in four patients and mediastinal abscess in ten.
- Potential mediastinitis (group 2) - Nine patients presented with swelling and/or a purulent discharge through the scar without sternal instability. The surgical treatment included scar re-opening, pre-sternal debridement and sub-cutaneous abscess drainage.

The therapeutic protocol included surgical, medical and HBO treatment. Antibiotic therapy was instituted from the first clinical manifestations or immediately after secondary surgery, and included – depending on policy at the time – two or three agents effective against staphylococci and gram negative bacteria. Patients were re-examined daily, and wound care or debridement was repeated as needed. HBO was started as soon as possible after the first re-intervention. Each patient underwent a session of 90 minutes at 2.5ATA with 100% oxygen (twice daily in group 1, once daily in group 2) for a minimum of ten consecutive days. The hyperbaric treatment was continued until sterilization of the lesions was confirmed by negative bacteriological cultures, resolution of fever and leukocyte counts, and local improvement verified by both the hyperbaric and surgical teams.

Overall results showed an average delay of 12 days between sternotomy and the first re-intervention (range: 4-35 days). The average number of HBO sessions per patient was 18 (range: 10 to 40). Systemic sepsis (temperature >38°C, leukocyte count >10giga/L) was identified in ten patients. Complete recovery was achieved in 22 patients at the time of discharge from the Hyperbaric Medicine centre; one patient died.

Comparing the groups, a higher mean number of HBO sessions was performed in group 1 than in group 2: Twenty-one (range:10-40) and 12(range: 10-30) respectively. This prolonged treatment corresponded to the time needed to achieve sterilization of the deep infectious focus, together with satisfactory healing.

Wound infection occurred after coronary artery bypass with internal mammary grafting in 16 patients (10 in group 1), and after a valvular procedure in seven. The risk of post-operative infection due to sternal ischemia generated by internal mammary harvest is revealed in these series, especially in group 1. A greater incidence of Staphylococcus aureus, notably including one methicillin-resistant and one coagulase-negative

staphylococcus, was identified in group 1 (Table 1). In addition, this group included the ten patients presenting with sepsis syndrome (all of them in the mediastinal abscess subgroup). One patient died in group 1; the multiple organ failure which caused the death, two months after admission, was not attributable to continuation of the infectious process.

These data correlated with the surgical findings, underlining the severity of group 1 compared with group 2 and emphasising the contribution of HBO in the treatment of clearly diagnosed mediastinitis.

Table 2.4.3-1. Tissue culture and markers of infection

	Group 1 (14 patients)	Group 2 (9 patients)
No pathogen	6	5
Staph. aureus	5 (1 meti-R)	2
Coag. neg. Staph..	1	
Enterococcus	1	
Serratia		1
Enterobacter	1	
Pseudomonas aeruginosa		1
Mean leukocyte count	11,2 giga /l	9 giga /l
Mean temperature	38,3	37,4

Two previous studies performed in our centre, in patients with infected sternotomy wounds after cardiac surgery, reported the following data:

Bianchi[18] studied 38 patients (19 wall suppuration, 19 with obvious mediastinitis). The average delay before the first surgical re-intervention was twelve days. Nine patients with obvious mediastinitis yielded a positive blood culture, four of which were due to Staphylococcus species. The mean number of HBO sessions was 19. Complete recovery was obtained in 36 patients. Of the patients with mediastinitis, two died (one due to persistence of the infection).

In the second study, Langlet et al.[20] treated 43 patients (17 with sternal wall infection; 26 with mediastinitis). Complete healing was achieved in 39 patients. Four patients who presented with mediastinitis died from cardiac failure.

Few other authors reported their experience in the treatment of post-sternotomy wound infections.

Botta et al.[13] performed a retrospective study on 19 patients (eleven superficial localized infections and eight sternal instability) all treated with HBO and surgery. Total recovery was obtained in all patients and mean hospital stay was shorter as compared with other series where HBO was not used.

Riddick[33] compared two series of two groups of patients. In a first group of 14 patients with acute infection and dehiscence, seven patients underwent conventional treatment versus seven with adjunctive HBO. Another group of 13 patients (five conventional versus eight with HBO), presenting with delayed infection, was studied in the same way. No patient died. The results were shorter hospital stays, less morbidity, and cost savings in the HBO groups.

Hencke et al.[4] reported a case of a woman who developed a severe sternal osteomyelitis after emergency myocardial revascularisation. After 63 HBO sessions, complete healing was obtained without surgical re-fixation.

In a patient who presented with serious delayed mediastinitis after heart transplantation, Petzold et al.[34] obtained complete recovery after 40 HBO sessions.

Siondalski et al.[35] treated 55 patients. HBO sessions (20 to 40) were performed before and after surgery. Total recovery occurred in all patients.

4. DISCUSSION

Surgical techniques, widely reported in the literature[12,15,23,26], still lead to a failure rate of 12-33%[4,19].

With respect to infected sternotomy and conventional treatments, all emphasize an extension of the duration of hospitalisation and consequently a higher cost of care compared with non-infected patients[36-41]. Adjunctive HBO, owing to the better improvement rapidly obtained, may be able to reduce this duration[13,33,35], the nursing workload, and morbidity, as well as offering cost savings[33].

Comparison between the data of the different studies is difficult because the evaluation criteria of mediastinitis are not always reported in the same way. On the one hand, superficial infections or wall abscess always produce complete resolution without any difference according to the literature whether HBO is used or not[14,25]. On the other hand, acute mediastinitis compromises the risk of mortality through the occurrence of complications which are often interlinked: decompensation of the heart, septicaemia, multi-organ failure. In such a disease, despite advanced antibiotics, intensive care and surgical treatment, literature with classical methods and whatever techniques[5,12,20,25,42,43], reports a mortality rate ranging from 10% to 39% with conventional treatments. This rate remains almost unchanged because open heart surgery is currently more often performed in patients presenting with risk factors[5]. Nevertheless, although care must be taken in drawing conclusions because the series are rather small, all the studies including HBO report a lower mortality rate[18,20].

5. CONCLUSION

Published data about HBO show that the risk of mortality and morbidity of these superficial and deep post-sternotomy infections can be improved by this technique added to surgical and medical care. However, at this time and contrary to previous recommendations[44], post-sternotomy mediastinitis is not a recognised indication for HBO because the latest publications on the topic are uncontrolled studies with no consensus expert opinion[45].

Even if the low frequency of the disease partly explains this conclusion, HBO must retain a place in the treatment of infected sternotomy. The consequences of nosocomial complications justify active research into their prevention, as well as into the reduction of the costs of treatment; their economic impact could certainly be limited by the use of HBO.

Moreover, HBO can play an important role in the prevention of this disease; and its use from the first clinical manifestation could avoid the progression of limited infection into frank mediastinitis.

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Chapter 2.4.4

SICKLE CELL DISEASE

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Abstract: Sickle cell anemia, an autosomal recessive disease, is consecutive to the presence of high concentration of hemoglobin S. This induce a distortion in the red cell shape and a marked decrease in its deformability which leads to vaso-occlusive accident. HBO has been proposed because of its actions on ischemic tissue, on red blood cell deformability, on cell adhesion and activation. Potential HBO indications may include vaso-occlusive crisis, ocular complication and chronic leg ulcer, but clinical studies are still lacking to issue a positive recommendation

Keywords: Sickle cell anemia, hemoglobin S, vaso-occlusive crisis, chronic leg ulcer

Sickle cell anemia (SCA) is an autosomal recessive disease. Eight percent of the black Americans are heterozygous carriers of hempglobin S. 0.2% of them are homozygous and have sickle cell anemia[1,2]. The most serious and painful complication of the disease is the vaso-occlusive crisis (VOC). Although numerous attempts have been made to identify specific therapies, SCA remains a painful disease with unpredictable acute events. Mortality is higher in the SCA population than in the black population without SCA; and life expectancy is 25-35 years shorter. The median age of death for men is 42 years and for women it is 48 years[3]. Hyperbaric oxygen therapy (HBO) is actually not recognized as a treatment modality against the deleterious clinical consequences of SCA. However, clinical observations and pathophysiological findings have led us to conclude that this therapy should be evaluated for this indication. Diggs was the first to suggest in 1965, that the use of HBO could be useful in sickle cell disease (SCD)[4].

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 577–584.

1. PATHOPHYSIOLOGY OF SCA

Sickle cell anemia is consequent upon the presence of high concentrations of hemoglobin S in erythrocytes. Hemoglobin S is produced because of the mutation of one codon in the gene of the β-globin subunit, resulting in the replacement of β6-glutamic acid by valine. The accumulation of very high concentrations of hemoglobin (32 to 34 g/dL) into red cells requires that the protein be extremely soluble. Deoxygenated sickle hemoglobin results in a hydrophobic interaction with other hemoglobin molecules triggering an aggregation into large polymers. There is distortion in the shape of the red cell and a marked decrease in its deformability. These rigid cells are responsible for the vaso-occlusive phenomena which are the hallmark of the disease. Perfusion abnormalities have been documented by several techniques. Cutaneous flow as measured by laser Doppler velocimetry shows a delayed time to peak flow and longer time for flow to return to baseline[5,6]. Vascular perfusion of the lower limbs during exercise has been determined by clearance of Technetium-99m[7]. Perfusion was increased at rest; but with exercise, both clearance and peripheral vascular reserve were reduced.

The rate and extent of polymer formation depends on three independent variables - the degree of intracellular deoxygenation, the intracellular hemoglobin concentration and the presence or absence of fetal hemoglobin. This polymerization is extremely effective and leads to very large polymers. Growth and alignment of the polymers have a critical role in perturbing the structure and the function of the membrane in homozygous (SS) red cells. Polymerization of hemoglobin induce membrane damage and hemolysis. Sickle cells become dehydrated because of K^+ and Cl^- cotransport and Ca^{2+} activated efflux. The first has a major role in cell dehydration not only in SS erythrocytes but also in individuals with CC and SC diseases[8]. This leads to major potassium and water loss.

The rate of polymerization is probably overestimated ex vivo. If polymer formation were at equilibrium at the oxygen tensions in the microcirculation, all cells would contain polymer. The resultant marked decrease in deformability would lead to generalized vaso-occlusion and death. Hemoglobin F inhibits polymerization; and the solubility of a mixture of equal amount of hemoglobin S and F is twice that of hemoglobin S alone.

Another important factor of polymerization is transit time in the microvasculature[9]. Factors which increase that time contribute to polymerization. One mechanism of increased red cell transit time is molecular interaction with the endothelium. There is an increase of the expression of adhesion molecules on erythrocytes (α4β1, CD36)[10] and endothelial cells (VCAM1, CD36)[11].During VOC, there is an increase in the number of circulating endothelial cells, an increase in endothelial cells

activation as confirmed by increased ICAM-1, VCAM-1, E-selectin and P-selectin levels[12]. Sickled red cells can also induce endothelial genes encoding endothelin-1, a potent vasoconstrictor[13]. A second mechanism could be the activation of the coagulation system which has been demonstrated in central nervous system vessels[12,14] and in the lungs[15,16]. Activation of platelets inducing secretion of thrombospondin[17] and very high molecular weight von Willebrand factor may contribute strongly to adhesion.

High granulocyte counts are a risk factor for death in SCA[3]. Granulocytes interact with sickle cells and endothelial cells. They are then stimulated and release injurious cytokines[18,19].

Recent studies have suggested a role of nitric oxide during VOC. Altered NO production could contribute to the pathogenesis of acute lung injury[20].VCAM-1 upregulation induced by hypoxia is not counterbalanced by the production of cytoprotective mediators, including NO. Addition of NO donors is able to counterbalance the VCAM1 upregulation observed during VOC, with concomitant inhibition of VCAM1[21]. In another study, an inverse relation was found between subjective pain score and NO metabolites in patients with VOC[22]. Lack of NO and imbalance between VCAM-1 expression and NO synthesis seem to be characteristic of VOC .

2. CLINICAL FEATURES OF SICKLE CELL DISEASE

Sickle cell disease is a chronic condition punctuated by unpredictable acute events which shorten life. Patients experience acute episodes of severe pain in the chest, back, abdomen, or extremities, known as crises. The episodes last for days or even weeks. Stroke occurs in about ten percent of patients in childhood. Silent central nervous system damage with cognitive impairment occurs in between five and nine times as many patients. Acute lung injury is a frequent (40% of all patients) and sometimes fatal complication of the disease. It is most common but least severe in children and can lead, when recurrent, to chronic respiratory insufficiency. Other complications include osteonecrosis, osteomyelitis, infectious complications secondary to splenic sequestration, complications of acute and chronic anemia, leg ulcers in homozygous SS patients, priapism, cholelithiasis, proliferative retinopathy and renal insufficiency. Episodes of pain are sometimes triggered by infection, extreme temperature, or physical or emotional stress.

3. HBO AND SICKLE CELL ANEMIA

3.1 Rationale for use of HBO in SCA

Oxygen transport is impaired in sickle cell patients because hemoglobin S has a lower affinity for oxygen than hemoglobin A. The P50 of hemoglobin S is higher; and the mild hypoxemia found in sickle cell anemia is related to a low oxygen saturation and a low oxygen arterial content. Sickling is also responsible for chronic and acute episodes of anemia. Cutaneous hypoperfusion leads to leg ulcers difficult to heal using conventional treatment. HBO could be useful in a situation with diminished oxygen transport and ischemia.

The most interesting feature of the action of HBO is the analysis of its cellular effects. Recent studies showed a potential contribution through NO production by the neuronal NO-synthase to the neurological toxicity of HBO[23]. Regional cerebral blood flow (rCBF) decreases during HBO exposures, but as exposure time is prolonged, NO production increases and augments rCBF in anticipation to neuronal excitation. The neuronal excitation is mediated by the N-methyl-D-aspartate (NMDA) receptor; and its inhibition prevents EEG spikes[24]. HBO is also able to stimulate inducible NO synthase in the endothelial cells of the trachea, leading to an increase of plasma exudation. In another model, Kurata demonstrated that HBO was able to reduce cytostatic activity, peroxynitrite synthesis and transcription of iNOS mRNA of mouse peritoneal macrophages stimulated with lipopolysaccharide and gamma-interferon, reducing its cytostatic activity. This could be a beneficial effect of HBO by decreasing the deleterious effects of cell adhesion and activation. In an endothelial ischemia-reperfusion model, a recent study demonstrated that HBO was able to downregulate the expression of ICAM-1 through the induction of endothelial NO synthase (eNOS)[25]. This finding could be very interesting because eNOS is known to be beneficial in most experimental models. Downregulation of ICAM-1 could have a beneficial effect in VOC.

3.2 Clinical applications

HBO has been used in three complications of sickle cell disease: painful vaso-occlusive crisis, ocular surgery in sickle cell patients, and leg ulcers of the homozygous (SS) patients.

3.2.1 Vaso-occlusive crisis

Results of using HBO in acute painful crisis are controversial. Old studies reported a lack of improvement in six patients treated with a 30-60 minutes session of HBO[26]. Laszlo reported two patients with VOC without clinical improvement after a one hour session despite a marked decrease in the number of circulating sickle cells[27]. Cœur reported successful treatment of two patients with painful limb VOC resistant to usual therapy[28]. Reynolds reported a success in one patient with abdominal VOC on four different occasions[29]. In another study of 24 episodes of VOC including 13 limb crisis, 7 patients (29%) had a good response to HBO[30]. Two patients relapsed after a single session of HBO.

We retrospectively reviewed our results between 1990 and 1994. We analyzed the results of 17 sessions for 15 patients with VOC. Patients were homozygous (SS) in twelve cases, heterozygous with associated hemoglobin C (SC) in four cases, heterozygous (AS) in one case. The last patient had an abnormal hemoglobin called S "Antilles" migrating in the same range as hemoglobin A. Pain relief or decrease was obtained in twelve cases (74%) after the first HBO session (2.2ata, 90 mn). Pain localization was in the chest (four cases), the abdomen (four cases), the limbs (eleven cases), the spine (two cases). Patients underwent a mean of 4±4 (SD) sessions of HBO. Three patients who had the session less than 24 hours after onset of the VOC were discharged from the hospital less than 24 hours after a single HBO session. One patient relapsed after a single session.

3.2.2 Ophthalmology

An experimental study of sickle cell hyphema showed the ability of HBO to raise aqueous humor partial pressure values and to decrease the sickling of erythrocytes[31]. HBO was also successfully reported to avoid ischemia of the anterior ocular segment, which is a frequent complication of ocular surgery in sickle cell patients[32].

3.2.3 Chronic leg ulcers

Fifteen patients received HBO because of chronic leg ulcers. Healing was always obtained. All were homozygous (SS) patients. They underwent a mean of 11±9 sessions (one patient with skin graft underwent 35 sessions). Relapses occurred in eight patients.

In our experience, the only adverse effect was seizures, which occurred twice.

4. THERAPEUTIC PROTOCOLS AND FUTURE RESEARCH DESIGN

Although therapeutic protocols remain to be more precisely determined by further studies , some principles arise from the previous reports.

4.1 Patient care

The cardiac function of the patient should be evaluated before HBO. An epidemiological study of the heterozygous military recruits carrying the sickle cell trait (AS) who participated in basic training – an especially harsh conditioning experience – showed an incidence of sudden death 20 times that of recruits with normal hemoglobin[33]. Chronic anemia can also have long term consequences on cardiac function. The risk of seizure is inherent to sickle cell patients even without a past medical history of stroke because of the silent central nervous system damage which frequently occurs in this disease. Pre-medication could be useful to avoid this complication. A good explanation of the HBO session should be made in order to avoid emotional stress, which can intensify the symptoms.

4.2 Indications

Reports have been made on the management of painful VOC and leg ulcers. However, well designed studies remain to be conducted. HBO might also be evaluated in osteonecrosis.

4.3 HBO sessions

In the previous reports pressure varied between 2 and 2.5ata.. Pressure should be as low as possible in order to limit the risk of neurological oxygen toxicity. Pressure variations (compression and decompression of the chamber) should be done slowly to avoid extreme temperature variations. Episodes of relapse[30] suggest that a single session is insufficient.

4.4 Goal and endpoints

Pain is the most serious symptom of vaso-occlusive crisis. The use of HBO as the single analgesic therapy is ethically impossible. HBO can be associated with patient controlled analgesia and its efficacy evaluated by patient drug consumption before and after the HBO session. In the hypothesis of endothelial mediation of pain, this should be evaluated over several hours and not only immediately after the HBO session.

Among the biological data, the degree of hemolysis can be evaluated by the plasma total and free bililirubin concentrations, the lactate-deshydrogenase (LDH) concentration. Other studies have also measured circulating endothelial cells (CD36+). In experimental models, ICAM-1 and VCAM-1 expression levels, and eNOS, and NO metabolites should be measured. The ratios between NO and ICAM-1, NO and VCAM-1, also needs to be evaluated.

5. CONCLUSION

Patient afflicted with sickle cell anemia should benefit from HBO during acute phases of their disease. Fundamental research has helped us better to understand the pathophysiology of this complex disease. The most recent studies have led us to conclude that well designed studies on experimental models are necessary, and that clinical studies are now ethical.

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Chapter 2.4.5

BRAIN INJURY AND SPINAL CORD INJURY

From experimental to clinical evidence

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Abstract: There has been several evidence based review on the use of HBO in Spinal cord injury and in head injury. All come to the conclusion that there is good experimental evidence showing that HBO has potential in the treatment of SCI and HI. Unfortunately, there are only few low quality RCT's using different treatment regimens and reporting conflicting results. The best points out to the necessity of good quality RCT including: systematization of dosage for HBO (duration of session, pressure used, total number of sessions); careful recording of adverse effects in order to prove that HBO – including transportation to the chamber – does not worsen the patient's condition

Keywords: Hyperbaric oxygen, brain injury, spinal cord injury

1. INTRODUCTION

The manifestations of head injury (HI) and spinal cord injury (SCI) are clinically very variable. Lesions depend on the duration and intensity of trauma. Immediate treatment is directed towards surgical decompression, hemostasis, fracture stabilization and – if possible – prevention of reperfusion injury. The effect of HBO on reperfusion injury (I/R) has been well investigated (*see chapter 1.7*). This seems to apply also to I/R in the spinal cord and the brain. Naidu et al[1] for instance have shown that medullar ischemia increases the expression of ICAM-1 and that its inhibition reduces the extension of medullar I/R injury and they therefore recommend therapies aimed at reducing the expression of ICAM-1. Within the spectrum of I/R injury to tissues in general and in brain or spinal cord tissue in particular, two type of cell death have to be considered: necrosis and apoptosis[2]. Many substances have been investigated in animal models, all showing significant

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 585–590.

effects in the prevention of I/R injury. So far these have only been successful when applied prior to ischemia.

2. EXPERIMENTAL EVIDENCE

2.1 Spinal cord injury

The early application of HBO reduces the number of apoptotic cells one day after traumatic SCI[3]. This effect is thought to be due to a down regulation of inducible nitric oxide synthase (iNOS) gene by HBO. In a rabbit model of motor neuron damage, a single one-hour HBO exposure applied after 30 minutes from ischemia could salvage a significant number of motor neurons from delayed death. Neurological outcome was also improved. HBO had no effect if applied after 6 hours of ischemia[4].

2.2 Brain injury

Li et al[5] found an increased apoptosis with massive cell necrosis in the hippocampus region in a rat model of global ischemia-hypotension. HBO was able to reverse this effect, probably by a direct effect on multiple apoptotic genes. In another model of focal ischemia, Yin et al showed that early HBO abolished apoptotic DNA damage of cerebral ischemic cells. This effect correlated with a smaller infarct size and better neurological outcome[6]. In a model of beagle cardiac arrest, Rosenthal also found an improvement in cerebral necrosis with a good correlation for neurological outcome if HBO was applied within one hour of cardiac arrest[7]. In a model of standardized severe cold trauma- induced brain injury, Niklas et al found smaller areas of brain necrosis, brain edema ($p<.005$), and reduced mortality with 3 HBO sessions in 48 hours[8]. Intra-tissue pO2 increased with the number of sessions. It could also be shown that one HBO session was able to restore the damaged mitochondrial REDOX potential in injured brain 4 hours after injury[9]. Palzur et al[10] has shown in a vacuum model of brain injury that HBO significantly diminishes the extent of secondary brain damage by reducing the extent of apoptosis in cortical neurons.

3. CLINICAL EVIDENCE

3.1 Spinal cord injury

3.1.1 HBO as a treatment adjunct

There are only few prospective studies on the treatment of SCI. One of them has shown a better outcome with the use of high dose of methylpdrednisone[11]. No prospective studies involving HBO have yet been done. Gamache[12] compared the outcome of 25 SCI patients treated with HBO (within 7.5 hours after trauma) and patients treated without HBO during the previous years. HBO allowed a faster recovery but no difference in outcome after one year. Sukoff, as quoted in Jain[13], treated 15 patients with an intensive protocol of 4 to 5 HBO sessions per day during 4 days. Sukoff felt that patients treated within 6 hours of injury showed better motor improvement. Recently Asamoto et al published a report on the effect of HBO on acute hyperextension traumatic cervical spinal cord injury without bone fracture[14]. The authors selected this subtype of acute spinal cord injury in order to avoid as much as possible inter individual variation of lesions and symptoms. Patients were assessed using the Neurological Cervical Spine Scale and American Spinal Injury Association (ASIA) scales. Three quarters (75.2%) of 13 patients receiving HBO improved (range: 25% to 100%) and 65.1% of 21 patients who did not receive it improved (range: 25% to 100%). This improvement was significant. HBO was applied at a pressure of 200 kPa (2 ATA) for 10 sessions starting within 25 hours of trauma. These results have to be interpreted cautiously due to the small number of patients and due to the retrospective nature of the study. Several older retrospective studies also report improvement with HBO.

3.1.2 HBO as a tool to assess late outcome in spinal cord injury

HBO has been suggested as prognostic tool in SCI. Ishihara et al[15] applied HBO to 22 patients with various grades of neurological and functional impairment after SCI. They compared the clinical in-chamber status during a single HBO session held within 10 days of injury (range: 1 to 33) according to the Frankel grading and to the ASIA score. HBO improvement was assessed as being either excellent, good, fair or poor. If the patient's response during the HBO trial was excellent, it was found later that this patient had a better outcome than patients whose reaction to the HBO test was poor. Comparing the HBO response to the ASIA or Frankel grading,

they found a better prognostic reliability using HBO at 6 (range: 2 to 9 years) than with the Frankel and ASIA grading system.

3.2 Brain injury

3.2.1 HBO as a treatment adjunct

Artu et al[16] studied the effect of HBO in 60 coma patients from head injuries. HBO neither improved mortality nor clinical outcome at one year except for a subgroup of young patients with brain stem lesions. Rockswold et al[17] did a RCT on 186 patients to assess the effect of HBO on the outcome of severe closed head injury. They found a statistically improved survival with HBO but no difference in clinical outcome. Trying to find an optimal treatment dosage, they suggested that short but multiple daily treatments might improve the efficacy of HBO[18]. Shi et al[19] assessed the effect of 2 to 4 HBO sessions in a RCT involving 320 patients. They found that with HBO there was a significantly better outcome in clinical symptoms; better control of epileptic sequelae; and less hydrocephalus. The improvements were confirmed in serial Pc ECD SPECT scans. Several retrospective studies[20-22] have also reported improved outcome with HBO.

4. CONCLUSIONS

There have been several evidence based reviews on the use of HBO in SCI and HI[23]. All come to the conclusion that there is good experimental evidence showing that HBO has potential in the treatment of SCI and HI. Unfortunately, only few RCT's have been completed. These are of low quality use different treatment regimens and reporting conflicting results. The best one[24] points out to the need for good quality RCT's including systematization of dosage for HBO (duration of session, pressure used, total number of sessions), and careful recording of any adverse effects to prove that HBO, including transportation to the chamber, does not worsen the patient's condition.

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Chapter 2.4.6

MYOCARDIAL INFARCTION

From experimental to clinical evidence

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Abstract: Acute myocardial infarction even if treated with a short time delay carries the classical problem of reperfusion injury. There is experimental and animal studies presenting grade 1 level evidence that hyperbaric oxygen (HBO) can reduce the extent of myocardial necrosis. Two different reperfusion modalities – one using thrombolysis and the other percutaneous coronary intervention combined with a single session of HBO – have shown a beneficial effect

Keywords: Hyperbaric oxygen, acute myocardial infarction, percutaneous coronary intervention, thrombolysis, reperfusion injury

1. INTRODUCTION

Acute myocardial infarction (AMI) occurs due to a sudden interruption of the coronary circulation. Due to the specific anatomy of coronary arteries, this interruption leads to myocardial ischemia and – if this is not rapidly treated – to myocardial death. Depending on the duration of ischemia, restoration of coronary circulation may aggravate the pre-existing myocardial damage.

2. PHYSIOPATHOLOGY AND CONSEQUENCES OF REPERFUSION INJURY ON THE HEART

The general mechanism of ischemia-reperfusion injury has been described in Chapter 1.7. After temporary coronary occlusion, reperfusion of previously ischemic tissue may remain incomplete within the cardiac

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microvasculature, despite complete reopening of the epicardial artery. This "low-" or "no reflow" phenomenon is characterized by decreased basal myocardial blood flow, ultra structural vascular alterations, and distinct areas of hypoperfusion evolving to myocardial necrosis with clinical correlations of: (1) extension of myocardial ischemia; (2) decreased cardiac output; (3) cardiac insufficiency, and (4) even death. Regardless of the duration of ischemia, the impairment in microcirculation can acutely worsen the regional myocardial circulation and thus the size of myocardial necrosis for as long as 2 hours[1] and this defect may persist for as long as one month[2]. The latter impairment can be reversed with HBO at least one week after AMI, as evidenced by Thalium scintigraphy[3].

3. CURRENT THERAPY

The treatment of AMI is mainly based on percutaneous coronary intervention with uncoated stents, thrombolysis or coronary artery grafting[4]. With the advent of new stents such as paclitaxel- and sirolimus-coated stents, further improvements have been made. The rate of major adverse cardiac events (MACE) at 6 to 9 months for the new coated stents now ranges from 4%[5] to 16%[6] and the rate of significant restenosis at 6 to 9 months ranges from 5%[7] to 11%[8].

4. WHY HYPERBARIC OXYGEN IN AMI

As seen in animal studies, HBO can reduce the extent of reperfusion injury in various organs subjected to reperfusion after a certain time of ischemia: intestine[9], testicle[10], liver[11], and brain[12]. AMI is a typical situation where acute HBO could be used with the intention to stop or reduce the harmful effects of reperfusion.

5. EXPERIMENTAL STUDIES

Stearling[13] et al have first shown in an open chest rabbit model of the left coronary, that HBO applied within 30 minutes of reperfusion could rescue 91.2% of the expected infarct area when compared to controls. Thomas et al[14], combining thrombolysis with plasminogen and HBO, achieved up to 96,9% myocardial rescue. According to Kim et al this could be due to

catalase induction by HBO[15] which could paradoxically reverse the stunning effect of free oxygen radicals introduced by tissue revascularization.

6. CLINICAL STUDIES

6.1 HBO and thrombolysis

Vhalvovic et al[16] used a single HBO in stable uncomplicated AMI and found a decreased CPK and a decreased wall motion score index as indicators of decreased myocardial necrosis compared to controls. Unexpectedly, diastolic filling was not improved by HBO, but this conclusion should be made with caution considering the small size of the study and because more complicated AMI – a group who may have derived greater benefit from the intervention -- were excluded. Dekleva et al[17] also used a single HBO session in stable uncomplicated AMI. HBO was started between 5 and 15 hours following thrombolysis. They found significant stabilization in end diastolic volume compared to controls (-8%); significant improvement of ejection fraction -- and increase of 4% compared to a 0.5% reduction in the controls and a significant decrease in the end-diastolic index (-12% vs. 6%) as compared to controls. Changes happened within the very first days following treatment. CPK was decreased by 35% compared to controls. Stavitski et al[18] did a similar study and found 7.5% decrease in CPK and a 5% improvement in left ventricular ejection fraction.

6.2 HBO and Percutaneous Coronary Intervention

Sharifi et al[19] used two HBO treatments immediately following, and then 18 hours after, successful Percutaneous Coronary Intervention (PCI) with uncoated stents for AMI or unstable angina pectoris. They found significant improvement in MACE (4% vs. 35%) and reduced rate of restenosis (4% vs. 24%) compared to controls at 8 months. This result is within the same range as actually found for in PCI using coated stents without HBO.

7. CONCLUSIONS

Bennet et al[20] did recently a review on the use of HBO in acute coronary syndrome. In their discussion, the authors state that HBO could have a role to play in the treatment of AMI by reducing the rate of MACE, dysrythmias and time to disappearance of precordial pain. They conclude however that

evidence is not sufficient and that large multicentre trials are needed to better assess the role of HBO. Considering the high cost of coated/drug-eluting stents[21], two HBO sessions, combined with an uncoated stent could be a more cost effective alternative if its efficiency can be proven.

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Chapter 2.4.7

MALIGNANT OTITIS EXTERNA

From experimental to clinical evidence

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Abstract: Malignant otitis externa is nowadays still a potentially fatal disease. Hyperbaric oxygen has been used as an adjunct for more than 20 years. Unfortunately only case reports about this subject have been published. Due to the rarity of this disease, only a multi-center randomized study is likely to show whether HBO can be of help in malignant otitis externa

Keywords: Hyperbaric oxygen, malignant otitis externa

1. INTRODUCTION

Malignant (necrotising) external otitis (MOE) is an invasive infection of the external auditory canal. Although elderly patients with diabetes remain the population most commonly affected, immunosuppressed individuals (e.g., HIV, chemotherapy, etc.) are also susceptible to malignant external otitis. *Pseudomonas aeruginosa* is isolated from the aural drainage in more than 90% of cases. Treatment consists of prolonged administration (up to 8 weeks) of an anti-pseudomonal agent (typically an oral quinolone). With the introduction and widespread use of both oral and topical quinolones, there are reports of less severe presentations of malignant external otitis and even the emergence of ciprofloxacin resistance. With aggressive treatment the mortality rate from this disease – which used to be 50% in the past – has now been reduced to 10-20%[1].

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 597–599.

2. EXPERIMENTAL EVIDENCE

There is no experimental model of MOE. It is well known experimentally that HBO acts directly as an antibiotic on certain microorganisms and indirectly through enhancement of the natural host defenses (*see chapter 1.6 for more details*). In the particular setting of MOE, HBO has been shown to have a bacteriostatic on *P. aeruginosa* at pressures greater than 150 kPa[2]. Further aminoglycosides[3] and antimetabolites[4] are more effective in the presence of HBO.

3. CLINICAL EVIDENCE

There are no prospective studies on the use of HBO in the treatment of MOE. Several case reports and retrospective series were identified: Bath et al[5] cured one case of MOE with involvement of the optic nerve. The patient, who was deteriorating, started to improve once HBO was added to treatment regimen. Gilain et al[6] had a similar experience with a case involving the facial nerve. The same applies to Shupak et al[7] who treated 2 patients with facial and skull involvement. Their patients, who were continually deteriorating, improved only when HBO was added. The report of Pilgramm et al[8] is also interesting. He treated successfully four cases; among them, one was cured using only HBO due to the patient suffering from multiple drug allergies. Davis et al[9] treated 16 cases with MOE. Amongst them were 6 with a severe presentation. Thirty HBO sessions were applied. All patients healed without relapse within 1 to 4 years of follow up. Martel et al.[10] treated 22 patients with MOE as inpatients. Treatment was by means of cephalosporins and/or quinolones and, in 10 cases, with an average of 15 HBO treatments at 250 kPa. The authors stated that the efficacy of HBO in their patients was difficult to assess due to the high efficacy of the newer antibiotics now making HBO less necessary. Tisch et al[11] reported finally their experience in the largest retrospective study on 22 patients treated with surgery, antibiotics, immunoglobulins and at least 20 daily sessions with HBO at 250 kPa. Relapse rates at 5 years were 27%. According to the authors the best effect was due to the specific use of anti-pseudomonas immunoglobulins.

In view of these results, it can be stated that despite the fact that there is good experimental in vitro and in vivo evidence for the use of HBO in the treatment of infectious diseases, there are only anecdotal cases of its clinical efficacy in MOE. Due to the rarity of the disease, a multi-centre RCT seems to be the only way to gain more evidence on the effect of HBO in MOE.

Such a study will however require a large number of patients due to the fact that quinolones and cephalosporines are highly efficient.

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Chapter 2.4.8

OTHER CONTROVERSIAL OR NON INDICATIONS

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Abstract: The use of HBO has been investigated in a number of diseases such as cerebral palsy and multiple sclerosis. Uncontrolled publications with weak levels of evidence have sometimes suggested a positive effect of HBO. However, thoroughly done RCT did not show any effect on the course of diseases or such studies have not been performed. It must be considered that HBO has no effect and can only be deleterious in these conditions

Keywords: Hyperbaric oxygen, multiple sclerosis, cerebral palsy, facial palsy, Crohn's disease, interstitial cystitis, retinitis pigmentosa, migraine, sport injury

1. CEREBRAL PALSY

Montgomery et al.[1] did first an observational study on the effect of HBO on cerebral palsy. They found an overall improvement of 5% gross motor function independently of the pressure used. Despite its poor level of evidence, basing only on Montgomery's publication as well as on uncontrolled Internet claims, HBO has been increasingly used in the last years to treat children with cerebral palsy. In order to gain more clarity on the effect of HBO, a multi-centre RCT study was finally done in 2001. After enrolling 111 children with cerebral palsy they were randomly assigned to two groups of treatment, one with HBO at 174 kPa (1.7 ata; pO2: 1.7 ata) and one with air at 130 kPa (1.3 ata; pO2: 0.27 ata). Children were examined before and after 20 and 40 HBO treatments as well as 3 months later. The primary outcomes were a change in gross motor function. Secondary outcomes were: speech, orofacial structure and function, voice, visuospatial and verbal function, attention and memory. All children improved about 3%

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 601–608.

in gross motor function with time. There were no differences in improvement in primary and secondary outcome between both groups but significantly more otitis media in the HBO group[2]. In view of these results, HBO cannot be recommended and may even be considered as harmful for treatment of cerebral palsy.

2. MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic recurrent disease for which no curative treatment is available. The clinical use of HBO started with some anecdotal reports from early 1980. An initial small randomized controlled study showed benefit to patients[3]. After this first result, several randomized studies were published[4]. In a recently published review on the effect of HBO on MS (504 participants in total), Bennett et al[5] found two trials with generally positive results, while the remaining seven did not report any improvement in the patient's condition. Different subgroup analyses were unable to explain this difference. The two generally positive trials reported an improvement in the Expanded Disability Status Scale positive outcome at 12 months (16% of 504 participants). The authors came to the conclusion that HBO does not improve MS. Another independent review[6] came to the same conclusion. HBO was also tried as a long lasting repetitive treatment. Kindwall et al[6] did a 2 year survey of an MS register involving 312 patients. The drop out rate was very high. Only 28 patients completed an initial treatment of 20 sessions followed by monthly boosters. All 28 patients had a continuous deterioration, including bladder control. In view of these results, HBO cannot be recommended for the treatment of MS at any stage.

3. FACIAL PALSY (BELL'S PALSY)

Facial palsy is a viral disease possibly due to herpes viruses. It is characterized by a high rate of spontaneous recovery. There is no proven treatment for facial palsy. Acyclovir and cortisone are often tried. There is however no evidence of improvement and deleterious effects are possible[7]. It is thought by some authors that there is a "compartment syndrome" phenomenon and that HBO would help overcome this nerve edema and ultimately save nerve tissue from necrosis. There is no evidence from experimental or animal research to justify the use of HBO however. Some small anecdotal reports (in Russian or Japanese) claim good results with HBO. Racic[8] compared the effect of HBO with daily prednisone. HBO patients additionally received a placebo tablet and the prednisone group

received sham exposures in the chamber. Both groups were treated with 30 sessions or until complete recovery. Follow up time was 9 months. 95% of the HBO group versus 75,7% of the prednisone group recovered completely. HBO patients healed significantly faster and showed significantly more normalization in previously abnormal EMG.

Though there is no convincing rationale for the use of HBO in the treatment of facial palsy, results of a small underpowered RCT are positive. These results should be confirmed in a larger RCT taking in account the high rate of spontaneous recovery of facial palsy. Presently the evidence of a positive effect of HBO in facial palsy is weak.

4. NON HEALING WOUNDS IN PERINEAL INVOLVEMENT OF CROHN'S DISEASE

It is unknown why some patients with Crohn's disease develop ulceration and fistulas in the perineal region. However, it seems that there is a dysfunction of the microvasculature of the end arterial network of the mesenteric margin. The standard of care in the treatment of fistulas and non healing wounds in Crohn's disease is a combination of antibiotics, immunosuppressive drugs and infliximab. In resistant cases, surgery is used[9]. The relapse rate of these chronic wounds is not known.

There is no consensus about the treatment of non healing perineal wounds or fistulas in Crohn's disease. Only retrospective studies or case reports have addressed this problem. It is therefore impossible to assess the efficacy of the different drugs or procedures as there is no basis for comparison. Ardizzone et al[10] reported a closure rate of 60% in peri-anal and 30% in recto-vaginal fistulas with Infliximab. In his trial, Ardizzone could eliminate all fistulas but recurrences could not be eliminated.

The rationale for the use of HBO lies in the improvement effect of wound healing and infection control as stated (*see chapter 1.6 & 1.8*). HBO has been used mainly in refractory cases. Studies are small and of a retrospective nature; relapse rates have not been considered. The last studies were published 1994-5.

Colombel at al[11] treated 6 patients with 30 consecutive sessions of HBO. Three closed their wound and 3 had an improvement at the end of the treatment. All patients were refractory to previous treatments. The authors recommended HBO as last ditch treatment or as an adjunct to surgery.

Lavy et al[12] reported on 10 patients with Crohn's disease. All had refractory peri-anal wounds with symptoms like: painful induration, stenosis, discharging fistulas, and fissures. Five patients were healed after 20-40 daily treatments and 2 after 60. One patient improved, 2 did not. Follow up was

over 18 months. Several other smaller case studies have reported good results but follow up is unknown.

5. TINNITUS

Tinnitus is a symptom related to many different underlying conditions. It is often considered to be the end result of cochlear disorders – like sudden deafness or acute acoustic trauma. In these two diseases, acute circulatory impairment with consequent hypoxic damage to the cochlear cells is speculated. The rationale of most types of treatment relies on the correction of hypoxia: improvement in blood rheology; increasing circulating volume or; as is the case with HBO re-activating or salvaging "idling" cochlear cells through rapid and efficient oxygen delivery to these cells.

In a meta-analysis[13] of 50 clinical studies carried out on a total of 4,109 patients who received HBO therapy following unsuccessful conventional treatment with drugs, 4% of patients no longer had tinnitus; 81.3% reported a decrease in tinnitus intensity; 1.2% a temporary increase in tinnitus intensity; whereas 13.5% revealed their condition to be unchanged. These results were confirmed in more recent studies.

Treatment with HBO has been reported as useful in several retrospective studies: a decrease in noise intensity was reported by 60 to 70% of the patients with refractory tinnitus[14,15].

Delb et al[16] found a measurable improvement of tinnitus in 22% of 192 patients. A moderate improvement was seen in 17% of cases. In 10.4% there was an excellent improvement and the tinnitus disappeared completely in two patients. This improvement rate decreased in those cases where the time from onset of tinnitus to HBO exceeded 40 days.

In the treatment of 20 severe chronic tinnitus cases of more than one year duration, Tan et al[17] reported 4 drop outs; improvement in 6; no change in 8; and deterioration in 2 cases worsened at one year follow up.

Kau et al.[18] prospectively studied 359 patients with refractory tinnitus. For patients who had suffered from tinnitus for less than 3 months excellent improvement was seen in 6.7% and noticeable improvement in 44.3% expressed by means of a visual analog scale. In 44.3% the tinnitus was described as unchanged.

As a consequence, it must be stated that there is only weak evidence that HBO has a role to play in the treatment of chronic tinnitus. Some improvement has been noted in retrospective studies in patient suffering from tinnitus not older than 3 months. There is no follow up and no control group in these studies. Due to the subjective and variable nature of tinnitus, a

large double blind study will be necessary to asses the role of HBO in tinnitus.

6. INTERSTITIAL CYSTITIS

In a prospective pilot study, van Ophoven et al[19] treated 6 patients suffering from interstitial cystitis with 30 daily HBO treatments and followed them prospectively over one year. In this disease of unknown etiology, HBO was found to be objectively and subjectively helpful in 4 of 6 patients at 12 months follow-up: the baseline functional bladder capacity of the responders had increased from 37-161 ml (range) to 160-200 ml and the 24-hour voiding frequency decreased from 15-27 to 6-11 voids per day. On a visual scale, pain improved from 20-97 mm at baseline to 3-30 mm and urgency from 53-92 mm to 3-40 mm, respectively at 12 month follow-up. The symptom and pain index score decreased from 23-35 at baseline to 3-17 at 12 months follow-up. HBO was well tolerated and rated as excellent to good by the responders.

As a conclusion, HBO cannot be recommended for the treatment of interstitial cystitis. While the data presented in the study of Ophoven et al[19] are prospective and objective, a higher powered RCT will be required to confirm them.

7. RETINITIS PIGMENTOSA

This genetic degenerative disease of the retina has no definite treatment up to now. It presents itself as a collection of clinically and genetically heterogeneous inherited retinal degenerative diseases, characterized by a bilateral progressive visual loss ultimately causing blindness. The rationale is that intermittent HBO may help retinal cells not to degenerate. There are no basic or experimental studies to support this assumption.

HBO has been tried, as have many other therapies for this condition. Indeed HBO seems to improve the electroretinographic response in humans. Unfortunately, the effect on visual acuity has not been conclusively documented. There are only 8 indexed publications in Medline using HBO. Most report subjective improvement with only a few cases each (Verin et al[20]).

A controlled study, done in 48 patients by Vingolo et al[21], reports an improvement of the electroretinogram in all treated patients. Patients were treated daily for a month and then weekly for 11 months. At 3 years follow up, all patients treated with HBO reported a subjective stabilization or small

improvement in vision. According to authors, the results are not conclusive because of the small number of patients.

Actual treatment research is mainly directed towards gene therapy, growth factors, electronic tools as well as night vision glasses. There is presently not sufficient clinical or experimental evidence to show that HBO can improve the vision of patients suffering from retinitis pigmentosa. It is doubtful that HBO could play a significant role in the treatment of these patients.

8. MIGRAINE

Migraine pain is thought to be due to vasodilatation of extracranial arteries. It is well documented that oxygen and HBO have a vasoconstrictive effect on cerebral vasculature[22]. Myers et al[23] randomized 20 patients with migraine to receive 100% oxygen at 100 kPa (NBO) or HBO at 200 kPa (2 ATA). One out of 10 patients reported relief with NBO compared to 9 of 10 in the HBO group. The study was repeated by Wilson et al[24] with the same result. Eftedal et al[25] used 3 consecutive sessions of HBO as a prophylactic treatment in randomized double blind trial on 40 subjects. This treatment did not show a difference in hours of migraine between both groups.

As a conclusion, HBO seems efficient in the acute treatment of migraine attack. However, a larger trial is required to confirm the results of the small RCT mentioned above. The cost of HBO may discourage its use irrespective of its efficacy. In the presence of relatively cheap, efficient and uncomplicated alternatives – the tryptans[26] -- it is unlikely that HBO will achieve a significant role to play in the treatment of an uncomplicated acute migraine attack. Its potential role in resistant migraine; migraine with aura; and migraine during pregnancy, remains to be determined.

9. SPORT INJURY

Many professional athletic teams, like hockey (NHL), football (NFL), basketball (NBA) and soccer (MLS), use HBO in USA as adjuvant therapy for numerous sports-related injuries.

Borromeo et al.[27], performed a randomized double blind trial in 32 subjects with acute ankle sprains. Treatment consisted of 3 sessions of HBO at 200 kPa (2 ATA). With this regimen, HBO did not influence ankle edema, subjective pain indices, passive motion indices or time to recovery. Staples et al[28] also ran a randomized placebo controlled trial in 66 patients with muscle soreness of the quadriceps. They compared the control group, sham,

immediate and delayed HBO groups. Delayed treatment and delayed sham were done at 3 or 5 days following injury using 200 kPa. Immediate HBO patients had a better recovery than those treated within 3 days of HBO, while a delay of 5 days to HBO provided the best result. In all groups, pain was similar.

More and larger randomized trials will need to be done before the place of HBO in the treatment of sport injuries can be formally assessed.

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PART III

PRACTICE OF HYPERBARIC MEDICINE

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Chapter 3.1

HYPERBARIC CHAMBER AND EQUIPMENT

Multi- and Monoplace Chambers

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Abstract: Administration of hyperbaric oxygen to patients requires a special pressure vessel - hyperbaric chamber (multiplace or monoplace), installed as a part of hyperbaric systems. The hyperbaric chamber is a medical device, but to conduct the treatment it is usually necessary to introduce some other medical devices into it (ventilators, syringes and pumps, etc.). In the following chapter European regulations applicable to hyperbaric systems are presented by P. Müller, the hyperbaric fire fighting systems and related national standards are described by R. Houman, and the minimum requirements for the multiplace chamber according to the prEN14931 and safety aspects of medical equipment used inside hyperbaric chambers with a list of specific devices tested under hyperbaric conditions are discussed by J. Kot

Keywords: Hyperbaric chamber; equipment; medical devices; safety; fire fighting

1. MULTIPLACE CHAMBER AND EQUIPMENT

1.1 Introduction

The hyperbaric chamber is an active medical device, which is potentially hazardous taking into accounts its application and exposure of people inside to increased ambient pressure and increased partial pressure of oxygen. Use of medical devices in the hyperbaric environment is also related with additional hazards due to increased pressure, oxygen-enriched atmosphere,

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 611–636.

electricity and confined space. Therefore all hyperbaric systems and internal medical devices have to be in accordance with appropriate regulations.

1.2 European regulations

One of the main goals of the European Union is to facilitate the free flow of goods and merchandise within the European market. This has largely been made possible thru harmonisation and normalisation of the previously differing standards in the EU member states. This harmonisation process is the task of the European Committee for Standardisation (CEN).

In 1985 a new regulatory technique and strategy was laid down by the Council Resolution on the New Approach to technical harmonisation and standardisation[1] with a fundamental principle to limit legislative harmonisation to the essential requirements that are of public interest. These requirements deal in particular with the protection of health and safety of users (e.g. consumers and workers) and sometimes cover other fundamental requirements[2] (e.g. protection of property or the environment).

In Europe, the medical hyperbaric chambers are medical devices, which fall under the dispositions of the Medical Device Directive 93/42[3], with all consequences[4]. Moreover, as pressurised devices they also fall under the Directive for Pressure Equipment 97/23[5].

1.2.1 The Medical Devices Directive (MDD 93/42)

Purpose

The Medical Devices Directive[3] (MDD 93/42) provides for a harmonised regulatory environment for all medical devices sold within the European Economic Area (EEA). All products, which fall within the scope of the Directive, must meet certain essential safety and administrative requirements and are to be CE marked to show that they comply. The Directive was brought into force with effect from 1 January 1995. Transitional arrangements permitted equipment, which complied with national regulations to be sold until 14 June 1998 after which the MDD became fully enforced.

Scope

The Medical Devices Directive is one of a suite of three directives, which together cover all medical equipment. The associated directives are the Active Implantable Medical Devices Directive[7] (AIMDD) and the In Vitro Diagnostic Devices Directive[8] (IVDD). The Directive defines medical devices as:

> "Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, or alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Therefore the MDD only applies to chambers used for hyperbaric oxygen therapy, not for chambers used to decompress caisson workers or divers.

Application

The scope of the Directive is extremely wide and potentially there is overlap with other Directives. However, the MDD includes provisions for all relevant hazards, including mechanical and electrical safety and provisions for electromagnetic compatibility. Devices, which fall within the scope of the MDD, the AIMDD and the IVDD, are generally excluded from the scope of the other directives.

Classification

The MDD applies different administrative requirements to devices depending on the risk, which they present to the user. There are four classifications:

- Class I - generally regarded as low risk
- Class IIa - generally regarded as medium risk
- Class IIb - generally regarded as medium risk, but potentially hazardous
- Class III - generally regarded as high risk

Once it has been decided that a device falls within the scope of the Medical Devices Directive, the actual classification of an appliance is determined by a series of rules, which are laid out in annex IV to the Directive.

A hyperbaric chamber falls into Class IIb. Under this rule it is recognised as particularly dangerous. This requires additional instruction of the staff working with this product: the manufacturer has to entrust a person specified by the operator who then may instruct the personnel working with the medical device, a record of this has to be kept and this has to be checked annually during the inspection by the government delegate.

Essential Requirements

The essential requirements of the Directive apply to all medical devices. The most basic requirement is for the manufacturers or their authorised representative in the EU to register with the appropriate agency in the country in which they are based. This makes the MDD different from other directives in that there is actually a specific provision, which requires manufacturers and suppliers of devices to appoint a representative within the EU, and for that representative to be registered with an appropriate government agency.

Administrative requirements

In addition to Registration, manufacturers (or their agents) must typically:

- Comply with the essential requirements of annex 1 of the Directive
- Demonstrate design verification
- Carry out a risk assessment
- Demonstrate clinical evidence of the effectiveness of the device
- Implement a procedure for post market surveillance
- Complete a Declaration of Conformity
- Maintain a file of technical information about the product
- Put the CE mark on the product (or its packaging)

Safety requirements

Annex 1 of the Directive lays down a series of essential requirements for the design of medical devices. These include (among others):

- A general requirement for safe design
- The minimisation of risks from contamination
- Compatibility with materials with which they are likely to come into contact
- The minimisation of hazards of infection and microbial contamination
- Provision of sufficient accuracy (for devices with a measuring function)
- Protection against radiation
- Adequate product marking
- Adequate user instructions

The details of these essential requirements are laid out in a series of standards, prEN14931 for example (see below), which have been or are being developed to meet the requirements of the Directive.

Vigilance procedures

One of the other provisions which distinguishes the Medical Device Directives from the other New Approach Directives is, that a formal vigilance procedure is established by the Directive, through which manufacturers, health professionals and others must report certain problems

(e. g. malfunctions, mishaps) which arise in the use of medical devices and in clinical trials. This vigilance system is administered by the competent authority in each of the member states, and requires each manufacturer to have a procedure in place for post market surveillance and reporting of adverse incidents.

Risk assessment ISO EN 14971[27]

The EN ISO 14971: Medical Devices – Application of Risk Management to Medical Devices (2000) offers a framework for effective management of the risks associated with the use of a medical device. It suggests a "Risk Analysis Procedure" following certain steps and identification of:

- Intended use/purpose and identification of characteristics related to the safety of the medical device (Step 1)
- Identification of known or foreseeable hazards (Step 2)
- Estimation of the risk(s) for each hazard (Step 3)
- Risk Evaluation (Step 4)
- Risk Control (Step 5)
- Risk reduction
- Option analysis
- Implementation of risk control measures(s) (Step 6)
- Residual risk evaluation (Step 7)
- Risk/benefit analysis (Step 8)
- Other generated hazards (Step 9)
- Completeness of risk evaluation (Step 10)
- Overall Residual Risk Evaluation (Step 11)
- Risk Management Report (Step 12)
- Post-production Report (Step 13)

1.2.2 Directive for Pressure Equipment (PED 97/23)

The "Directive for Pressure Equipment"[5] was given by the European Parliament on May 29, 1997 to harmonise the existing laws about pressure devices of the members of the European Union. In the present edition devices that are exposed to a maximum pressure of 0.5 bar are excluded because they do not imply a significant pressure risk.

Besides the requirements arising from the MDD in this directive several additional requirements have been harmonised within Europe for pressure devices and do apply to hyperbaric systems. A large addendum deals, however very superficially, with "Basic Safety Requirements". This addresses pressure stability and aspects of loads, preventive measures for operational safety, feasibility of inspection, possibilities to load and unload, corrosion and other chemical effects, wear and tear, compression and

decompression, prevention of over-pressurization equipment and safety functions, external fires, CE marking, operating manual, used materials and pipelines.

1.2.3 CE marking

To be sold within the European market certain products require CE-marking. The initials "CE" do not stand for any specific words but are a declaration by the manufacturer that his product meets the requirements of the applicable European Directives. Such products may then be freely sold throughout the EEA without being subject to additional national regulations. Applicable requirements are set forth in various European Directives that replace individual country safety standards. The Directives apply to products manufactured within but also exported to the European Union.

1.2.4 Quality and Administration of Gases

Since 1 January 2000 breathable gases for medical purposes must comply with the European Pharmacopoeia[9], now available in a 5th edition. Several Monographs within this work deal with air, nitrogen and oxygen. Oxygen is now recognized as a drug in the gaseous form (not as a liquid). Liquid oxygen storage therefore requires transforming it into the gaseous form prior to the application and this is a process of producing a medication, which requires a pharmacist to do.

Air to pressurise the chamber(s) must at least comply with EN 12021[10].

1.2.5 European Norm for Multiplace Therapeutic Hyperbaric Chambers (prEN 14931)

The European Norm concerning manufacturing and testing of multiplace hyperbaric chambers for medical purposes[6] has been prepared by the Task Force 127 of the Technical Committee of the CEN under a mandate given to CEN by the European Commission. This norm will be applicable to the performance and safety requirements and their associated test methods for multiplace chamber systems for hyperbaric (oxygen) therapy designed for pressures in excess of ambient atmospheric pressure. It shall be employed in medical installations for therapeutic purposes.

In the norm prEN14931[6] the following minimum requirements are defined:

- Requirements for operational range:
  The minimum operational pressure for hyperbaric chambers should be at least 2 bar. The upper limit of pressure is not defined in the norm and

the manufacturer can meet specific requirements of clients including for example high-pressure systems for saturation.

- Requirements for structure, size and dimensions:

  The pressure chambers should comprise at least two compartments, one as a main chamber used for treatment and one as an antechamber used for transferring people or equipment. The main chamber should provide space for at least one person lying down in such a way that they are accessible from both sides with a space around the patient sufficient for resuscitation procedures.
- Requirements for breathing systems:

  For each person inside the chamber, including medical attendants, a breathing unit for treatment gas (a demand system, a free flow system or a mechanical ventilator) should be available independent from chamber atmosphere with an overboard-dumping system.
- Requirements for pressure control:

  Each pressure chamber (including ante chamber) should have separate controls and installations for compression, decompression, ventilation and supply of treatment gas to the breathing systems as well as internal pressure measuring and indicating devices. The overall control of the hyperbaric system should be at all times under the control of en external operator.
- Requirements for environmental control:

  In every compartment the ventilation should be possible to maintain the chamber atmosphere within specified limits (oxygen $\leq$ 23,5%, carbon dioxide < 0,5 kPa, impurities organic compounds < 0,5 mg/m^3, relative humidity 40% – 60%).

  The maximum compression and decompression rates both for main and ante-chamber should be possible to be compatible with decompression schedules and recompression treatment tables. The main chamber should have also the possibility for rapid decompression.
- Requirements for electrical installation:

  The voltage of the electrical installations in the hyperbaric chamber should be kept below 42 V, unless the construction of installation is proven to eliminate the hazards of this higher voltage.
- Requirements for fire protection:

  Inside the pressure chamber readily ignitable materials, combustible liquids, gases and vapours and spark-generating devices are not permitted. The use of any combustible materials for hyperbaric chamber equipment should be avoided or if impossible, shall be kept to a minimum. Electrical and heating equipment should be protected to prevent spark generation and overheating during normal operation and in case of single fault condition.

It should be possible for the chamber operator to shift from treatment gas to air on the control panel. An alternative source of breathing air should be available for chamber operator in the event that the air in the vicinity of the chamber is not breathable.

- Requirements for control console:

  The purpose of the control console is to enable all the controls and displays to be observed from a central observation point. It should be designed in such a way that instruments are clearly marked, arranged according to function, adequately illuminated and grouped in areas functionally distinct on the panel dedicated for each compartment.

  The oxygen concentration needs to be measured, displayed and recorded separately for each compartment. Due to the possibility of local concentration of high amount of oxygen, the sampling point should be located close to the ventilation outlet to allow measurement in mixed gas. For large hyperbaric chambers additional measuring device is needed to allow measurement in the point where the highest oxygen concentration is to be expected.
- Requirements for compressed air supply system:

  The system should supply air, which conforms at least to the purity requirements specified for compressed air for breathing apparatus (EN 12021).
- Requirements for communication:

  A communication system between each chamber and control console should enable constant listening of internal sounds and additionally at least one emergency signalling system should be installed between each chamber and control console.
- Requirements for emergency power supply:

  All equipment required to ensure operational safety including chamber and control console emergency lightings should be supplied with uninterrupted electrical power supply system.
- Other requirements for oxygen/treatment gas supply, for piping systems, valves and fittings, for supply locks, for internal paints, for operating instructions and for markings.

The norm prEN14931 also includes annexes which concern adaptor set for compression chamber, recommendations for medical devices used in hyperbaric chamber systems and relationship between this European Norm and the essential requirements of the MDD 93/42.

As the norm prEN14931 defines only minimum requirements, which need to be met by new multiplace hyperbaric chambers and systems, actually installed multiplace hyperbaric chambers can differ significantly from them.

Some constructions already installed differ in size, dimensions of openings, environmental control parameters, lights, control console, etc from the minimum requirements given in the European Norm. Many of them are based on diving chambers, which previously have been used for decompression and recompression of divers. The construction of such systems has fulfilled all criteria for long exposition of healthy people including gas supply storages, life support systems, communication, power and control systems. However, usually they were lacking some medical features necessary for medical assistance of the patients, for example easy access for patient for medical procedures, mechanical ventilators and monitoring devices, suction systems. Therefore, before putting them into the operational status for medical purposes, they needed to be adapted by some structural and functional modifications as well as preparation of operational and emergency procedures dedicated for such systems. If specific procedures based on the risk analysis have been developed to fulfil the safety criteria, such systems can still perform hyperbaric treatments with acceptable level of safety for patients and personnel. Whole surgical rooms have been constructed that way allowing conduct of cardiac, pulmonary and vascular surgical procedures under pressure.

On the other hand, newer installations can be much more advanced than the minimum defined in the norm prEN 14931, with computerized control systems for automatic conduction of the pressurizing – depressurising profiles, higher maximum working pressure and more advanced life support systems. Advanced technical solutions make it possible to build the multiplace chambers allowing for enough space to accept several critically ill patients with all the necessary equipment and personnel to conduct intensive care while being exposed to hyperbaric oxygen therapy (“pressurised rooms”).

1.3 Hyperbaric fire fighting systems

In Europe, it was only after the drama, which happened in Milan (1997) that fire inside hyperbaric chambers was looked differently upon. Until then, it was considered only normal that, a fire deluge system should be mandatory and that in case of fire patients and attendants would keep their mask on, while air would be distributed in those masks. No one seemed to imagine that these measures might not perform adequately or sufficiently with regard to the problems encountered in such a situation.

Inside this part it will be reviewed which regulations are in existence worldwide and if the answers, provided by these regulations, stand up against the scrutiny of the current-day knowledge about hyperbaric fires. Finally, expected future developments will be discussed.

1.3.1 Safety and Regulatory Standards published around the world

a) National Fire Protection Association[11] - NFPA 99 (USA):

This standard is generally considered as the "bible". Nevertheless, it has certain weaknesses with regard to the quality of water diffusion methods (also with regard to the duration of deluge) inside the hyperbaric chamber. Similarly we could question the minimum quantities per m², the duration of deluge and the duration of quick decompression. For the record, Tewarson[12] estimates that "the NFPA tests standards, designed for the evaluation of flammability of materials under normal atmospheric conditions, are not suitable for materials for use in oxygen enriched atmosphere chamber". It should be noted that this author only deals with the oxygen problem; we should add the pressure and the enclosed space.

b) DIN 13256 – 2[13] (Germany)

This German norm takes certain elements of the NFPA standard into account, yet leaves the opportunity to demonstrate the pertinence of another system, which shall at least obtain similar results to the NFPA standard. In the near future, this norm will be replaced by the EN norm.

c) ISPESL[14] (Italy)

This guideline, which was drawn up after the 1997 Milan tragedy, builds on a number of lessons learned from this tragic fire. It comprises both a passive and an active approach and deals with procedural aspects. Moreover, the guideline is not content with merely an extinguishing system; a monitoring (detection) system is also demanded. Finally, even though minimum water quantities have been taken from the NFPA (81 litres/ min), the duration of the deluge has been brought to 3 minutes.

d) BHA - British Hyperbaric Association[15] (United Kingdom)

This guideline draws attention to certain passive as well as active preventive measures. The document is completed with a risk analysis regarding possible causes of fire.

e) France – Decree dated March 28th 1990[16]

This document does not have a normative scope but is related to the legal provisions, which protect the workers. Nevertheless and because it is the only document in France, it must be quoted.

This Decree doesn't dictate any tangible solution except that the extinguishing materials have to be efficient and the means of surveillance in smoky surroundings have to be available.

f) AS 4774.2[17] (Australia)

The Australian standard refers to the NFPA 99.

g) SABS 0377[18] (South Africa)

A lot of articles take over the terms of the NFPA 99.

h) prEN 14931[6] (European Community)

This new norm, to be issued by the European Committee of Standardization (CEN) will soon replace all the "national" norms of the European Community with regards to the manufacturing of new therapeutic hyperbaric chambers.

Only article 4.2.21 is concerned with the protective measures against fire. This rather generalist article is restricted to the passive protection measures with only minor concepts of active defences. A separate norm relating to the performance tests of fire control systems is in progress.

There exist standards/norms and guidelines for the requirements of deluge systems. However some doubts still exist, because it is not clearly defined upon which test or fire scenario they were based on, and whether it was taken into account that the occupants of a hyperbaric chamber on fire are most likely not professional divers.

These aspects are difficult to quantify, or control, which can explain many of the difficulties one encounters when attempting to interpret the results of standard test methods and apply them to “real life tests”[19].

According to the observations realised during fires in hyperbaric chambers[20], no deluge system is capable of controlling a fire in a hyperbaric environment at 2.5 ata filled with 30% oxygen, if no other action is linked to it.

For the record, previous publications[21, 22] advise the distribution of air in masks in case of fire inside the chamber. However, reality teaches us that in the case of a major incident, all the occupants of the chamber head for the exit, rendering this precaution inadequate.

In the future, it will probably not be adequate to speak about a «fire deluge system» or a «fire suppression system», but more likely the term «Hyperbaric Fire Fighting System (FFS)» will be used, to enclose the problem in its entirety: passive means, such as prevention and early detection, and active means such as alerting, suppressing or extinguishing the fire and the evacuation of the chamber occupants.

The passive measures

Fire retardant products can react differently depending on normal atmospheric or hyperbaric conditions. It will be necessary to study all these aspects in order to integrate them in a future standard.

Nevertheless, this standard-to-come should integrate a notion of “fireproof-ness” which should be defined according to a validated method. But the author suggests, while waiting for the technological developments and specific standards, to require for now on, a 5 minutes yield point; the standard ISO 6941[23] being the means of determination (textile fabrics, measurement of flame spread properties of vertically oriented specimens).

To reduce dependency on the human factors ("force of habit"), various means of prevention and detection can be used, such as:

– Automatic message regarding safety rules before each compression: this message is not a substitute for the operator's attention, but repeats day after day, session after session, the importance of following the safety rules. It can be compared to the mandatory safety briefing in airplanes.
– Automatic alarm when the oxygen level inside the chamber is about 22%: it gives a warning to the operator who can thus proceed before the critical point of 23.5% is reached.

The utility of a fire detection system can be discussed. From a list of some possible ignition sources for hyperbaric environment, proposed by Beeson D., the author points out, that outside electrical sparks, open flames and hand warming devices are a major risk of ignition.

Most fire detection systems are based on Infrared (IR) and/or Ultra Violet (UV) spectra. Both systems are based on the spectral analysis and thus the detection of open flames. Each one of these systems can react in a few seconds. Nevertheless, taking into account the speed of the process of the ignition, one cannot affirm that these systems answer our problems.

Indeed, the literature reports[24] to us that heating sources, not flames or sparks, caused the most fatal cases of fires. Why await the first flames? Why not search for reliable detectors of variations in temperature? That might give us an advantage of invaluable seconds.

The question is to find out if such detectors, which can fulfil the two missions (detecting heat and flames), exist on the market.

Concerning the oxygen distribution the reference literature retains a maximum allowable level of 23.5% of oxygen inside the chamber, however it is not clearly obvious why it is 23.5% and not 23 or 24%?

The answer seems to come from the protection of workers in confined space[25], where a maximum rate of 23.5% is clearly mentioned, but this value is related to the normobaric environment.

It is worthwhile to remember that air compressed at 1.5 bars of pressure represents an amount of oxygen equal to that in a normobaric mixture containing 52% of oxygen! However, on the three essential sources of the danger (the pressure, the oxygen and the confined space), only the danger resulting from the accumulation of oxygen inside the chamber can be technically lowered.

For that, it is necessary to be able to ensure a total sealing of the distribution and evacuation systems, as well as a control, individually for each station, of the quality of distribution.

The active measures

Unfortunately, the activation of the deluge system is the result of a failure of the prevention policy!

Nonetheless, it is vital that this system should at least guarantee a control of the fire during the time required to save the occupants.

The approaches found in the standards and recommendations concentrate on minimum technical requirements, which the systems have to meet (means and duration of deluge, etc). Many people seem to consider that fire fighting stops at the activation of the deluge system. However, this is not a satisfactory answer in an overall approach to the problem, and therefore, to the solution. To come close to the solution, the deluge system should be only a part of the global fire fighting system.

For this, the author recommends that besides the deluge system, also the evacuation (quick decompression) and alert systems be considered part of the fire fighting system.

Water has physical properties that make it an excellent agent for extinguishing a fire; it is important to maximise the use of these properties. Two of the physical properties in particular can be used: it's energy absorption capacity and it's cooling properties. Inside a confined space such as a hyperbaric chamber, the rapid and uncontrolled temperature rise is a major problem, which has been noted already by others[26]. A distribution of water in the form of small droplets will be the most appropriate method to maximise the energy absorption capacity of the water. Nevertheless, there are also flames to be extinguished, so it is necessary to direct powerful jets of water straight towards those points that are producing the flames.

A balance between these two deluge methods (minuscule droplets and powerful jets) needs to be found, providing at the same time for a uniform and abundant dispersion throughout the chamber. Water should occupy a maximum possible fraction of the chamber volume. Taking into account that a majority of the chamber's occupants will flee towards the main exit door (in a protective reflex reaction), this zone should likewise be generously sprayed with water. Finally, it makes good sense to guarantee water dispersion at least until the opening of the doors.

Even in the presence of a powerful deluge system, owing to the exponential dimensions of the fire in oxygenated environment, it seems unlikely, that the treatment in progress will continue after an extinguished fire! In all cases, it will be necessary to evacuate the chamber.

The question is to know in what time period? As beginning to an answer one can undoubtedly consider the maximum time during which men can survive a full respiratory stop. In the calculation of this maximum time, it is

necessary to include the total time of the decompression but also of the complete evacuation of the chamber (which is, until evacuation of the patient furthest away from the main door). Taking into account the maximum allowed ascent speeds of underwater divers, the author suggests a return of the hyperbaric chamber to atmospheric condition from 2.5 ata in one minute. Technically, this is perfectly possible.

During this minute, the system should provide for alerting the emergency services and giving them full information about the type of patients they will have to deal with. Likewise, special equipment is indispensable to provide for the outside personnel in order to evacuate the persons inside the chamber.

Unless having a specially trained team, a maximum of these actions should be automatic. Technically, this is again perfectly possible.

In conclusion, many technological improvements are still waiting. One thing remains essential though: an "active" approach to fire prevention starts necessarily with a proper education and training of all the personnel involved.

1.4 Hyperbaric equipment

1.4.1 Introduction and general notes

According to the MDD 93/42[3] all equipment, which is introduced into the hyperbaric chamber should be CE marked covering the hyperbaric environment conditions. However, up to date only few devices are CE marked for this purposes. Therefore users are still forced to perform some checking of devices on their own responsibility before putting them into the chamber.

The general risk management process applicable for all medical devices is described in the ISO EN 14971[27], but recommendations for medical devices used specifically in hyperbaric chamber systems are presented in the Annex B of the prEN14931[3]. This Annex describes:

- The potential hazards which certain medical devices represent
- The risks induced by medical devices likely to be used within hyperbaric chamber systems intended for hyperbaric oxygen therapy
- The recommendations for manufacturers of medical devices and users of hyperbaric chamber systems, in order to achieve the highest possible level of safety of the patient and the attendants.

There are three hazards related with the use of medical devices in the hyperbaric chamber:

1. A raised pressure and changes of pressure - it can significantly affect structure or/and function of the medical devices designed and manufactured for use at atmospheric pressure leading to physical damage or deterioration of performance
2. Accidentally increased content of oxygen in internal atmosphere - it gives risk for fire when associated with a combustible product or with a source of ignition, e.g. sparks.
3. The electricity powering medical devices in the hyperbaric environment - it gives risk for fire as potential source of ignition such as sparking or overheating.

In any case a single fault condition should not lead to a hazard and means should be provided so that electrical medical devices in a hyperbaric chamber do not cause a risk of ignition. Medical devices, which are introduced into the hyperbaric chamber should be certified by the manufacturer for hyperbaric conditions and marked accordingly. Unfortunately, nowadays only a few medical devices, which are needed for continuation of intensive care inside the hyperbaric chamber are marked by manufacturers as compatible with hyperbaric conditions (see below).

In cases when the medical devices need to be introduced into the hyperbaric environment and the manufacturer for use in such conditions does not certify it, the user (personnel of hyperbaric centres) has to check it before installing. The structure of the device is checked from a point of view:

1. Of raised pressure to make certain that it is pressure resistant or it does not contain any closed compartments under atmospheric pressure
2. Of oxygen enriched atmosphere to ensure that it does not contain an easily combustible material
3. Of electrical supply to ensure that is uses low energy (low voltage and low current) inside the hyperbaric chamber.

Furthermore, the function of the device is checked under hyperbaric conditions to verify the controls (e. g. the keyboard pads), the performances of the device's probes, the operating of the device's built-in electronics, the device's display and its operating parameters (flow rates, pressures, etc).

In case of any doubt, the installation of this medical device in hyperbaric chamber should be abandoned.

1.4.2 Monitoring devices

Monitoring of patho-physiological parameters during the HBO session strongly depends on severity of the illness and current status of the patient. The set of measured parameters can be as simple as only 3-leads electrocardiography (ECG) up to many critical points of measurement including for example pulmonary capillary wedge pressure (PCWP) or electroencephalography (EEG)[28].

For safety reasons the optimal method of collecting measurements is to perform acquisition of signals under hyperbaric conditions, transfer it into the electrical signal of low voltage or current and to transfer it out of the chamber through the wall to the outside monitor to be displayed and recorded. The transfer of the signal from the inside to the outside of the chamber can be effectively performed via wire connection or telemetric transmission. The significant disadvantage of a wire connection through the chamber wall is the need for two additional connectors to switch the cable from inside to outside. This may result in decreasing the signal quality, especially with a low signal-to-noise ratio. Transmission using telemetry ensures the continuous monitoring of the patient during all phases of the session including transportation of the patient to and from the chamber. The quality of the signals transmitted depends on the quality of the emitter and receiver, the position of the antenna and the thickness of the chamber wall. Unfortunately, such systems usually allow transmission of only some basic signals, like ECG, with no possibility to transmit more data collected from the patient.

The alternative method is to put the monitoring device under the hyperbaric conditions and to collect, display and record all signals at the patient bed inside the chamber. This solution is easier to be conducted and – in the basic version - does not need to make any modification to the existing construction of the chamber. If the user needs, it is possible to collect data inside the hyperbaric chamber and then to send it out of the chamber (again via cable connection through electrical ports or using telemetry) to a more sophisticated monitor located outside for further analysis. It is important to remember that introducing of the electrical device into the chamber increases the risk of fire, and therefore its careful evaluation is obligatory.

The following methods and techniques of clinical monitoring were reported as used safely inside hyperbaric chambers:

1. NON-INVASIVE:
a) Electrocardiography
b) Pulse oximetry
c) Non-invasive blood pressure
d) Temperature
e) Transcutaneous partial pressure of the oxygen ($TcPO_2$)
f) Electroencephalography (EEG)
g) Evoked potentials (EP)
h) Laser-Doppler flowmetry (LDF)
i) Trans-thoracic bioimpedance
j) Echocardiography and Doppler studies
k) Transcranical Doppler
l) Near infrared spectroscopy (NIRS)
m) Spirometry and airway pressure
n) Breathing gas analysis

2. INVASIVE:
a) Blood pressure (BP)
b) Cardiac output (CO)
c) Intracranial pressure (ICP)
d) Blood gas analysis (ABG)
e) Venous saturation of the blood (SvO_2)
f) Tissue oxygenation
g) Blood glucose level

1.4.3 Ventilators

According to indications accepted for HBO therapy some sessions need to be conducted with intensive care or emergency patients. This means that general treatment of critically ill patients, including artificial ventilation, must be continued while inside the hyperbaric chamber. Therefore the hyperbaric chamber should be equipped with a pre-installed or transportable ventilator to support ventilation during the HBO session.

Ideally, such a device should ensure the same parameters and modes of ventilation as every ICU ventilator. However, the performance of all pneumatic devices inside the hyperbaric environment is changed by increased pressure and altered density of gases. Unless this phenomenon is technically compensated, the clinical consequences are hypoventilation due to decreased flow[29, 30] and/or increased work of breathing in any assist mode

of ventilation (continuous positive airway pressure [CPAP] and pressure support ventilation [PSV])[31, 32].

Knowledge of physical properties of gas under pressure and construction and type of operation of the ventilator helps in prediction of the changes of its working parameters in the hyperbaric environment.

The exact level of pressure-induced changes in ventilator's performance strongly depends on its type and technical design. Therefore it is almost impossible to precisely predict its performance while under pressure considering only physical laws and basic knowledge of its construction[29]. Empirical data need to be obtained under hyperbaric conditions for each particular ventilator type.

Moreover, the compatibility of the ventilator with the hyperbaric conditions must be carefully checked to ensure that it does not create any unnecessary additional risk. For those reasons, standard ICU ventilators cannot be used inside hyperbaric chambers, unless they are modified for hyperbaric environment.

Up to now, only two ventilators have been CE certified for use in a hyperbaric environment. This is the French ventilator RCH-LAMA and Italian ventilator Siaretron 1000 Iper (60 VF).

The RCH-LAMA[33] is a volumetric ventilator with pneumatic logic controlling inspiratory flow on a constant level regardless of ambient pressure up to 6 ata. The ventilator is equipped with a system of automatic pressure control in the balloon of the endotracheal tube.

Siaretron 1000 Iper[34] (Iper 60 VF) is an electro-pneumatic ventilator which has automatic compensation of the ventilated volume delivered up to a pressure of 7 ata measured by a special absolute pressure transducer. The ventilator can operate in IPPV, PSV, SIMV and CPAP modes. The user can set the oxygen concentration between 21 and 99%.

There is also another ventilator – Hyperlog Draeger[34-36] – that has been constructed with automatic compensation of working parameters to the environmental pressure, however it has not been CE certified for use in hyperbaric environment. It is a pneumatically controlled volumetric ventilator with auto-compensation of changes in delivered volume due to compression and decompression. It can be used up to 6 ata but it is lacking any sophisticated methods of ventilation needed for modern intensive care.

Several other ventilators have been modified to make their structure compatible with hyperbaric environment. Users in different conditions most often with positive results have tested them. The list of ventilators which have been used in multiplace hyperbaric chambers includes: Ambumatic, Bennett PR-2, Bird Avian, Campbell EV 500, Emerson Can, EVITA 4, Impact Uni-Vent Eagle Model 754, Lifecare PLV-100, Microvent, Monaghan 225, Newport Medical 300m, Ohio 550, Omni-Vent Series D,

Oxylator EM-100, Oxylog, Oxylog 2000 HBO, Penlon Multivent, Penlon Oxford, PneuPAC HC, Servo 900B, Servo 900C, Servo 900D, Servovent 99 D and TXP.

It should be kept in mind that regardless of its testing, usage of those devices inside the hyperbaric chamber requires constant adaptation of settings as depending on the environmental pressure to assure proper ventilation. This is especially important in volume-controlled ventilation, when the tidal volume delivered to patients usually decreases with increasing ambient pressure. Unless the ventilator has the automatic function for compensation of this phenomenon, the user needs to adjust the tidal volume during any change of pressure. Results of such modifications should be carefully and constantly evaluated. For this reason a pressure controlled ventilation is preferable in hyperbaric conditions due to the stable tidal volume.

Regardless of the type of ventilator used for artificial ventilation there is a need for independent control by monitoring of the gas exchange, at least by measurement of expiratory volume and partial pressure of carbon dioxide in expiratory gas. In most cases of critically ill patients additional monitoring of cardio-respiratory status is also necessary in mechanically ventilated patients including heart rate, arterial blood pressure and transcutaneous partial pressure of oxygen.

1.4.4 Infusion pumps and syringes

The cheapest method of fluid delivery in multiplace chamber is using a free fall system. The only pitfall is to regulate the volume of gas compartments in the fluid bottle and in a drip chamber of the fluid line during the HBO session according to changing pressure. Using flexible PVC pre-packed solutions allows avoiding of the hazards of too fast fluid application, blood draw-back into the line and introducing gas into the blood vessel, which are hazards of gas bubbles entrapped in the rigid bottles being exposed to changing pressure. Nevertheless, due to changes of gas volume in the drip chamber the user must constantly adjust the fluid flow. Therefore electrical syringes and infusion pumps are needed inside hyperbaric chamber to accurate titrated delivery of drugs as a part of intensive care, usually for inotropic agents and sedatives.

As all medical devices being introduced into the hyperbaric chamber, infusion and syringe pumps need to be carefully checked for additional hazards created by their usage in hyperbaric conditions. The important point in the pre-compression checking is validation of performance under increased pressure[37], because there are several reports of significant

reduction in infused volume during the HBO session for different models[38-41].

Up to now only one syringe pump (Pilot HYPERBARIC, Fresenius Vial S.A.) is CE marked for usage in hyperbaric environment up to 7 ata.

Some other models – even if not CE marked for hyperbaric conditions – have been already tested in hyperbaric environment: Atom 235, Ballon Infuser, Baxter Colleague CX, Baxter PCA Infusor, Imed 965, IMED Gemini PC-1, IMED Gemini PC-2TX, Imed series, Infusion Dynamics Power Infuser, Infutec 520, IVAC 770, IVAC Alaris Medsystem III, IVAC P300, MiniMed 506 (an insulin pump), MTP military, Rateminder III, SE 200, SE 400B, TE-171, TE-311, TE-312, Terumo STC-3121, Terumotec and Top.

Regardless of the model of electric syringe or infusion pump used, the user should be aware of the hazard related to use of such devices to minimize the risk of critical incidents for seriously ill patients receiving hyperbaric treatment. This is of most importance for inotrope–dependent patients. Such patients need accurate continuous haemodynamic monitoring and a preparedness to rapidly titrate inotropes to physiologic endpoints[38].

1.4.5 Cardiac support

Defibrillation

The necessity to use defibrillation in the hyperbaric environment is a logical consequence of treating critically ill patients in hyperbaric chambers. The procedure of defibrillation is inherently dangerous to use in hyperbaric chambers because of the danger of fire caused by electrical discharges and voltaic arc, which may be generated between the paddles. Therefore it is absolutely contraindicated in the pure oxygen atmosphere of the monoplace chamber[42]. On the other hand, in multiplace chamber defibrillation can be performed safely, if several precautions are taken:

1. The chamber is compressed with air and oxygen is kept below 21.5%[43].
2. Large surface adhesive plates are attached to the patient's chest[44, 45]. The gel is applied to assure conductive bridge between the skin and the plates, and the area around the plates is kept free from flammable materials[46].
3. Transmission cable of wide diameter and low resistance passes through the chamber wall outside[45].
4. The defibrillator (including switches) is located outside[43-46].
5. Three persons are needed to perform the operation: 1) medical attendant inside the chamber is responsible for attaching paddles; 2) an external defibrillator's operator is controlling the discharge unit located outside

the chamber and 3) chamber operator is ready for immediate activation of water-deluge fire suppression system[43].

When following this rules the risk of fire is kept on an acceptable low level, so general opinion is that defibrillation may be performed safely in the multiplace chamber[42, 43]. If technically impossible to be conducted under hyperbaric conditions, defibrillation is performed after emergency surfacing of the patient from the hyperbaric chamber to the outside, assuming that pre-oxygenation with hyperbaric oxygen gives a few minutes extra before brain death occurs.

External pacing

Some temporary external pacemakers have been reported to malfunction under hyperbaric conditions[47, 48], some others have been shown to function satisfactorily up to 8.7 ata[49]. Therefore the use of untested external pacemakers should be avoided, and other alternatives should be used in case of need. One is to locate the pacemaker outside the chamber[46] and to transfer wires through the wall similarly to defibrillation described above. The other is to use permanent hermetically sealed pacemaker attached to the patient's temporary external leads[47] or to the catheter-based wires.

Implanted pacemakers

The number of patients with implanted pacemakers and automatic implanted cardiac defibrillators treated inside hyperbaric chambers for other medical reasons is growing. According to general opinion, internal cardiac pacemakers are unaffected by the hyperbaric environment[50], however – obviously – it can be true only for a limited range of pressures. Most implanted devices are rated to at least 2.4 ata[51, 52], but some authors report that all pacemakers tested by them were adequate to treatment pressure below 3 ata, and some even to 7 ata[53]. During the ISO-compatible ETO-standard sterilization process the pressure is up to 2.5 ata, therefore all devices sterilized by this method are unintentionally tested for such overpressure[54].

Nevertheless, it is highly advisable to constantly monitor ECG of patients with implanted pacemakers and cardiac defibrillators during every HBO session.

1.4.6 Drainage and suctioning

Before pressurisation of the chamber the active devices for suctioning (battery-fed aspirators) or general hospital vacuum-line with pressure regulators are used. During the HBO session negative pressure needed for drainage and/or suctioning is created by the difference between inside and

outside of the hyperbaric chamber. This creates an additional hazard of extremely high and dangerous negative pressure being applied to body cavities or organs. For safety reasons negative pressure needs to be under control of both a manometer and a Venturi valve, which is also regulated by a second manometer. One manometer serves to adjust the negative pressure to safety values of 0.2 – 0.3 bar, which should remain constant throughout the treatment, and the second manometer should be used for fine-tuning of the aspiration pressure according to clinical need[55].

Under hyperbaric conditions any passive drainage of collections works fine if the drop sacs are flexible. If containers with rigid walls need to be used, the equalisation of pressure between inside of the device and the chamber atmosphere must be ensured at any change of pressure during compression and decompression[56].

The general suggestion is that chest tubes must not be clamped during the session to avoid tension pneumothorax in the presence of bronchial or alveolar fistulae[46]. However, if patient's condition allow for temporarily clamping of the chest tube at ambient pressure, it is possible to safely conduct the HBO session with clamped lines (to avoid entering of gas into body cavity) and to release clamping just before the start of decompression to avoid increase of any gas volume, which could have been created anyway.

2. MONOPLACE CHAMBER AND EQUIPMENT

According to definition the monoplace hyperbaric chamber is capable to fit only one patient at one time, usually in the supine position, sometimes sitting. The maximum working pressure for most monoplace chambers is 3 ATA (6 ATA for few exceptions), limiting their usage to medium-pressure treatment schedules not suitable for a recompression treatment, which requires greater pressures and longer durations.

During the session the patient can breathe oxygen directly from internal atmosphere or through a mask. In the first option, the patient is breathing from the oxygen atmosphere, without any mask or hood, but placing the patient in the atmosphere of pure oxygen introduces a serious hazard of fire in case of any spark or uncontrolled heating source. Moreover, breathing from the internal atmosphere prevents of changing breathing mixtures during the treatment, for example for routine procedure of switching from oxygen to air to extend pulmonary tolerance for oxygen toxicity. The other solution, breathing from masks inside the monoplace chamber allows switching of breathing mixtures by external control or by manual putting on and taking off the mask by the patient himself, but in that case requires the patient to be

fully conscious and cooperative. In cases, when the patient looses consciousness and vomits, the mask creates an additional serious hazard.

If the patient is breathing oxygen from the internal environment, a constant or intermittent ventilation of the chamber is obligatory to keep the carbon dioxide on an acceptable level and to prevent the retention of vapour inside. The alternative is to use a recycling unit, but – due to higher cost – this is a favoured solution only in countries where the cost of the treatment gases is of concern.

For many years of clinical use of monoplace hyperbaric chambers a lot of efforts have been made to adapt equipment to support patients which need intensive care during the session[42,57,58]. The general rule is to keep all devices outside the chamber to allow the operator to control it, and to avoid contact of electronic circuits with the oxygen environment. All tubes, lines and wires are transferred to the chamber through ports in the bulkhead. All equipment must be correctly installed, checked and calibrated before the session and all sensors have to be checked for proper fixation to the patient. Patients treated inside the monoplace chamber can be supported with:

- Artificial ventilation
- Intra-vascular infusions
- Chest tube drainage
- Non-invasive automated blood pressure devices
- Invasive measurement of arterial and venous pressure
- Temporary cardiac pacing and pacemakers
- Other measurements: non-invasive laser flow-meters, transcutaneous measurement of partial pressure of oxygen and carbon dioxide, body temperature measurement (including skin, rectal and oesophageal probes), electrocardiography (EKG), Holter, electroencephalography (EEG) and passive electromyography (EMG), automated tissue gas monitoring (using polarographic or mass spectroscopy probes).

Monoplace hyperbaric chambers have some advantages mainly related to relatively low cost of operation[58]: small space needed, small number of personnel for operation and maintenance, no occupational hazard for the attendant and no special decompression required. On the other hand, regardless of an oxygen-filled environment and the risk of fire, and difficulties to follow some treatment schedules (pressure, time, “air breaks”; eg. recompression treatment tables), the intrinsic disadvantage of such chambers is the impossibility to directly assist the patient under pressure in the case of an emergency. In order to get in contact with the patient it is necessary to decompress the chamber. However, it has to be clearly stated that the process of decompression can negatively affect the non-cooperating patient inducing procedure-related complications like pulmonary barotrauma and arterial gas embolism. The real occurrence of such episodes is unknown,

but cannot be neglected. Taking into account all risks some countries do not allow the use of monoplace chambers as medical devices. Because of the number of monoplace chambers installed all over the world during the 7th European Consensus Conference on Hyperbaric Medicine[59] (Lille, France, 2004) it was agreed that "oxygen filled «monoplace chambers» may be accepted and used according to internationally accepted guidelines".

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Chapter 3.2

ORGANIZATION OF A HYPERBARIC CENTRE

General design of a therapeutic hyperbaric centres

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Abstract: The design of a hyperbaric centre covers all aspects of structure, organization and functioning of the hyperbaric medical facility for treatment, education and research in the international network of hyperbaric institutions and organisations. In this chapter the general description of all items (from hyperbaric chamber and medical devices used in pressurised environment, by medical personnel and procedures up to classification of hyperbaric centres) is presented

Keywords: Hyperbaric centre; design; organisation

1. INTRODUCTION

Hyperbaric oxygen therapy (HBO) is a relatively new branch of medicine with historical roots to diving and working under pressure. For a long time, chambers were used to treat divers and compressed-air workers suffering from decompression illness. Such treatment was applied on-site in chambers routinely used only for decompression, lacking any support for medical procedures. Increasing usage of HBO and expanding of indications also to critically ill patients have been a challenge for modern hyperbaric centres. In this chapter the general design of hyperbaric centres is presented including hyperbaric chambers with supporting equipment, staff team, operating and emergency procedures, codes of good practice and quality assurance. The main interest will be placed on the functional organization of the hyperbaric centres, and only recent documents on the European level will be referenced. All readers interested in standards, regulations and other documents on the national level from different countries should review some classic

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 637–650.

literature[1, 2, 3]. To avoid any misunderstanding of terms used to describe different hyperbaric structures and functional items the definitions presented in a European Code of Good Practice for Hyperbaric Oxygen Therapy (May 2004) will be used[4]. The general structure of different levels of hyperbaric centres is summarized on the Fig. 3.1-1. It will be discussed in a hierarchical order starting from hyperbaric chambers and going to most extended design of hyperbaric centres.

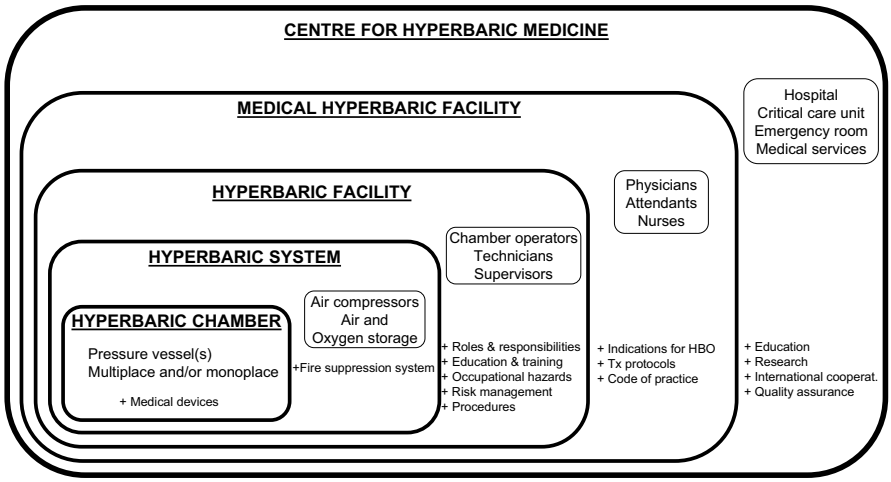

Figure 3.2-1. General structure of the hyperbaric medicine centre (modified from the European Code of Good Practice for Hyperbaric Oxygen Therapy)

2. HYPERBARIC MEDICINE CENTRE

2.1 Hyperbaric chambers

The very basic device used in any hyperbaric facility is hyperbaric chamber. Since 1998 according to the European Council Directive 93/42 concerning medical devices (14 June 1993), the hyperbaric chamber has to be treated as medical device with all consequences[5]. There are numbers of different chambers used nowadays and their structure and installed equipment define the capability of the centre to treat particular patient. The most important feature is the possibility of attending the patient under pressure; therefore the type of the chamber used in the centre (monoplace or multiplace) defines its overall capability. Until now in Europe there is no

harmonized regulation for manufacturing of monoplace chambers. On the other site, the CEN/BT/Task Force 127 fulfilled its objective to prepare the European Norm for manufacturing of multiplace chambers. The final result is the prEN14931 "Pressure vessels for human occupancy (PVHO) – Multiplace pressure chambers for hyperbaric therapy – Performance, safety requirements and testing"[6]. At the time of preparation of this chapter, the prEN14931 is under approval. This norm, if finally accepted by European countries, will normalise the production of multplace chambers on an European level.

The design of a hyperbaric chamber should include also individual breathing systems, for example free flow systems, demand valves and mechanical ventilators, as well as monitoring devices being permanently fixed inside the chamber. Other medical devices that are introduced into the chamber with the patient (pumps, syringes, pacemakers, transportable monitors, etc) are not treated as a part of the hyperbaric installation. Nevertheless its manufacturer should certify them for hyperbaric conditions. If there is a necessity for pressurisation of a device not certified for hyperbaric environment, it is the responsibility of the user to perform checking of its compatibility with such conditions.

The number of chambers installed in the hyperbaric facility depends on several factors. The most important one is the cost effectiveness. Larger multiplace chambers are more expensive at installation than smaller ones, but during operation they are cheaper due to lower usage of personnel (operators and attendants). In most European hyperbaric centres there are only single multiplace chambers installed. Regardless of its high cost effectiveness, in such installations it is impossible to ensure the immediate HBO treatment in case of urgency because the chamber is used also for routine pre-planned sessions. There are also many difficulties in isolation of infectious patients (gas gangrene, MRSA, etc.). Therefore in some centres there are several (at least) multiplace chambers installed.

2.2 Hyperbaric system

The term "hyperbaric system" covers not only hyperbaric chambers, but also air and oxygen storage, air compressors, pipelines, control consoles, communication systems, electrical systems with emergency power supplies and fire suppression system dedicated for hyperbaric conditions. The requirements presented in the prEN14931 cover the whole system, but only in minimum options for using air and oxygen for treatment. If the hyperbaric centre needs to expand its capability to use breathing gas mixtures other that air and oxygen, the reference to diving standards and regulations is necessary. The experience from working under pressure and from

commercial diving helps a lot in designing hyperbaric systems capable for extended HBO treatment including saturation recompressions with different breathing gas mixtures. If there is a need for compatibility of the hyperbaric system with a transportable chamber to allow transfer under pressure (TUP) the usage of common NATO entrance is preferred to ensure the interchange ability. All supporting systems for the hyperbaric chambers should be designed with the capacity allowing for backups. This is important mainly for gas storages and electrical power supplies. Design of hyperbaric systems covers also operating manual with a maintenance program included.

Fire suppresion systems and fire prevention

The special attention in the design of the hyperbaric facility is dedicated also for fire prevention and protection, as fire is recognised as the single most hazardous factor leading to a fatal disaster during hyperbaric sessions. The basic requirements for fire suppression systems as a part of a hyperbaric system are defined in the prEN14931. However those requirements are only general and therefore there is a need for preparation of a dedicated European Norm, which will cover this particular subject in detail. Regardless of the fire fighting system for hyperbaric chambers, the equally important problem is protection against and prevention of fire outside the chamber, in its proximity. Such an event is a potential serious hazard for chamber occupants, as there is a possibility that the chamber operator will be unable to safely finish the session due to direct threat to his health, or the evacuation of the chamber occupants through the zone of fire and smoke outside the chamber presents the risk of burns or carbon monoxide intoxication. Therefore the design of the hyperbaric system should cover also fire fighting systems inside and outside the hyperbaric chamber as well as a maintenance program, frequent checking of the system and regular training of the personnel in its usage.

2.3 Hyperbaric facility

To operate the hyperbaric system and to convert it to fully operational hyperbaric facility there is a need to have qualified technical personnel, including chamber operators, technicians and supervisors, as well as medical personnel, including physicians, nurses and attendants. Details on education, training and responsibilities within the team are presented elsewhere in this book and therefore only the minimum team size needed for conducting a HBO session is discussed here.

2.3.1 Personnel

As depending on types of hyperbaric chambers used, type of patients treated in the facility and system of work (continuous system versus system with predefined working hours and on-call stand-by) different functions are involved and therefore different number of personnel is required to keep the facility working.

During the session in the monoplace chamber the minimum team of staff consists only of a hyperbaric physician to supervise the treatment and for emergency assistance (if necessary), and an operator to conduct the session[4]. This implies that only two persons can effectively conduct the hyperbaric session. On the other hand, due to relatively small dimensions of such chambers there is a possibility to install more that one chamber in the room. The open question is whether a small team consisting of only two persons can operate safely more than one monoplace chamber at the same time. In centres where there are monoplace chambers installed, one operator can sometimes serve for several chambers. Such practice depends on the status of patients and the needed level of supervision. In every case the decision should be left to the medical supervisor with all responsibility, however the logical restriction is that the maximum ratio should not be higher that 3 or 4 chambers per one operator and that all chambers controlled by one operator need to be located in the same room.

During the session in the multiplace chamber the minimum team size consists of a hyperbaric physician for supervision of the treatment, a medical attendant for taking care of patients inside the chamber (under pressure) and an operator to conduct the session from the outside[4]. Because the size of multiplace chambers differ from 2 to even 30 patients, the actual number of medical attendants inside the chamber can be higher that one. Generally, one attendant can take care preferable of 4 to 6 patients, and a maximum of 8 to 10 elective patients that are familiar with the hyperbaric environment. There is a need for increasing the number of attendants if there are more patients for the first time under pressure or there are patients who need special attention (child, handicapped, mentally retarded), or the hyperbaric system consists of several chambers with some restriction of smooth movement of the internal personnel. The open question is whether the medical attendant should stay under pressure for the whole session. In most European centres with multiplace chambers there is an obligation for the medical attendant to stay under pressure for the whole session. However, in some countries it is possible that in some circumstances the medical attendant can leave patients under pressure alone. For example, if elective patients who can take care of themselves are familiar with the procedures (it is not their first time inside the chamber), they can be left during the plateau phase with the medical

attendant staying outside the chamber ready for immediate access to the inside if required. The exact location of the individual members of the minimum team is the responsibility of either the duty physician or duty supervisor, however the whole nominated team should remain in the facility and immediately available including the possibility of the need to give immediate assistance under pressure[4].

Actual team size that is needed to keep the medical hyperbaric facility working depends on several factors:

- System of work: 24 hours / 7 days a week vs. predefined working hours with or without on-calls
- Type of patients treated: emergency patients / intensive care patients / chronic patients / injured divers
- Type of chambers used: monoplace / multiplace, number of seats
- Type of sessions conducted: recompression / non-recompression schedules, time / pressure / breathing gas mixtures
- Multi-role abilities of the available staff
- System maintenance: self-conducted vs. contracted by third parties.

The organisation of the hyperbaric facility should include clear definitions of all skills involved in the treatment process (physicians, nurses, supervisors, attendants, chamber operators, technicians and others) and clearly defined functions and responsibilities are mandatory. For all members of staff there is a need for ensuring the initial background, education and training in the field of hyperbaric medicine, as well as planning of refreshment courses and continuous education.

The important step in harmonisation of knowledge and skills needed to work in hyperbaric facilities on the European level was done in 1997 by the European Committee for Hyperbaric Medicine (ECHM) by publication of "Educational and Training Standards for the Staff of Hyperbaric Medical Centres" with definitions of professional qualifications, functions, definitions of jobs, as well as description of learning modules needed to train the personnel[7]. During the preparation of this book, the ECHM document is being updated by the Working Group "Education and Training" of the COST Action B14 "Hyperbaric Oxygen Therapy" mainly by précising the content and volume of courses, as well as requirements for continuous education. The problem of internationally recognized certification of hyperbaric personnel with reciprocal recognition of qualifications between the academic and training institutions in Europe is well recognized by the community. The initiative to create an accreditation body for hyperbaric medicine resulted in creation of the European College of Baromedicine (ECB), officially launched in 2000 in Malta. In the future, the harmonised

certification of hyperbaric specialists will allow free movement of the staff between European hyperbaric centres.

The important aspect of organisation of the hyperbaric facility is the multidisciplinary approach to treatment. Due to general effects of the hyperbaric oxygen on the human body, HBO is used in many different pathologic entities. Moreover the interaction of hyperbaric oxygen with other treatment modalities and concomitant diseases cannot be neglected, as in some cases this can offer synergistic and in others antagonistic reactions. Therefore the hyperbaric treatment needs to be performed with close cooperation with many specialists (including anaesthesiologists, intensivists, surgeons, laryngologists, pulmonary specialists, oncologists, radiologists, diabetic specialists, etc). The system of clinical consultations, coordination of the medical procedures and multidisciplinary follow-up of patients should be prepared for every clinical indication being treated in the hyperbaric facility.

Many other professionals with different qualifications may be engaged within a hyperbaric facility, depending on the special characteristics of the facility and the hospital or institution where it is located.

2.3.2 Occupational hazards

The pressurize environment by itself, as well as medical devices, including hyperbaric chambers, used in the hyperbaric treatment introduces additional risks for patients, personnel and third parties present in the facility. It is especially important when there is an exposure to the pressurised environment by medical attendants resulting in occupational hazard similar to professional diving. This implies that the hyperbaric facility should for its personnel develop a system of appropriate medical examination, prevention of decompression illness, and reporting of any work related negative consequences[8]. In order to cooperate in prevention and reporting of pressure related health problems, all personnel need to be adequately trained in recognising signs and symptoms of decompression illness. Procedures for recompression of ill personnel need to be prepared in advance altogether with adequate gas volume to conduct the recompression schedule. To decrease the incident rate of decompression illness of hyperbaric staff oxygen decompression is recommended[8]. Some centres further decrease the risk of decompression illness by avoiding decompression obligation of medical attendants using the system of exchange of the inside attendants according to no-decompression limits[9].

2.3.3 Risk management process

To minimize all risks that can affect patients, staff or the third parties, the risk management process is necessary and it should cover any activity within the hyperbaric facility. The risk management process should be documented and should include risk analysis, risk evaluation and risk control[10]. Parts of the risk management process are generic for all medical facilities allowing partial usage of solutions from other facilities. On the other side, some hazards are specific for hyperbaric medicine and strongly depend on its specialized equipment. Therefore, each hyperbaric facility should prepare those parts by themselves. As a basis, some general European documents can be used, including Final Report of the Working Group "Technical Aspects" of the COST Action B14 "Hyperbaric Oxygen Therapy" with hazard identification for HBO as a part of a risk analysis[11]. One of the results of such a process is the collection of operating procedures – standard and emergency – that describe in detail the working practices for all anticipated activities within the facility. Those procedures should be included in the operating manual of the facility at the design time; they should be reviewed periodically and updated as appropriate[4].

2.3.4 Clinical indications for HBO

Every HBO centre should prepare the list of clinical indications being treated there. Nowadays, there are lists of clinical indications for HBO prepared and approved by hyperbaric societies and organizations. In Europe the ECHM regularly organizes Consensus Conferences to update the list of indications. The procedure of including, updating or excluding the indication to or from the list is based on evidence-based medicine. Independent experts perform the review of clinical trials in every particular indication and results of this review are discussed by the jury of the conference selected from a broad range of relevant background to provide consideration of all aspects of the topic and maximum objectivity. Based on the level of evidence, the recommendation status could be:

1. "strongly recommended" (type 1 recommendation) for indications in which it is recognised that HBO positively affects the prognosis for survival,
2. "recommended" (type 2 recommendation) for indications in which it is recognised that HBO constitutes an important part of the treatment of that given condition, which, even if it may not influence prognosis for patient's survival, it is nevertheless important for the prevention of serious disorders,

3. "optional" (type 3 recommendation) for indications in which HBO is regarded as additional treatment modality that can improve clinical results.

Due to local regulations, reimbursement agreements and capability of the hyperbaric facility, the accepted list of clinical indications treated in the centre can be adapted with some modifications. In every case, the rationale for starting treatment should be clearly stated and progress of treatment should be carefully monitored in order to avoid overuse of hyperbaric oxygen therapy as a "last chance treatment". This justification is particularly important for indications that are not yet classified as "recommended" or "optional". In every such situation a careful evaluation of a risk/benefit ratio should be performed and it is strongly advised that for such indications the quality research protocols are put in place to assure and reinforce the credibility of hyperbaric oxygen therapy[12].

The HBO Therapy Committee of the Undersea and Hyperbaric Medical Society (UHMS) has also published a list of clinical indications for HBO treatment that is widely accepted[13]. It consists of pathologic entities for which HBO has substantial scientific support demonstrating therapeutic benefit. The main difference between the ECHM and UHMS lists is that in the UHMS list there is no level of recommendation stated explicitly.

2.3.5 Treatment protocols

Like other medical services, the hyperbaric facilities shall operate according to ethical principles using the best knowledge and accepted or well-documented medical protocols.

Medical protocols for HBO therapy should include:

- Type of sessions: pressure, time, breathing mixtures (if different from 100% oxygen), air breaks
- Intervals between sessions and total number of sessions
- Concomitant treatment (antibiotics, dress changing, surgical procedures, others if appropriate).

There are a lot of different types of sessions used nowadays in hyperbaric facilities. The optimal conditions for standard HBO session have not yet been defined, but it is generally accepted that in order to be clinically effective the HBO treatment should be done under pressure of at least 2 ATA and it should last at least 60 minutes[14].

2.3.6 Code of practice

Codes offer best practice being prepared and agreed by international groups of experts. In 2004 the members of COST Action B144 published a

European Code of Good Practice for Hyperbaric Oxygen Therapy. This document covers staffing (responsibilities, competencies and education, minimum team size during HBO sessions, fitness and health surveillance), equipment and gas supply, risk management and procedures (standard, emergency, maintenance and record keeping). It is closely related to the ECHM documents: "Educational and Training Standards for the Staff of Hyperbaric Medical Centres"[7] and "Recommendation for Safety in Multiplace Medical Hyperbaric Chambers"[15].

2.4 Centre for hyperbaric medicine

A centre for hyperbaric medicine is a medical facility that provides HBO for patients and additional treatments, surveillance and attention to the medical conditions of the patient. The design of the centre for hyperbaric medicine should cover also the links to other medical services, including emergency and operational rooms, consultants in different specialities, landing places for air evacuation, etc. The main difference between facility and centre is related to the extended scope of activity. The facility is mainly oriented on the therapeutical purposes offering the health services on the reference level depending on hyperbaric chambers and medical devices used inside chamber, as well as experience of personnel. The centre is conducting the services related to its hyperbaric facilities, however some additional activity is performed on its base. This includes research on basic and clinical hyperbaric and/or diving medicine, education and training of personnel of other hyperbaric facilities, international cooperation with other hyperbaric centres to conduct multicentric clinical projects and exchange of the staff.

2.4.1 Categorisation of hyperbaric chambers, facilities and centres

The categorisation of hyperbaric facilities is mainly done according to the type of hyperbaric chambers installed as well as overall capability to treat emergency and intensive care patients.

According to the NFPA 99[16] there are three categories of hyperbaric chambers:

- Class A chamber – a chamber used for multiple human occupancy (multiplace).
- Class B chamber – a chamber used for single human occupancy (monoplace).
- Class C chamber – a chamber used for animals, not human occupancy.

The British Hyperbaric Association defines four categories of hyperbaric chambers[17], which in fact are categories of hyperbaric facilities:

- Category 1 (multiplace) chambers – comprehensive hyperbaric facilities capable of supporting the treatment of patients who are critically ill, from any cause, and who may require hyperbaric intensive care.
- Category 2 (multiplace) chamber – facilities capable of receiving elective or emergency referrals for any accepted application of hyperbaric oxygen therapy, but excluding patients who are critically ill at the time of referral or are considered likely to become so.
- Category 3 (multiplace) chamber – facilities without some of the capabilities of categories 1 or 2, which are sited specifically to support diving projects (either commercial or recreational) and work in compressed air. These facilities should also be capable of providing elective treatment of residual symptoms of decompression illness.
- Category 4 (monoplace) chambers – facilities operating at relatively low pressure and without an air-lock capability. These facilities should be capable of receiving elective and emergency referrals of patients in any diagnostic category where the responsible doctor supervising the treatment judges that a requirement to have access to the patient during hyperbaric session is unlikely.

In the European Code of Good Practice for HBO Therapy[4] there are enlisted two types of hyperbaric facilities as depending on their relation to the hospital services:

- Hospital based facility which is a facility physically located on the hospital area.
- Standalone facility which can be distant from the hospital, however still there should be functional link to hospital services, like emergency, diagnostics and general medical support and the system of communication and transportation shall be defined in advance.

Generally speaking the capability to treat the critically ill patients and the connection to the other services in the hospital are the main features for the categorisation of the medical hyperbaric facilities. It is obvious that education, experience and size of the personnel are included in such categorisation.

On the other hand categorization of the hyperbaric centres should be performed according to their extended scope of work which means research capabilities, academic staff, education and training of hyperbaric staff from other facilities and centres by organizing conferences, courses, lectures, as well as international cooperation and independent quality assurance[12]. In the hyperbaric centres with the highest reference level, the qualification of personnel and the hyperbaric equipment used make them leaders responsible

also for conducting clinical and laboratory research in hyperbaric medicine, as well as participation in European programs in this field.

2.4.2 Quality assurance

The level of reference and quality of services should be subjected for independent survey in order for hyperbaric patients to be assured that the highest quality medical care is available to them, regardless of the facility's affiliation. Two different types of processes can be used: certification and accreditation.

Certification is a process by which an independent party (certification body) confirms by written notification that a product, process or service meets predetermined requirements. The worldwide mostly used basis for quality systems is the standard series ISO 9000 extended by some additional requirements that are specific for medical devices (including hyperbaric chambers). The compliance to these standards can be verified on voluntary request of the client by one of many worldwide certification bodies. The certification of compliance is given for a specific period of time (mostly for 3 years) and then it needs to be renewed. Up to now, the certification procedure for quality managements systems is mostly used for manufacturing medical devices, because – according to the Medical Device Directive 93/42/EEC – it is requirements for a conformity assessment by the certification body of the manufacturer's quality system and design criteria. However, there are no doubts at all, that a suitable quality system, which is implemented in all relevant stages, can be an important factor for the safety and performance not only of products but also services, including health care.

Accreditation, on the other hand, is a process by which association or agency (accreditation body) grants public recognition to a facility or centre that has met certain established qualifications or standards. When applied to clinical hyperbaric facilities it is the method to ensure that they are staffed with the well-trained specialists, that they are using properly installed and maintained quality equipment, being operated with the highest level of safety possible, that they are providing high quality of patient care and that they maintain the appropriate medical documentation including informed consent, treatment procedures, personnel involvement, etc. The only accreditation program for a clinical hyperbaric medicine facility has been introduced in 2000 by the UHMS and thirty-six medical hyperbaric facilities in the USA have been accredited according to this program until February 2005. At the same time as the UHMS started the accreditation program in the USA, the ECB has been launched in Europe as an initiative to create the accreditation body for education and training of hyperbaric staff. As a result

of internationally accepted accreditation, the reciprocal recognition of qualification between the academic and training institutions in Europe will allow free movement of the staff between European hyperbaric centres.

3. CONCLUSION

The design of the modern hyperbaric centre should cover all aspects of structure, organization and functioning of the hyperbaric medical facility for treatment, education and research in the international network of hyperbaric institutions and organisations. This is done on the basis of European norms and standards for hyperbaric medical chambers and systems. However, in some particular points where there is a lack of existing regulations, it relies on codes of good practice as well as clinical experience with the hyperbaric environment.

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Chapter 3.3

PATIENT MANAGEMENT

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Abstract: The modalities of HBO therapy application must be seen according to the patient's clinical situation. The range is from patients with minor impairment of state of health to critically ill patients. The potentially hazardous hyperbaric environment must be taken in to account in the selection of patients to be treated with HBO. With carefully performed patient assessment HBO therapy is a safe procedure for almost any patient. Absolute contraindications are rare

Keywords: Hyperbaric oxygen, Intensive Care, mechanical ventilation, monitoring

1. INTRODUCTION

There are well recognized indications for treatment with Hyperbaric oxygen (HBO) for which HBO therapy is either a first line therapy or a useful adjunct[1,2]. As these indications vary from treatment of acute hearing loss in an otherwise healthy and fit person to a patient suffering from severe gas gangrene with toxic shock and acute renal failure the modalities of HBO application must be seen according to the patient's clinical situation.

First, the appropriateness of hyperbaric oxygen therapy for treatment of the patient's disease must be considered. Guidelines are given by most of the national and international hyperbaric medical societies[1].

Second, the patient must be assessed for risks related to hyperbaric medicine by conducting a precise clinical examination with detailed history of the patient to confirm the absence of any permanent or temporary contraindication to hyperbaric oxygen therapy.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 651–669.

Third, essential patient care especially in critical ill patients must not be interrupted nor delayed by HBO. In chronic patients like diabetics the multidisciplinary therapeutic protocol must be continued at the hyperbaric unit. Documentation of the treatment progress is mandatory.

Fourth, HBO protocols may vary widely according administration of therapy pressure, breathing gases (pure oxygen, gas mixtures like Heliox), time duration, repetition and total number of treatments. HBO treatment can be the only therapy for the disease or it can be only one part of a complex multidisciplinary therapeutic regime. Standard operating procedures for the management of patients treated in hyperbaric facilities should follow the European Code of good practice for HBO therapy[3].

Fifth, there is a variety of chamber designs. Hyperbaric oxygen therapy can be performed in monoplace or multiplace chambers, with each of them having their own specific benefits and problems. In a monoplace chamber the patient is alone and there is no direct access to the patient possible during the hyperbaric treatment. Multiplace chambers are designed to either treat several sitting patients simultaneously or critically ill patients accompanied by attending staff. A clear advantage to monoplace chambers is the avoidance of exposure of the health care team to hyperbaric pressures, though complications due to hyperbaric exposure in attendances are rare.

Figure 3.3-1. Multiplace chamber, Hyperbaric Centre Murnau

In Europe multiplace chambers are more common. Modern multiplace „walk-in" chambers have several advantages regarding patient care and treatment possibilities specially in the treatment of critically ill patients under hyperbaric conditions.

Safety for patients and staff is the most important consideration. HBO therapy must not add any additional serious risk to the patient nor the staff.

2. CHALLENGES OF PATIENT MANAGEMENT UNDER HYPERBARIC CONDITIONS

Patient treatment in a hyperbaric chamber is not only treatment in an other area of the clinic or an other consulting room, HBO therapy exposes the patient to an environment which is potentially hazardous taking into account the exposure of patients to increased ambient pressure and increased partial pressure of oxygen. Nevertheless clinical experience over years has demonstrated the safety of HBO therapy when conducted under internationally accepted rules. The management rules for treating patients under hyperbaric pressure should follow the European Code of good practice for HBO therapy.

Any medical equipment used under hyperbaric conditions must be certified for this use. In cases when medical devices not certified by the manufacturer need to be used in the hyperbaric environment the personnel has to check it before installing (for more information see chapter 3.1).

Table 3.3-1. Environmental constraints on patient care under hyperbaric conditions

Care delivery	• Personnel • Treatment • Monitoring devices • Treatment devices
Location	• Hospital Based / non hospital based • Patient transportation • Limited space
Safety	• Device performance • Device safety (Fire risk) • Regulation issues

In multiplace chambers several sitting patients are treated simultaneously. The necessity for attendants inside the chamber during the treatment is depending on the decision of the responsible physician. At our institution any first treatment in a patient is accompanied, further treatments of more than one patient are performed unaccompanied. Single patient treatments always require an accompanying attendant. Critically ill patients are in any case accompanied by at least one attendant. Exact planning of the treatment course is necessary because physicians and nurses attending the patient are not able to freely move in or out of the chamber for obvious reasons. Modern chambers all are equipped with a small, separately locked front room, serving as a personal transfer lock, nevertheless changes in attendants have to be carefully planned to avoid any decompression problems[4]. Multiplace chambers are pressurized with air and patients breathe oxygen through tight fitting face-masks, head-tents or T-tubes, when intubated or tracheostomized. In contrast, the attending staff breathes air

from chamber atmosphere, except during decompression where 100% oxygen breathing via the built in breathing system (BIBS) is strongly recommended[4] to increase safety for nurses and physicians.

Equipment, medications etc. may only be available after some delay as they need to be transferred in or out of the chamber via an additional small transfer lock. Emergency medication and equipment for the individually treated patient must therefore be planned and stored inside the hyperbaric chamber.

2.1 Patient assessment

Before starting hyperbaric oxygen treatment in a patient for the first time a carefully performed medical examination must be performed. This should include the detailed medical history of the patient to confirm the absence of any permanent or temporary contraindication to hyperbaric oxygen therapy.

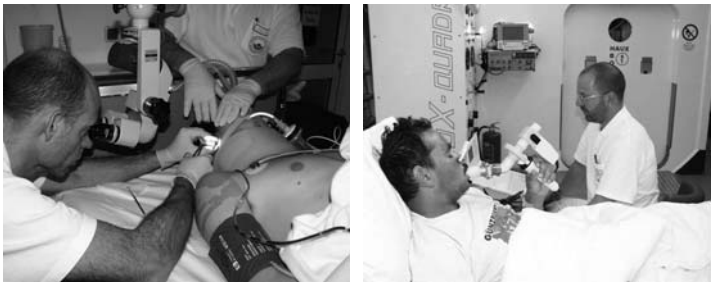

Figure 3.3-2 a: Otoscopy and myringotomy in a critically ill patient prior to HBO therapy; b: Lung function test prior to HBO therapy

Carefully performed clinical examination including nose and throat exploration, auscultation of the lung, otoscopy and lung function test has to be performed. To early detect changes in lung function caused by oxygen toxicity repeated lung function tests are recommended approx. after 20 hyperbaric sessions. Chest x-ray should be performed to detect any abnormality like bullae or pneumothorax.

Patients must carefully be instructed in ear equalization techniques and behaviour in case of emergencies like oxygen seizures. Safety instructions regarding fire risks, especially synthetic clothes and forbidden items inside the hyperbaric chamber should be given at the beginning of any treatment.

2.2 Side effects of HBO therapy

The side effects of hyperbaric oxygen therapy are well known. They are related to the three phases of the treatment course: compression, isopression and decompression. During compression there is mainly a risk for barotrauma of the middle ear, the inner ear and the sinuses. This risk can be minimized by instructing the patient in ear clearing techniques like swallowing, chewing and modified Valsalva manoeuvre. It is the duty of the hyperbaric nurse to assure that this procedure is well understood and performed by the patient. The administration of decongestants might be helpful. In intubated and unconscious patients myringotomy should be performed prior to the HBO treatment. Local anesthesia can be performed by filling the auditory canal with 2% lidocaine with epinephrine which vasoconstricts bleeding vessels after the myringotomy and offers some local pain relief. If repeated treatments in a mechanically ventilated and sedated patient are planned the insertion of a myringotomy tube is recommended.

Side effects at isopression are due to the toxicity of the breathing gas or its components namely oxygen and nitrogen. N_2 toxicity does not play a role in HBO treatment as the full symptomatology of N_2 toxicity is generally limited to ambient pressures beyond 500 kPa and the oxygen breathing patient is not prone to this side effect.

Oxygen toxicity is of particular practical importance for the patient. It affects the central nervous system, the eyes and the lung[5]. Oxygen toxicity is the limiting factor for HBO therapy regarding maximum pressure (pO_2) and duration[6]. The risk can be minimized by applying repeated air breaks (5 min air break for every 30 min oxygen breathing)[7]. Cerebral oxygen toxicity presents in the occurrence of cerebral seizures. Therapy is the immediate removal of the oxygen mask and switch to air breathing for the patient. Additional treatment like benzodiazepines or barbiturate is almost never indicated. Decompression must be stopped immediately when oxygen seizures occur to avoid an over inflation and consecutive barotrauma of the lung. Important factors that influence the risk of oxygen seizures are common in ICU patients: administration of steroids, adrenergic drugs, thyroid hormones, fever, sepsis and respiratory acidosis, whereas sedatives and anaesthetics are protective.

The effect of oxygen toxicity to the eyes is only seen in patients receiving HBO over several weeks and manifests as myopia. It is normally reversible in a short time[8].

In contrast to acute CNS toxicity pulmonary oxygen toxicity is cumulative[9]. It manifests as decrease in functional residual capacity with subsequently impaired gas exchange. The protective effect of antioxidants such as Superoxide dismutase, N-aceytylcysteine, or Vitamin E, documented

in animal studies must still be confirmed in humans. (For details on oxygen toxicity see chapter 3.8)

Despite the fact that arterial gas embolism (AGE) and pneumothorax due to pulmonary over pressurization are well known in divers, pulmonary barotrauma during decompression in hyperbaric chambers is rare. At our institution we experienced one case of a patient developing pulmonary barotrauma and consecutive AGE. During decompression the patient had to cough heavily and became unconscious a few minutes later. Immediate intubation and recompression to 300 kPa under 100% oxygen was performed. Patient's Consciousness was regained after few minutes. During the following slow decompression the patient was extubated and left the chamber without residuum. No pneumothorax was detected in the following chest x-ray. The risk especially for the group of patients requiring chronic hyperbaric treatment for ischemic wounds and osteomyelitis seems to be given, as most of them are heavy smokers and have significant obstructive lung disease which could lead to air trapping and alveolar over distension during decompression.

2.3 Location and patient transport

Hyperbaric chambers are no standard equipment inside hospitals. World wide only few hospitals have direct access to a hyperbaric chamber. Rarely there is direct connection to the ICU. Transportation of a critically ill patient to a sometimes distant location in the hospital or even outside might be necessary. It is well recognised that both inter- and intrahospital transfer may ad an independent risk to patient morbidity[10]. Guidelines for patient transportation published by the SCCM should be followed[11].

Figure 3.3-3 *a.* Patient transfer into a standard hyperbaric chamber with round opening *b.* Transportation of a critically ill patient into a hyperbaric chamber using a special transport device (Trauma Centre Murnau)

Transportation as well as HBO treatment itself may result in the patient's absence from the ICU for a couple of hours. For certain patients there might be the need to repeat the transportation process two to three times within a 24 hour period. Overall treatment in the ICU should not be impaired by HBO therapy and transportation.

The risk of transportation can be reduced by minimising patient transfers using dedicated hyperbaric beds. Care must be taken that the selected bed is suitable for hyperbaric conditions. Special transportation units with adequate intensive care ventilators allow similar ventilator settings to those used in the ICU during transportation. Especially after HBO treatment, there is a risk of atelectasis formation in mechanically ventilated patients if adequate PEEP is not kept. Unfortunately most ventilators which are in use under hyperbaric conditions do not meet the requirements for modern respiratory therapy (see below). The possible benefits and potential risks of hyperbaric oxygen therapy should always be carefully considered. If for example the well established treatment protocol for an intensive care patient is effectively disturbed because of hyperbaric therapy, in most cases this optional therapy becomes questionable. The option for HBO therefore should always be a multidisciplinary decision.

2.4 Personnel

Manual and mental performances of the chamber attendants may be impaired by noise, temperature changes following pressure alterations and rarely by inert gas narcosis during treatments at high ambient pressures. Any member of the staff entering into the hyperbaric chamber must be medically fit and educated to work under pressure. Legal aspects according to national laws have to be considered.

Figure 3.3-4. Intensive care nursing work inside a hyperbaric chamber and at the control unit

Successful patient management in hyperbaric institutions depends on a motivated team of specialists with good experience both in patient care and hyperbaric issues. It is obvious that, for the best treatment of the critically ill patient with HBO, the hyperbaric unit should also be staffed with personnel who are well and regularly trained in treating critically ill patients. The best way to meet this demand is by running the hyperbaric chamber as an extension of the ICU. Proximity allows for quick and safe transport and immediate consultation when needed. Equipment and personnel is easily accessible.

2.5 Monitoring

Monitoring of physiological parameters during HBO session strongly depends on the severity of the illness and clinical status of the patient. The set of measured parameters can be as simple as only 3-leads electrocardiography (ECG) up to sophisticated measurements including pulmonary capillary wedge pressure (PCWP) or electroencephalography. (For technical aspects see chapter 3.1.)

Blood pressure measurement can be done manually acc. to Riva Rocci but may be somewhat difficult as ambient noise level might be high. Automatic blood pressure measurement devices need to place the electrical pump for inflation cuff inside the chamber to ensure working at equal pressure. This might ad an additional fire risk and therefore careful examination of the mechanism is necessary prior to the use inside a hyperbaric chamber. Monitoring displays inside the chamber normally work without any problems.

Direct arterial blood pressure, as any other direct pressure measurements can be easily performed during HBO therapy. The indwelling arterial catheter has to be continuously flushed. This is performed by a pressure bag, which is surrounding the saline container and pumped to approx. 300 mmHg with air. Due to compression in the chamber this pressure bag has to be refilled under pressure. It has to be kept in mind, however, that this additional portion of air needed while under pressure will expand massively during decompression. Therefore, the manometer of the pressure bag has to be controlled carefully during decompression, and the bag pressure has to be adjusted to prevent the bag from over inflation or even explosion.

Efficacy of HBO therapy may be assessed by monitoring transcutaneous partial pressure of oxygen ($TcPO_2$) .Measuring $TcPO_2$ at a reference side (subclavial point) and at the wound level is a useful technique to objectively estimate the quality of oxygen delivery to the tissue. Transcutaneous oxygen monitoring has been shown to reflect tissue perfusion[12].

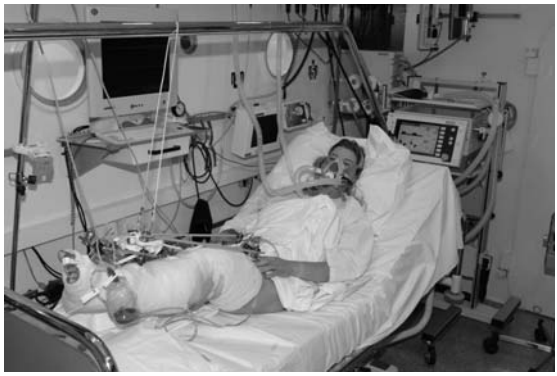

Figure 3.3-5. Monitoring devices inside a hyperbaric chamber

$TcPO_2$ measurements at HBO treatment pressures are an accurate non-invasive method for predicting the final outcome of major vascular trauma of the limb[13] and other ischemic diseases treated with HBO. Repetitive measurements during the treatment course may help to follow the healing process[14].

Together with measurement of the transcutaneous partial pressure of carbon dioxide ($TcPCO_2$) $TcPO_2$ can be used for control of ventilation / perfusion status of the patient.

Moreover, it can be used as one method for quality assurance, giving independent measurement of the dose of oxygen absorbed by the patient leading to early detection of any leakage in the breathing systems. An other possibility is to measure the expired oxygen concentration near the over board dumping system. Only minor leakages of the oxygen mask lead to a significant drop of the expired oxygen concentration.

Laser-Doppler flowmetry is used for assessment of peripheral microcirculation and is suitable for non-invasive monitoring of skin perfusion under hyperbaric conditions.

2.6 Respiratory effects

Respiration under hyperbaric conditions is effected by a number of variables: hyperoxia, elevated pressure (elevated gas density), temperature changes, and patient behaviour.

The influence on the human autonomic respiratory control normally is insignificant. Only in patients depending on hypoxic (oxygen triggered) drive the introduction of hyperoxia can ablate their respiratory drive. As pressure increases, the gas density increases and thereby work of breathing increases. Under standard treatment protocols this increased workload is hardly noticed by patients. Only in respiratory impaired patients or in long

lasting treatments (diving accidents) there might be some problems. Tight fitting masks and helmets can easily used for non invasive ventilation (NIV) in patients with minor respiratory distress, especially in elderly patients.

Patient anxiety sometimes leads to hyperventilation. In most cases this can be solved by calming the patient verbally down.

In patients with pre-existing respiratory insufficiency like pneumonia, lung oedema or ARDS depending on the clinical situation, intubation should be liberally performed before HBO therapy is started. It is easier to have the patient intubated before beginning the HBO session, rather than running into an emergency situation and to have him intubated inside the chamber during the treatment.

2.7 Blood gas analysis

Blood sampling during HBO treatment requires meticulous attention to avoid bubbles in the probe. Fast sample decompression in a transfer lock produces bubbles and may thereby render analysis impossible[15]. With very slow decompression rates in the transfer lock, bubbling can be minimized, but any bubbling will lead to false low values of oxygen partial pressure. In pH and PCO_2 values minimal changes will occur[16]. Weaver and co-authors have shown that PO_2 values can be measured reasonably accurate if the sample is processed immediately after decompression[17]. Exact measurement would require a blood gas machine operated and calibrated at ambient pressure of the chamber. Practically this is feasible only under research conditions.

2.8 Fluid therapy

The easiest method of fluid delivery in multiplace chambers is using a free drop system. Care has to be taken to regulate the volume of gas compartments in the infusion bottle and in the drip chamber of the fluid line during the HBO session according to changing pressure otherwise rapid infusion or gas embolism may occur. Using flexible PVC pre-packed infusions allows avoiding of the hazards of too fast fluid application, blood draw-back into the line and introducing gas into the blood vessel of the patient. According to Boyle-Marriott's law gas volume changes in the drip chamber while the pressure inside the hyperbaric chamber is changed. The drop-rate of the administered fluid must constantly be adjusted. This method is not suitable for administration of fluids and drugs which need to be administered at a constant rate.

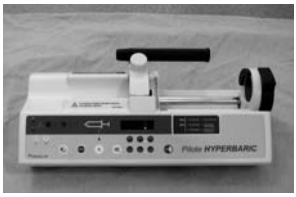

Figure 3.3-6. Syringe pump for use in hyperbaric environment

Electrical syringes and infusion pumps are needed to accurately deliver active drugs like inotropic agents and sedatives as a part of intensive care. As any medical device being introduced into the hyperbaric chamber, infusion and syringe pumps need to be carefully checked for additional hazards created by their usage in hyperbaric conditions. Usually these pumps work safely when the soft key pad is connected to ambient pressure and care is taken that the electric pump is equipped with a spark free type motor.

Intravenous lines should be placed prior to the start of the HBO therapy since insertions under hyperbaric conditions might be more difficult than under normobaric conditions due to vasoconstriction.

Under hyperbaric conditions special emphasis must be paid to intravenous lines, especially central venous lines as they can be a source of severe gas embolisation. Entrance of even small amounts of gas into the vessels under hyperbaric conditions can cause severe injury during decompression just by expansion of the gas bubbles.

If a central venous canulation via a subclavian or jugular vein in a patient prior to HBO therapy was necessary, a chest x-ray is strongly recommended to exclude any iatrogenic pneumothorax.

2.9 Other treatment devices

When HBO is performed as part of a surgical treatment protocol, wound drainage is not uncommon. Several pressure or/and suction regulators may be necessary for each patient. Very often in the draining containers a negative pressure is kept to create a suctioning of blood and secretions. Under hyperbaric conditions the ambient overpressure adds to the already high forces which rest on the container walls. This can result into an implosion of the container which may not only injure the patient but can also lead to a wide spread and difficult to clean contamination of the chamber. Therefore only HBO tested containers should be used.

Drainage of chest tubes should be connected to a constant pressure suction side or a Heimlich valve must be added to prevent loss of suction. Any untreated pneumothorax is a contraindication for HBO-therapy and may

easily result in an acute life-threatening tension pneumothorax just by decompression and expanding gas in the pleural space.

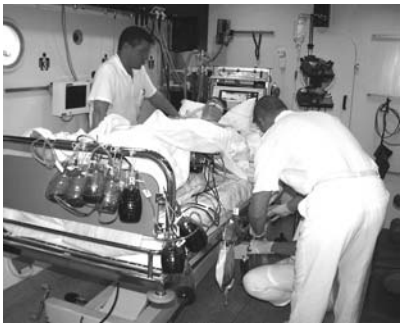

Figure 3.3-7. Drainage systems used during HBO therapy

There is some discussion on the use of external defibrillators. Defibrillation inside a chamber includes the risk of fire. Therefore, the defibrillator itself should be placed outside the chamber, and the leads with the defibrillation pads should be lead through an electrical porthole inside the chamber. It is questionable if these efforts are useful. The safest approach is to decompress while performing conventional CPR and to defibrillate out side the chamber. As the patient is super-oxygenated there should be no risk due to the short time delay when appropriate resuscitation is performed.

3. INTENSIVE CARE UNDER HYPERBARIC CONDITIONS

There are well recognized indications for treatment with HBO for which there is a need for intensive care. In some cases HBO is the main therapy, in others intensive care is necessary in the interval between hyperbaric sessions, or primary treatment is intensive care and HBO is an adjunct[18,19]. In either case, intensivists may be faced with HBO issues, and HBO therapists may be confronted with patients from the ICU.

Critical care units provide specialized monitoring, organ-support systems, and intensive care to patients with severe or potential major organ dysfunction that could become rapidly life threatening. The effective treatment of these patients must not be interrupted due to hyperbaric therapy.

Figure 3.3-8. Few chambers worldwide offer the opportunity to treat patients with hyperbaric oxygen in a standard clinical bed
(Hyperbaric chamber, The Alfred hospital, Melbourne, Australia)

Little is known about the physiological changes and the problems of hyperbaric oxygen therapy in intensive care patients. Larger practical experience exists only in a small number of specialist hyperbaric units. Only few publications refer to how HBO therapy is performed in ICU patients. Under the European COST B14 program a working group "Intensive care under HBO therapy" was established to further investigate this special therapy. First results were presented at the 7th ECHM Consensus Conference of Lille[20].

There are well accepted requirements for the systematic use of HBO in critically ill patients:

- The hyperbaric chamber should be specifically designed for the use with intensive care patients
- The hyperbaric chamber must be fully equipped to allow continuation of patient monitoring and special treatment
- The hyperbaric chamber should be located in or in immediate vicinity to the ICU
- The hyperbaric chamber must be run by a sufficient and well trained team with broad experience in both intensive care and HBO (physicians, nurses, chamber operators, technicians)
- Any device to be introduced in the hyperbaric chamber must have been evaluated, tested and acknowledged as safe in hyperbaric environment
- Any standard or emergency procedures must have been tested and documented before being implemented
- Quality assurance is to be implemented.

3.1 Circulatory effects of HBO therapy

Haemodynamic changes under hyperbaric conditions are described in a number of animal studies[21,22] but there are few human studies which focus the hemodynamic responses to HBO at clinically relevant pressures[23]. Usually the presence of high oxygen concentrations in the arterial blood is related to peripheral vasoconstriction and reflex bradycardia.

A reduction of blood flow under hyperoxic conditions has been documented in various tissues and organs[24,25]. This effect is restricted to tissues with preserved autoregulation and derives from reactive vasoconstriction. A decreased release of nitric oxide from its binding to cystein in the haemoglobin molecule caused by high oxygen tensions results in vasoconstriction[26]. An increase of the oxygen diffusion radius from the capillaries prevents a decrease of tissue oxygenation. This effect leads to oedema reduction and increased microcirculatory blood flow, an important therapeutic issue in acute traumatic ischemia.

Cardiac output decreases in proportion to the increased systemic vascular resistance (SVR). Bradycardia is common during HBO treatment. The mechanisms which lead to bradycardia are still not fully understood; possibilities include direct influence on the pacemaker function of the heart, hyperoxia itself, increased work of breathing with dense gases or the effects of dissolved inert gases[27]. Reduced cardiac output most probably relates primarily to this combination of heart rate reduction and increase in systemic vascular resistance. Normally, over the course of a hyperbaric exposure the initial bradycardia will become less pronounced, but does not tend to return to baseline levels until the treatment is completed. In critically ill patients this effect normally is overlapped by other haemodynamic effects leading to higher heart rate.

Whalen et al.[28] showed in a study of volunteers that cardiac output decreased significantly at the beginning of hyperbaric oxygen exposure, but this effect recovered during the later part of the exposure. Effects on human circulation under prolonged hyperbaric oxygen exposure have been studied by Pisarellio et al.[29]. Breathing oxygen under 200, 250 and 300 kPa for hours, volunteers showed a decrease in cardiac output in the early phase, that recovered in the later phase related to heart rate changes. Standard hyperbaric treatment profiles with intermittent air breaks were examined by Pelaia[30] in healthy volunteers. Cardiac output, heart rate and stroke volume were all significantly reduced in the early phase, while mean arterial pressure increased compared to atmosphere conditions. Cardiac output and stroke volume reduction rapidly reverted to control levels after cessation of HBO, but no change was noted during air breaks. Hordness et al.[7] demonstrated that the reduced cardiac output was independent to the ambient

pressure but strongly correlated to oxygen partial pressure. Wattel and Mathieu[31] measured haemodynamic parameters of critically ill patients in hyperbaric conditions, finding a reduction in heart rate and an increase in all mean pressures (MAP, MPAP, MRAP, MRCP).

It must be noticed that in critically ill patients special attention must be given to a well performed fluid balance as in "under resuscitated" patients HBO therapy might be ineffective because the expected rise in tissue oxygenation will not occur due to a lack of circulating volume.

3.2 Mechanical ventilation

Ideally a ventilator used in hyperbaric environment should ensure the same parameters and modes of ventilation as a modern ICU ventilator[32]. However, the performance of all pneumatic devices inside the hyperbaric environment is changed by increased pressure and altered by density of gases. There are a number of technical issues to be considered before using an ICU ventilator in hyperbaric chambers (see chapter3.1).

Ventilatory management has been successfully accomplished in monoplace and multiplace chambers using a variety of clinically used ventilators. Most of those ventilators have a tendency to change operating characteristics as ambient pressure changes. Further more most of the modern ICU ventilators use gas density dependent monitors for expired volume.

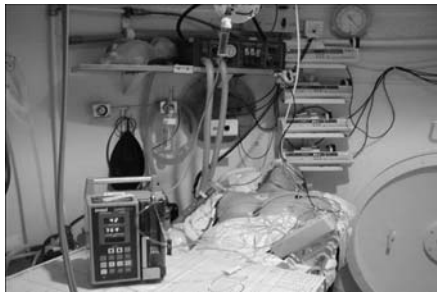

Figure 3.3-9. Intensive care patient under mechanical ventilation (RCH-LAMA) in a hyperbaric chamber (Service de Médicine Hyperbare, Hospital A. Calmette, Lille, France)

Up to now, only two ventilators have been CE certified for use in a hyperbaric chamber: the French RCH-LAMA ventilator and the Italian Siaretron 1000 Iper.

Draeger has made an attempt to modify the Draeger Evita 4 ICU ventilator for hyperbaric use. Although this ventilator meets all requirements

for modern respiratory care strategies it has to be stated, however, that there only exist two single prototypes modified for hyperbaric use. The Evita 4 ventilator designed for clinical use is not suitable for the use in hyperbaric chambers.

Measurement of airway pressure and exhaled tidal volume is mandatory for patients during mechanical ventilation under hyperbaric conditions. Mechanical spirometers are extensively used in hyperbaric chambers due to their simplicity.

Side-stream analysis of end tidal carbon dioxide partial pressure in expiration gas can be performed easily and reliably outside the chamber using decompressed expiratory gas.

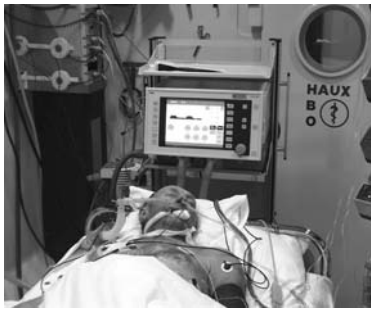

Figure 3.3-10. Mechanical ventilation using Draeger Evita IV during HBO therapy

Intubated patients may be ventilated by bag-to-tube ventilation during transportation, or in rare occasions even during therapy. In this case it is crucial that the bag is equipped with a device which ensures that the exhalation gas is vented out of the chamber and cannot contaminate the chamber atmosphere, as the exhalation gas is still oxygen-rich and increases the risk of fire. Ventilation bags used under pressure must be equipped with a regulating system ensuring appropriate gas delivery at higher pressures because of increased gas density.

In intubated patients special care must be given to the endotracheal blocking of the tube. The volume of the cuff changes during compression and decompression according to Boyle Marriot`s law. Therefore, prior to HBO therapy, air has to be evacuated from the endotracheal cuff, which is then filled with the same amount of liquid to achieve an appropriate seal. Distilled water should be preferred to saline as crystallization in the blocking system might occur resulting in malfunction. Foam cuffed tubes may be an alternative.

The safest solution is the use of an automatic cuff blocking device that keeps the cuff pressure constant in relation to the ambient pressure.

In the case of endotracheal suctioning care must be taken on the applied negative pressure to avoid any damage to the mucosa. Pressure regulated suction devices are recommended.

3.3 ICU equipment under hyperbaric conditions

Only few multiplace chambers have the size to allow the ICU patient to stay in normal hospital beds. In most cases, special stretchers designed to fit perfectly into the chamber have to be used. When a patient is transferred from his bed to such a stretcher, special attention has to be paid to any dislocation of endotracheal tubes, drainage or tubing.

Normal beds, especially high-tech beds commonly used in ICU units may not be suitable for hyperbaric conditions as any electronic device not encapsulated or specially adapted for high ambient pressures can be a source of problems.

4. CONCLUSION

In conclusion, hyperbaric oxygen is an important therapeutic modality for critically ill patients. However, the hyperbaric environment presents many unique challenges in the care of intensive care patients. To administer HBO therapy safely to these patients, a thorough understanding of the physical and physiologic changes is essential. The decision to treat an intensive care patient using hyperbaric oxygen should always be made in accordance with the other involved faculties.

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Chapter 3.4

A COST-EFFECTIVENESS EVALUATION OF HYPERBARIC OXYGEN THERAPY

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Abstract: Hyperbaric Oxygen Therapy (HBO) is currently widely used for the treatment of many disease conditions. Although considered effective at both obtaining a rapid healing and a reduction in overall treatment costs, not many studies are available to determine the cost-effectiveness value of the use of this treatment modality. This chapter examines the cost-benefit ratio of using HBO for some of the most common currently accepted indications. The use of HBO can imply significant saving for a nation's health-care system, in the order of hundreds of millions Euro per year

Keywords: hyperbaric oxygen therapy, cost-benefit, cost-effectiveness

1. INTRODUCTION

Hyperbaric Oxygen Therapy (HBO) is generally aimed at treating complex and serious disorders, either acute or chronic, frequently resistant to standard treatment and requiring prolonged and reiterated hospitalization as well as implying high medical, social and human costs.

HBO can often represent a uniquely effective treatment modality for such conditions, where abnormal oxygen demand/supply/utilization ratio is a cause and its normalization can reactivate natural repair processes.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 671–678.

2. COST-EFFECTIVENESS EVALUATION

The goal of an effective cost-benefit evaluation should be to evaluate the convenience of a new form of treatment as compared to the "standard" alternative.

A correct evaluation should take into consideration not only the direct costs of the clinical procedures involved, but other factors, such as the quality of life, long term health care and social costs, etc.

Such an evaluation should not be intended as a substitute to clinical evaluation and judgement, but it should be used as an essential instrument for health management decision making

Many attempts to evaluate the economical benefit of HBO with respect to standard treatments modalities have been made [1-3].

A proposed modality, which has been frequently adopted for this task, derives from the application of a predictive model elaborated by the U.S. Air Force School of Aerospace Medicine, as reported by Persels in 1987[4,5].

The possibility to estimate the number of HBO sessions which can be required / necessary in a given territory can be provided by the use of the following formula:

P5 = P1 x M1 x M2 x M3

where:

P5 = total HBO sessions for a given patient population in one year

P1 = number of hospitalizations for a given diagnosis in one year

M1 = correction factor for outpatients affected by P1 condition

M2 = fraction of P1 diagnosed patients effectively responding to HBO treatment

M3 = mean number of HBO sessions required for the P1 diagnosed HBO indication.

This formula can be applied for several conditions, provided the "M" values for each different one are properly identified.

On the basis of previous research and publications[1-3], the cost benefit ratio of the use of HBO for some of the most frequently used applications of HBO was re-examined, using the following M values

Diagnosis P1	M1	M2	M3
CO intoxication	1	0.6	5
Gas Gangrene	1	1	13
Necrotizing Infections	1.4	0.4	40
Diabetic Foot	2	0.4	30
Bone radio-lesions	2	0.7	35
Soft Tissue radio-lesions	2	0.3	35

The data were confronted with the epidemiological and economical information obtained through the Italian Ministry of Health during the years

1989 – 2000, regarding the average cost of hospitalization, based on the DRG system.

The resulting costs were confronted with the average cost for Hyperbaric Oxygen Therapy, as currently adopted in Europe, and for the number of treatment sessions defined by the assigned M value.

We referred to an average cost for HBO of 100 Euro per session (Italy), and to an average cost of one Hospital Day of 500 Euro/day for health facilities - i.e. hospitals belonging to a multi-facility Local Health Authority - and 603 Euro/day for "hospital authorities" - i.e. autonomous multifunctional hospitals - according to the current Italian data[6]. We used the average amount of € 550 for our estimates.

A DRG (Diagnosis Related Group) is a group of conditions which are related by their overall similar cost. This instrument is used to evaluate the complexity of a disease condition and the adequacy and efficacy of treatment. In the Italian Healthcare System, disease conditions are grouped into 456 DRGs, where each of them includes the conditions which are likely to generate a given level of overall cost.

DRGs are also classified by "weight", where "heavier" DRGs imply more complex disease conditions / health-care facilities and higher costs.

However, every DRG is assigned a maximum number of hospital days, called "Trim Point". The fee paid for any DRG is independent of the duration of the hospital stay until reaching the Trim Point, beyond which an additional daily fee is paid to the treating facility.

The DRG fee includes hospital "hotel" costs, personnel, the majority of drugs and the majority of surgical and nursing procedures. Some more complex procedures and necessities may be computed outside the DRG fee. HBO treatment, in Italy, is included in the DRG under code 93.95.

3. HBOT VS NO-HBOT COST-EFFECTIVENESS ANALYSIS BY CONDITION

3.1 Carbon Monoxide Intoxication

HBO is considered one of the fundamental treatments for this condition and it is believed to favourably affect both the length of hospitalization and the incidence of long term neurological sequelae and of acute mortality, with an average number of HBO sessions of 5.

Table 3.4-1. Economical indicators and HBO treatment of CO poisoning

	Mortality	Morbidity	Hospital stay (€ 550)	HBO Cost	Total Cost
HBO	1.7 %	4 %	15 days	€ 500	€ 8750
Non-HBO	7%	30%	30 days		€ 16500
Potential saving/pt					€ 8250 / pt
Potential saving %					50%

3.2 Gas Gangrene

HBO is a primary adjunctive therapy in the modern treatment of this disease. Both mortality and morbidity are reported as significantly higher in patients not treated with HBO, who also suffer from a higher incidence of major and seriously disabling surgery which has a high mortality rate itself.

The average number of HBO sessions is 13 during the acute phase and 30 during the tissue repair phase.

Table 3.4-2. Economic indicators and HBO treatment of gas gangrene

	Mortality	Morbidity	Hospital stay	HBO Cost	Total Cost
HBO	20%	15 %	7 days (acute)	€ 1300	€ 5150
			40 days (chron.)	€ 3000	€ 25000
Non-HBO	49%	60%	15 days (acute)		€ 8250
			90 days (chron.)		€ 49500
Potential saving/pt					€ 27600 / pt
Potential saving %					48%

3.3 Necrotizing Infections

The use of HBO in the treatment of serious necrotizing infections of soft tissue has been associated with a significant reduction of mortality and morbidity, as well as with a reduction of major surgical procedures and a reduction of hospitalization, with the frequent possibility to complete the course of HBO and surgical treatment as an outpatient.

Table 3.4-3. Economic indicators and HBO treatment of necrotizing soft tissue infections

	Mortality	Morbidity	Hospital stay	HBO Cost	Total Cost
HBO	20%	25 %	15 days	€ 4000	€ 12250
Non-HBO	50%	60%	30 days		€ 16500
Potential saving/pt					€ 4250 / pt
Potential saving %					26%

3.4 Diabetic Foot

In the diabetic the risk of major surgery and disability is considered to be 15 times higher than in the non-diabetic, and to increase with age and preceding amputations. Contralateral amputation is necessary in over 50% of the cases within 4 years from the first intervention. Ipsilateral re-amputation is also frequent and necessary in about 27% of amputated patients.

The use of HBO and an adjunct to the treatment of these patients has shown to reduce the incidence of major surgery up to 82%[2,7,8], as well as the general morbidity and the length of hospitalization periods

Table 3.4-4. Economic indicators and HBO treatment of the diabetic foot

	Mortality	**Morbidity**	**Hospital stay**	**HBO Cost**	**Total Cost**
HBO	---%	5 %	60 days	€ 3000	€ 36000
Non-HBO	31%	30%	100 days		€ 55000
Potential saving/pt					€ 19000 / pt
Potential saving %					35%

3.5 Radio Lesions

Tissue radiation injuries are generally divided into acute, sub-acute and delayed complications. Acute injuries are normally self-limited. Sub-acute injuries are typical of certain organ systems, e.g. radiation pneumonitis after lung cancer radio-therapy; these lesions can occasionally evolve into delayed complications. Delayed complications are seen after a latent period, which can be of even some years after the exposure to radiation.

HBO has been used extensively and effectively in the treatment of radio induced lesions for many years, mainly for the treatment of mandibular radionecrosis but also for the treatment of radiation injuries to other sites and organ systems.

In general the reported results are univocal and favourable to the use of HBO, with success rates varying from 60 to 100% and a number of required HBO sessions ranging from 30 to 40.

The reduction of morbidity, disabling or disfiguring sequelae, further need for corrective or major surgery is also a commonly reported results, by all the authors and regards both bone and soft tissue radio-induced lesions.

Table 3.4-5. Economic and HBO treatment of radio-lesions

	Mortality	Morbidity	Hospital stay	HBO Cost	Total Cost
HBO	---%	5 %	25 days	€ 3500	€ 17250
Non-HBO	1%	60%	38 days		€ 20900
Potential saving/pt					€ 3650 / pt
Potential saving %					17%

4. HBOT VS NO-HBOT GENERAL COST-EFFECTIVENESS ANALYSIS

We used Persels' formula on the number of patients annually discharged from Italian hospitals between 1989 and 2000 to determine the potential number of patients who should / could have been treated with HBO for their condition, thus calculating the potential number of necessary HBOT sessions nation-wide.

The average cost of a hyperbaric treatment session has been evaluated at 100 Euro per HBO session. The average cost of a hospital-day has been estimated in the range of 500 – 603 Euro per day (average 550), based on the DRG system described above, although it is understood that this cost may be somewhat under-estimated, especially for severely ill patients, needing intensive medical and surgical care.

Table 3.4-6. Estimated number of potential annual HBO treatments and costs in Italy

Condition	Patients	Persels Formula	HBO Treatments	HBO cost
CO Poisoning	300	300 x 1 x 0.6 x 5	900	€ 90,000
Gas Gangrene	555	555 x 1 x1 x 13	7215	€ 72,150
	acute repair	555 x 1 x 1 x 30	16650	€ 166,500
Necrotizing Infections	2760	2760 x 1 x 0.5 x 30	41400	€ 4,140,000
Diabetic Foot	7700	7700 x 2 x 0.4 x 30	184800	€ 18,480,000
Tissue Radio-lesions-Bone (mandible)	1493	1493 x 2 x 0.7 x 35	73157	€ 7,315,700
Tissue Radio-lesions Soft Tissue	1837	1837 x 2 x 0,3 x 35	38577	€ 3,857,700
Total	14645		362699	€ 36,269,000

Table 3.4-7 shows the potential nation-wide annual saving if HBO treatment of the indicated conditions would be regularly adopted and the parameters considered by the studies we referred to are used in the calculation.

Table 3.4-7. Estimated HBOT + Hospital costs vs. Treatment costs without HBOT. In Euro

Condition	Hospital Costs with HBO	Hospital Costs w/out HBO	Potential Net Saving
CO Poisoning	2,625,000	4,950,000	1581
Gas Gangrene	16,733,250	32,051,250	1332
Necrotizing Infections	33,810,000	45,540,000	1428
Diabetic Foot	277,200,000	423,500,000	1400
Bone and Soft Tissue Radio-lesions	31,688,250	38,393,300	1700
Totals	3915	3526	7441

These figures indicate a potential annual saving for the National Healthcare system of more than 180 Millions Euro, if Hyperbaric Oxygen Treatment were included as a standard adjunctive treatment modality in the therapy of the conditions we used for this evaluation, which are included in the indications for Hyperbaric Oxygen Therapy currently recommended by the European Committee for Hyperbaric Medicine and the Undersea and Hyperbaric Medical Society.

5. CONCLUSION

Hyperbaric Oxygen treatment for the currently internationally recommended indications not only appears to be clinically effective, but it also likely to induce considerable savings in the general costs of a nation's healthcare and social system and a better quality of life for the patients.

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Chapter 3.5

EDUCATION AND TRAINING OF HYPERBARIC CENTRE PERSONNEL

Roles,Tasks and Responsibilities

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Abstract: This is a short review on the respective primary roles and responsibilities of staff in a Hyperbaric Medicine centre. Daily experience, discussions in meetings and in congresses, and a critical review of our success in spite of any mistakes, will enhance this quality assessment and ultimately redefine some duties in the near future. Specific teaching and study of a European Code of Good Practice in Hyperbaric Medicine is strongly recommended

Keywords: Education - Medical Director - Hyperbaric Physician - Nurses - Attendants - Chamber Operators - Technicians - Courses - Syllabus - Staff - Academic requirements - Background - Development of a hyperbaric session - Hyperbaric team

The European History of Hyperbaric Medicine will probably be divided in the period before and after the 1st European Consensus Meeting held in Lille in 1994. This landmark event set the stage for the modern development of HBO in Europe.

Although not all the questions involved in the practice of Hyperbaric Medicine enjoyed unanimous and definitive agreement, possibly the most valuable contribution was the process of reviewing our primary challenges and deciding how to address them. In reviewing our work over the past 10 years, it is now apparent that many problems have been addressed and we have learnt a lot since then. Committees, working groups, and concerted individual efforts have provided great impetus to these efforts. The appearance of the COST-B14 programme was extremely valuable. In addition, the European College of Baromedicine may become a very useful tool in the development of the educational programmes that have been proposed in recent times.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 679–690.

We are learning from our mistakes and those of others. We should avoid being judgemental as most errors are not unique and we are not immune to making them ourselves. Nevertheless we should probe and benefit from these experiences and revisit former practices and beliefs to confirm their validity in the light of these findings.

In section 5 of the 1st Consensus Congress, we defined all the personnel levels involved in staffing a Hyperbaric Medical Centre (HMC). Each of these was defined in terms of functions, background, educational profile, academic requirements, continuous education, and optimal application. Now is the time to review some of these elements.

1. THE MEDICAL DIRECTOR

It was agreed that the Medical Director is fully responsible for all functions and activities in a HMC. He or she may delegate some of these functions and will obviously be assisted by as many professionals as are needed depending on the level of competence and the scope of practice of the centre.

Some of these duties are:

1. Supervision of the correct operation of the hyperbaric facility.
2. Study and development of the best practice for the specific centre followed by (1) the selection and appointment of an appropriate team of physicians, nurses, technicians and chamber attendants – both full and part-time; (2) determining chamber time and decompression procedures to avoid injury or illness.
3. Organizing adequate and continuous training for all staff (i.e., physicians, nurses, attendants, and chamber operators).
4. Risk assessment and safety procedures.
5. Quality assurance of all medical activities.
6. Definition of protocols and procedures for treatment.
7. Organising and arranging participation in multicentre protocols and studies.

We are perfectly aware of the situation in some hyperbaric facilities where hyperbaric medicine is conducted by engineers, technicians, or other professionals with limited technical knowledge of hyperbaric medicine, assisted by nurses and even by physicians under their control. The figure of the so-called **Hyperbaric Provider** has arisen as a person invested of all responsibilities inherent to the Hyperbaric Medical Centre, partially assisted in relation to medically oriented activities by one or several physicians trained in hyperbaric Medicine. These situations have been largely discussed and finally the commission strongly insisted on the following: Being

Hyperbaric Medicine a pure and conventional branch of medical practice, and being a hyperbaric system the tool or the instrument with which a drug called oxygen is applied, this kind of medical service must be absolutely under the direction and full responsibility of a physician called Hyperbaric doctor.

The background, education, and academic profile of the Medical Director are not easy to define in a few words. He or she is a Medical Doctor with a wide multidisciplinary education. Internal Medicine, Critical Care, Anaesthesiology and Reanimation, can provide the best background however, any specialty can be valid if the doctor receives adequate training. His/her educational programme will need to include Occupational Medicine, Sports Medicine, and other specialties like neurology, angiology, and pneumology.

Following the agreements achieved in the 1st Consensus Congress, a joint sub commission on Education was created with the European Diving Technology Committee (EDTC) with the scope of developing the basis for an educational programme in Diving and Hyperbaric Medicine. This commission was formed by Jordi Desola, Pasquale Longobardi (replacing the initial position of Paolo Pelaia) - ECHM, David Elliott, , and Jurg Wendling- EDTC.

A complete document was elaborated by this sub commission detailing the minimum educational requirements for Hyperbaric Physicians, in the framework of University level courses; directed by fully recognized and expert specialists. The document defined three levels of competency corresponding to: (1) introductory level -- necessary for Medical Examiners of divers; (2) more advanced competence in hyperbaric or diving medicine; and (3) that of a Diving/ Hyperbaric expert.

It was difficult to agree on what constituted an expert and how this was to be achieved. For the moment, the title is reserved for the Medical Director of a facility -- corresponding to level 3 -- but with multidisciplinary experience and advanced specialization; the training programme cannot easily be reduced to a single syllabus or a simple accreditation after completing a course, even though this may represent many classroom hours.

It is generally agreed that the Medical Director needs a level 3 education programme, complemented by a minimum of three years of work: either in an active hyperbaric medicine centre or in a high-level diving medicine centre. The future development, standardization and accreditation of courses will be based on this assumption.

Obviously this high level of specialization will need an active system of regular updates and continuous education. Prestigious institutions and

societies will provide Courses, Workshops and Conferences in the field of Hyperbaric Medicine. Annual Meetings of the EUBS, UHMS, ICHM, Consensus Congress and Workshops organized periodically by the ECHM, provide excellent tools for this purpose.

The medical director will also need to collate up-to-date training in special topics related to other associated medical specialties, i.e., resuscitation; angiology; neurology; and others, as well as specialized technical courses, i.e., fire-extinguishing devices, fire-prevention and safety of hyperbaric equipment.

As is the case in all fields of medicine, education and research should complement patient care services. Hyperbaric medicine is not an exception, and under the direction of the Medical Director, the highest qualified Hyperbaric Medical Centres should organise Courses, Workshops and periodical activities aiming to improve the education of staff at all levels, and to share this knowledge with other colleagues.

2. THE HYPERBARIC PHYSICIAN

Under the supervision and direct control of the Medical Director, the medical activity of the HMC is conducted by a variable number of collaborators of the same or similar background and education. Hospital-based HMC's, especially those treating patients in emergencies or critical care patients, will need support from several doctors.

The hyperbaric physician is directly responsible: for treatments provided around and within the hyperbaric chamber; for selecting the most appropriate treatment protocol; for performing direct monitoring and supervision of patients during treatment; and verifying the that treatment is running according to plan.

According to this policy, some of the tasks of the Hyperbaric Physician will be:

1. Selecting patient candidates for HBO treatment; verifying that the patient is suffering from an approved indication for HBO; detecting any contraindications; and identifying those patients in need of special care during their hyperbaric treatment.
2. Establishing the number, duration and profile for HBO treatments.
3. Conducting and implementing the results of multi-centre studies.
4. According to the protocol and procedures established by the Medical Director, organizing for an appropriately trained nurse or chamber attendant to accompany the patient in the chamber.
5. Assisting patients in the chamber when their condition requires it. In the case of patients in critical condition the hyperbaric physician may need the help of other specialised staff, like other physicians or nurses trained

in providing specific procedures in the chamber. This implies that the hyperbaric physician must have enough experience in critical care/resuscitation to maintain the intensive care procedures that a patient is receiving in the Intensive Care Unit (ICU), although adapted to the hyperbaric environment.

6. Assisting or managing complications related to hyperbaric treatments, i.e. barotrauma, panic attacks, or acute hyperoxic crises.
7. Controlling and assisting patients after the treatment, mainly in relation to the possible side effects of the HBO session.
8. Following-up the patients being treated for chronic diseases that may need more sessions of HBO. These include the assessment of the efficacy of the treatment, the outcome of the treatment, and to detect the possible manifestation of long-term undesired effects of HBO.
9. Communicating and collaborating with physicians from other centres that have referred patients for HBO.
10. Compiling reports, documents, and letters relative to the patients, as well as collective reviews of groups of patients being treated for specific illnesses.
11. Last, but not least, and in collaboration with the rest of the staff, carefully controlling and monitoring all safety measures in order to prevent technical and dysbaric accidents.
12. In the treatment of dysbaric illness – which is also an HBO indication – the same patient care principles should be observed by both diving and hyperbaric physicians even though the treatment schedules may be slightly different.
13. Similarly, hyperbaric physician may be competent to perform medical examinations for fitness to dive, as outlined in the recommendations of the ECHM/EDTC medical sub commission.

The nature of physician supervision during HBO treatment is a matter of ongoing debate. While there is the general feeling that a hyperbaric physician must be physically present in close proximity to the chamber, there are varying degrees of availability and oversight such and there might be alternatives such as (1) being within the facility; (2) within a certain distance or time from the chamber; (3) accessible by phone; and (4) supervising the chamber via a TV monitor. Following years of experience, specific enquiries and lengthy discussions it has been agreed that the hyperbaric doctor must be physically present in the immediate vicinity of the hyperbaric chamber i.e., in the same room, hall, or ward where the chamber is located, with direct contact with the staff and ready for immediate first response if necessary.

The education of Hyperbaric Physicians should also be multidisciplinary – as for the Medical Director.

We are also aware that there is a difference of opinion in some countries as to the preferred specialty for hyperbaric physicians. As of now there is consensus that no single specialty is preferred and several may be appropriate as long as this is accompanied by adequate training in hyperbaric medicine, complemented by documented experience. The minimal requirements of such education have been developed in the Training and Educational document delivered by the ECHM/EDTC Educational sub commission, and correspond to levels 2a and 2b. However, more advanced approaches will be developed for future educational programme according to the recommendations of COST- B-14.

There are frequent discussions on the differences in emphasis in training diving vs. hyperbaric specialists. In 1994 it was agreed that both specialties were of the same origin, differing only in the application of knowledge: Diving and the Hyperbaric Specialists both receive the same basic education. It is only the job-related application that differs. At present the intention is to supplement this common basic training with additional courses which afford super-specialisation in the more detailed and technically demanding areas. For example: composition and management of gas mixtures in deep diving is not essential for a clinical hyperbaric specialist working in a hospital-based centre of hyperbaric medicine; similarly in-depth knowledge of adjunctive hyperbaric treatment of soft tissue necrotizing infections is not necessary for diving medical specialists working in the offshore industry.

As for any member of the medical disciplines, those in hyperbaric medicine require continuous medical education by accredited participation in Meetings, Congress, Symposia, workshops, and by following the refresher and update programmes suggested or provided by the Medical director.

3. THE HYPERBARIC NURSES

The role of nurses in a HMC is of great importance. She / he is responsible for the practical implementation of patient care during hyperbaric treatment.

Hyperbaric Nurses perform the usual functions of their profession with some variations due to the characteristics of the hyperbaric activity. They are responsible for the direct administration of drugs, procedures, and meeting special needs that patients may require. In the case of those patients requiring intensive care in the chamber, nurses also take care of all the medical devices connected to the patient as prescribed by the hyperbaric physician’s orders. They are in constant support and vigilance from the

moment a patient leaves the ICU, en route to the chamber, throughout treatment and during the transfer back to ICU.

These procedures and activities include:

- Nursing assistance of patients inside the hyperbaric chamber, taking special care of the specific condition without disrupting the patient's normal treatments outside the chamber
- Adjusting of medical devices for operation within the hyperbaric environment, including drug administration; IV infusions; infusion pumps; perfusion systems; ventilators; transcutaneous Oximeters; etc.

This implies that the hyperbaric nurse needs qualification in or specialization in Critical Care. The training programme for hyperbaric nurses may be offered at the same institution where the HMC is located, and it should include the following topics :

1. General principles of Decompression Theory, Diving Technique, and Pneumatics.
2. Hyperbaric practice.
3. Safety and preventive measures.
4. Intensive critical care of patients.
5. Operation of monoplace hyperbaric chambers.
6. Other aspects inherent to both Diving and Hyperbaric Medicine, concerning their profession.

It was agreed that a special education programme for nurses should be developed. The Joint sub commission EDTC/ ECHM has acknowledged the need and will determine the primary nursing requirements in a Hyperbaric Centre, for the purpose of developing educational programmes, a syllabus etc., or at least a collaboration training programme in conjunction with nursing institutions. The recent creation of the European Association of Hyperbaric Nursing, will provide a practical solution to this challenge.

4. THE HYPERBARIC ATTENDANTS

Although it is clearly stated that the role of nurses in a HMC is of high importance, it is also agreed that their presence is not essential in all treatments. The hyperbaric attendant has been defined as member of staff, specially trained, although not necessarily highly paramedically qualified, in those whose functions related to taking care with basic medical requirements.

The term, hyperbaric attendant has had different meanings and connotations in the past. In some cases it may even be a physician or nurse accompanying patients in lieu of other personnel being available. As such it was agreed that a **hyperbaric attendant** could be any person responsible for direct care of

patients inside the multiplace chamber as determined by their respective scopes of practice and qualifications.

Therefore, all persons entering a chamber under pressure together with patients are attendants by definition. A hyperbaric attendant who is not a health care professional might therefore include individuals who:

1. Provide non-invasive and non-specialised medical support to patients both inside and outside the chamber.
2. Accompany patients who are receiving treatment inside the Multiplace Chamber, but who do not need special assistance (e.g., by doctors and nurses), but only basic support, oversight and assistance to give them confidence.
3. Teach patients how to equalize ears; how to fit the oxygen hood, and how to better adapt the oxygen-masks to their faces.
4. Control and secure oxygen mask or hoods to avoid oxygen leakage.
5. Perform other activities inside or outside the Chamber as directed by and under the supervision of the Medical Director, hyperbaric physician or hyperbaric nurse.

No specific background is required for such attendants, who are sometimes called advanced first aiders, emergency medical technologists (EMT's) or *Paramedics* in other countries. Even divers -- both recreational and professional – with an interest in first-aid, may be appropriate for this work, but this is not essential. They must receive simple but special training that should include the following:

1. Basic principles of work under pressure
2. Decompression theory and practice
3. Recognition of acute toxic effects of oxygen
4. Recognition of signs and symptoms of dysbaric disorders
5. Management of emergencies inside the chamber
6. Complete courses of Basic Live Support

It is presently not an uncommon practice in several hyperbaric facilities not to have attendants inside the chamber for the whole session, or even any part thereof. However, it is the ideal that patients should never be alone inside the chamber. It is obvious that this obligation present problems to some facilities even though it is mandatory. Ultimately each centre has to make its own determination on medical, nursing and paramedical coverage, bearing in mind that a standard of care comparison may view them unfavourably if complications were to arise.

As attendants also breathe compressed air during the hyperbaric treatment, and oxygen during decompression, they are potentially at risk for dysbaric injuries and need special skills to avoid them as described elsewhere in this book.

5. CHAMBER OPERATORS AND TECHNICIANS

In 1994 it was also agreed that while monoplace chambers can be operated by nurses and doctors and/ or hyperbaric specialists, a multiplace facility has a higher level of sophistication that requires specialised attention regarding chamber itself; air-compressors; pressurised gas sources; and the gas reserves. Managing this can be very complex. We also recommended that maintenance of the system should be performed by full-time Hyperbaric Technicians or by subcontracted specialised firms or enterprises -- both equally acceptable solutions.

Therefore, a Hyperbaric Medical Centre dealing with multiplace chambers must have qualified personnel to manage the hyperbaric facilities. These functions must be preferably carried out by specialised chamber Operators. Consequently, they are responsible for the safe operation of the chamber system according to the operating procedures. Among these a **supervisor** must be appointed.

The functions of the Chamber Operator in a multiplace facility are:

1. Operation of the internal and external devices of the Chamber.
2. Control and operation of the mechanisms for compression and decompression, and for delivering air, gas mixtures and oxygen.
3. Control and application of the safety regulations concerning prevention of fire, and oxygen toxicity.
4. Calculation, application and control of compression and decompression schedules for patients, nurses, attendants, specialists and doctors trained in hyperbaric medicine, including the use of decompression stops, when necessary.
5. Sometimes, to service the chamber under pressure from the inside to control or check the correct operation of determined parts of the pneumatic circuits or devices.
6. Adapting and checking medical equipment and patient care devices before they are introduced into the Chamber, so as to avoid malfunction of a fire hazard.
7. Control and checking of the operation of auxiliary parts of the chamber such as air-compressors, compressed gas sources, air reserves, pneumatic circuits, fire suppression and control systems.
8. Maintenance of the facility: Small technical repairs due to problems which occasionally might occur and do not require elaborate intervention by highly specialised technical staff.

The chamber operator - mainly the Supervisor - is responsible for all safety procedures within the centre.

However, it must be strongly noted that safety is not an exclusive responsibility of chamber operators, Supervisor and the Medical Director. Any person in the staff of a Hyperbaric Medical Centre has an inherent role and responsibility in relation to the safety for all activities performed within the facility as well as all technical parts of the system. It is the responsibility of any person to observe, detect, and to warn the chamber operator, supervisor and medical director, of any suspicions of malfunction or potential hazards during any time of the hyperbaric treatment.

The required background, specific educational profile, academic requirements, continuous education, and application of **chamber operators** as well as **technicians** is a new job description endorsed by the **Joint Educational Subcommission EDTC/ECHM;** the full programme is currently being developed. In the meanwhile, and as a reminder, the review of chapters 4 and 5 of the EDTC/ECHM Document on EDUCATIONAL AND TRAINING STANDARDS FOR THE STAFF OF HYPERBARIC MEDICAL CENTRES is recommended, as well as the EUROPEAN CODE OF GOOD PRACTICE elaborated by an international commission of experts within the COST-B-14 programme.

6. THE HYPERBARIC TEAM

6.1 Patient preparation

This involves:

1. Explaining and teaching the patients about the procedures to be followed.
2. Strongly and strictly alerting patients about avoiding any materials inside the chamber not specifically allowed by staff.
3. Alerting patients about the possibility of hazards (toxic effects, fire, loss of pressure) and teaching them about self preservation measures.
4. Teaching them to use oxygen masks and/or hoods.
5. Explaining to them how the chamber works and describing the devices inside.
6. Teaching them how to communicate with staff while in the chamber.
7. Instructing them to immediately notify HBO staff of any unusual experiences during the treatment.
8. Alerting them to the normal effects of pressure on the body and getting familiar with them: changes of temperature, humidity, noises, and voice.

9. Most importantly, explaining to them how to equalize their ears to pressure.

6.2 Attendance of patients during the HBO session

This involves:

1. Helping patients to enter the chamber safely.
2. Taking care of the patients during the compression phase, with special attention to the prevention of barotrauma of ears and of sinuses. This implies being extremely careful with patients who apparently seem to understand instructions but do not actively equalize their ears.
3. Helping patients to correctly use oxygen masks and/or hoods and to breathe quietly, smoothly, and deeply once at the scheduled treatment pressure.
4. Alerting patients to focus on their breathing pattern, to avoiding talking with others if not absolutely necessary.
5. Overviewing and controlling all activities and elements involved in the normal and correct progression of a hyperbaric therapy session.
6. Helping patients to take off oxygen masks and/or hoods during the air-breaks of the session.
7. Giving them direct assistance in case of any incident and/or any emergency inside the chamber.
8. Near to the end of the session, helping patients and preparing equipment for the decompression period.
9. Taking great care and paying attention to those persons and devices that can be especially sensitive to over-expansion effects of decompression.
10. Helping patients to leave the chamber after the treatment is finished.

A good and well coordinate team is necessary to correctly perform all the tasks required in a hyperbaric centre.

Thus, the minimum recommended team size for HMC using a multiplace chamber is at least three people who must remain in the facility and immediately be available at all times :

- One hyperbaric physician
- One attendant
- One operator

Obviously, the number of persons of the staff will be increased according to the needs of the facility or HMC. This is one of the tasks of the medical director.

Depending upon the type of HMC and of the services provided by the Hospital in which the Centre of Hyperbaric Medicine is located, continuous assistance may need to be provided.

If a 24 hours service is offered, complete hyperbaric teams may need to work in shifts. If this is to be maintained 7 days a weeks and 52 weeks a year, between 3 to 5 persons for each position will be necessary. For example, a HMC with 2 physicians per team, will need a medical staff complement of between 6 and 10 physicians in order to cover all the days of the year, 24 hours a day. This principle would apply to other staff as well.

There are no firm guidelines on the number of, or interval between, compressions for hyperbaric staff other than those determined by decompression schedules, Similarly there are no clear data related to adverse effects on the personnel of HMC's. Fortunately the incidence of dysbaric illness amongst hyperbaric staff is very low, and this is true even for very busy centres providing thousands of treatments over many years. The sixth Consensus Congress in Geneva, October 2003, dealt with safety of decompression procedures for staff of Hyperbaric Medical Centres. Oxygen decompression was recommended as a rule.

The general opinion is that more than one pressure exposures per day should be avoided and that the number should never exceed two compressions in the same day for a maximum of 5 continuous working days.

This has been a short review on the respective primary roles and responsibilities of staff in a Hyperbaric Medicine centre. Daily experience, discussions in meetings and in congresses, and a critical review of our success in spite of any mistakes, will enhance this quality assessment and ultimately redefine some duties in the near future. Specific teaching and study of a European Code of Good Practice in Hyperbaric Medicine is strongly recommended.

Chapter 3.6

SAFETY IN HYPERBARIC MEDICINE

Safety of patients and personnel

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Abstract: This chapter presents safety aspects of hyperbaric oxygen therapy (HBO) as a procedure affecting patients and personnel. It covers risk assessment, operating procedures, incidents/accidents and mishap reporting systems (by Roly Gough-Allen), hazards specific for HBO therapy affecting patients and personnel (by Jacek Kot), as well as fire prevention and fire fighting strategy (by Robert Houman)

Keywords: hyperbaric oxygen therapy; safety; risk assessment; risk management; hazard; emergency procedures; operating procedures; fire protection

1. INTRODUCTION

Medical hyperbaric facilities are parts of a general health care system and therefore its functioning depends on general regulations also concerning other medical services. Due to its specific nature hyperbaric oxygen therapy has some additional hazards[1] related with the hyperbaric environment, artificial breathing mixtures and the medical devices used inside hyperbaric chamber. These hazards can affect patients, as well as personnel involved in the treatment process. Identification of the hazards and the resulting risks[2] connected with the HBO therapy is the first step in safety management which should be done in every hyperbaric facility. For every identified

[1] The term "hazard" is defined as potential source of harm which could be physical injury or damage to the health of people, or damage to property or the environment.

[2] The term „risk" is defined as combination of the probability of occurrence of harm and the severity of that harm.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 691–711.

hazard, substitution of the existing arrangement by an alternative, safer procedure or method should be considered for implementation.

A safety policy must be prepared in every hyperbaric centre[1,2]. In most cases the medical director of the hyperbaric facility is responsible for all functions developed in the hyperbaric facility but usually he appoints a safety manager as a person directly responsible for preparation of a safety policy. The implementation of this policy effects the whole team taking care of the patients or operating the hyperbaric systems. During every HBO session a supervisor must be appointed who is responsible for the safety of operations during this particular hyperbaric session. However, all personnel must ensure the safety of the treatment by following written standards and emergency procedures. The crucial role of any safety program is education, training and the compliance of personnel. A periodical retraining of the emergency procedures should be instituted for every member of the team. Also patients need to be informed about the safety aspects before starting a hyperbaric treatment; an informed consent for treatment should include a statement about all safety precautions. Compliance of patients to these recommendations must be constantly controlled before every session.

The number of hazards in the hyperbaric facility is related to the system (chambers, pipes, compressors, gas storages, etc). The safety of the hyperbaric system is ensured by the proper design, installation and correct maintenance program. Details of the hyperbaric system and medical devices used inside chambers are presented in the chapter 3.1. HYPERBARIC CHAMBER AND EQUIPMENT.

For safety reasons, it should be assumed that every item of the technical equipment used within the facility including the hyperbaric chambers and supporting systems may at some time fail. In the event of an equipment failure, appropriate design and construction along with the correct use and maintenance of the system should allow for a safe hyperbaric session. However, it is virtually impossible to build a completely fail-safe system at a reasonable costs. The basic requirement for any system is that at any single-fault condition it should be possible to safely finish the hyperbaric session. This means that systems can work normally when any single unit fails. In this concept the term “unit” can mean any basic part (eg. any single valve), or it can mean whole sub-system (eg. gas compressors).

2. RISK MANAGEMENT

2.1 General notes

All employers must conduct suitable and sufficient assessments of the risks to health and safety of its employees or others coming into the work – place. Risk assessment is a pro-active process of assessing the risks associated with specific activities. This is an essential part of managing health, safety and environmental issues within the organisation.

The control of risk is referred to as risk management. Risk analysis can be carried out as part of a quality control system. Assessments should be carried out by a competent person who is a person having sufficient technical knowledge, training and experience to carry out this task. Risk assessments should be suitable and sufficient for every employee and other persons that they may affect. The person, who creates the risk, owns controls and regulates it.

A risk assessment is nothing more than a careful examination of what, in your work place, could cause harm to people, so that you can weigh up whether you have taken enough precautions or should do more to prevent harm. The aim is to take all reasonable steps to make sure that no one gets hurt or becomes ill. The important things you need to decide are whether a hazard is significant, and whether you have it covered by satisfactory precautions so that the risk is small.

The person carrying out the assessment must be methodical and comprehensive with an objective eye and mind to consider "what if this happens".

2.2 Steps for risk assessment

The risk assessment consists of the following steps[3]:

1. Look for the hazards. Decide who might be harmed and how. Evaluate the risk and decide whether the existing precautions and practices are adequate or whether more could be done.
2. Record your findings. Review your assessments and make any necessary improvements and then reassess these improvements. Remember: "risk assessments" are specific to your facility. You cannot use another facilities risk assessment. Other facilities may have some similar hazards but you own and create the hazards so it is your duty to reduce the risks to an acceptable level. Do not overcomplicate the issues and review your environment annually or when you introduce new equipment, machinery

or when other local events may effect your working environment. Take reasonable precautions to avoid injury.

3. Look for the hazards. If you are doing the assessment yourself walk around (if designing at this stage use your plan to walk around) the facility and the site and look afresh at what may reasonably be expected to cause harm. Concentrate on the significant hazards and ask other staff or interested parties for their comments.
4. Decide who might be harmed and how. Do not forget all office, maintenance, technicians or medical staff, contractors, cleaners, visitors or patients. Evaluate the risk and decide whether the existing precautions and practices are adequate or whether more could be done. Consider how likely it is that each hazard could cause harm. This will determine whether or not you need to do more to reduce the risk. Even after all precautions have been taken, some risk usually remains. What you have to decide for each significant hazard is whether this remaining risk is high, medium or low.
5. In taking your action to control risks apply the principles below, if possible in the following order:

a) Try a less risky option (e.g. avoid banned substances entering the chamber by having all occupants change into unique hyperbaric clothing).
b) Prevent access to the hazard (e.g. use guards on compressor belts).
c) Organise work to reduce exposure to the hazard (e.g. Have maintenance work carried out when the machinery is not running).
d) Issue personal protective equipment (e.g. modified ear defenders to all chamber occupants).
e) Provide welfare facilities (e.g. washing facilities to reduce the risk of cross infection). Improving health and safety need not cost a lot. (For instance use magnetic drip bag hooks instead of the conventional trolley/ pole set-ups.)

6. Record your findings. Record all you risk assessments. This means writing down the significant hazards and your conclusions. You should also inform all the staff or similar persons about your outcomes of your assessments. Risk assessments must be suitable and sufficient. You need to be able to show that:

- a proper check was made.
- you asked who might be affected.
- you dealt with all obvious significant hazards, taking into account the number of people who could be involved.
- the precautions are reasonable, and the remaining risk is low.

7. Keep your records for future reference. They will be helpful. To make things simpler, you can refer to other documents, such as: manuals, your

Health and Safety Policy, Company Rules, manufactures instructions, your fire procedures, existing Standard Operating Procedures (SOP's) or Emergency Procedures (EP's) or any other relevant information you can lay your hands on.

8. Review your assessments and make any necessary improvements and then reassess these improvements.

Sooner or later you will bring in new machines, substances and procedures that could lead to new hazards. If there is any significant change, add to the assessment to take account of the new hazard.

2.3 Standard and Emergency Operating Procedures

The safety of the patients and staff is of paramount importance for hyperbaric operations. It is essential that all team members be very familiar with the facilities policies and procedures (P&P) used to manage the system. The production of a manual containing all the facilities Standard Operating Procedures (SOP's) and Emergency Procedures (EP's) is perhaps the best way to manage this huge task. Most EP's are produced after completing the necessary risk assessments. This manual effectively becomes the facilities operating manual.

Once you have established what type of support and assistance is available within your facility you need to start the task of producing a simple list of all the procedures that need to be produced. This may be broken into two lists (EP's & SOP's). This is likely to end up with over 200 items of which 40 may be EP's. Once the list is well underway delegate the items to those best able to write the first drafts. The first drafts may be the most difficult to produce.

All anticipated procedures within the facility should be covered by SOP’s and EP’s. A safe working environment will only be achieved with close cooperation between management and all staff and skills.

The writing of clear concise SOP's and EP's requires a logical mind to simplify each procedure into easy steps from the beginning (as you expect to find the item) right though to the end of the procedure including the return of the equipment to an operational state. They must be simply written, in short sentences and too the point and must not assume a certain level of prior knowledge by the end user.

All SOP's and EP's should be written by at least two people (with skills in the relevant area) checking each others work to ensure the end product is a easy to understand and follow set of procedures. Once both team members are in total agreement with the content and layout then a top copy can be produced for a third person to check and approve.

If your facility is attached to another building/host like a hospital then your procedures need to be linked to your hosts.

All instructions should start with a point that the piece of equipment will normally be found. Keep all SOP's and EP's in one place near the chamber control panel.

All new or replacement procedures must be agreed by a team of three before they are implemented and put out for general use by the team. There must be a system in place to avoid new SOP's and EP's being issued without the necessary approval process. If the team has a health and safety officer/advisor then it may be appropriate for them to issue, manage and review all procedures along with occupational health matters, fire precautions, safety audits, patient questionnaires and their monitoring.

All documents should be catalogued and numbered and dated so that regular revisions can become a simple task. When the task is well underway it will be necessary to inform the team of there existence and make sure the whole team has read and understood the documents. This then needs to be documented in the facilities records. Design a template so all-future documents will be in a standard recognisable format. Replacement SOP's and EP's should be suffixed with a letter so team members know they have been updated and they need to re-familiarise themselves with the new editions and sign them off as read in the records.

All SOP's should be updated at least once a year.

Practice and test SOP's and EP's to make sure they work and do not assume they will work first time around.

2.4 Emergencies

The hyperbaric environment is a volatile environment. Patients and working personnel have lost their lives in the administration of hyperbaric oxygen therapy. Each time a patient or team member goes inside a hyperbaric chamber, they assume an acceptable risk of injury or death.

Safe and successful daily treatment operations require a team effort. From the moment a patient is consulted, a well-designed treatment plan should be followed. Patient teaching is the first step in patient safety compliance. Chamber personnel must diligently perform pre-treatment safety checks, equipment checks, and patient evaluations. Pre-treatment patient checklists provide a method of ensuring that patients have been medically evaluated and screened for items not compatible in the hyperbaric environment prior to being allowed in the chamber. Chamber start-up checklists provide a method for chamber operators to confirm all chamber systems are operating correctly prior to beginning a treatment.

For the inside attendant, the time spent at pressure can seem long and sometimes boring. During the patient's oxygen breathing periods, attendants should assume a comfortable non-restrictive position in the chamber and relax. Some attendants may choose to read during a treatment; however, constant awareness must be given to the patients and the surrounding environment. As evidenced in previous hyperbaric mishaps, it takes only a second for a patient to produce an unsafe item that could cause injury or death. The majority of treatments flow smoothly and are trouble-free. It may be easy for some to become complacent from what might seem monotonous work. However, complacency can kill. When things go wrong under pressure, they usually do so very quickly. Early recognition of potential problems is a vital safety concern for both patients and attendants. Treatments need to be performed with consistency. The safest, most proven treatment methods should be used everyday by everyone.

The list of emergency procedures every facility needs to produce will come from its risk assessments, however is likely to include the following as well as some more of your own. In reviewing international documents[1,2,4-9] they all have similar lists with only one or two additions:

– PATIENT
a) Barotrauma
b) Seizure
c) Pulmonary Barotrauma
d) Cardiac/Pulmonary Arrest
e) Claustrophobia
f) Pneumothorax
g) Accidental extubation
h) Loss of life support system
i) Aggressive, violent or dangerous patient behaviour
– STAFF
a) DCI
b) Ear or sinus barotrauma
c) Mechanical/Structural failure
d) Compressor malfunction (main, backup, HP or LP)
e) Loss of main electrical power
f) Intercom malfunction (Main and backup)
g) Loss of pressure integrity
h) Environmental contamination
i) Fire (inside/outside)

- Fire in chamber: Chamber not under pressure / Chamber can be decompressed with minimal risk to occupants / Chamber can not be decompressed due to DCI risk to occupants
- Fire/smoke in building/department

- Fire in hospital or host building
- Hospital-wide emergency response (natural disaster or terrorist threat)
- Assistance (medical or other) required at the chamber facility
- Accidental activation of the fire suppression system

j) Elevated Oxygen percentage
k) Omitted decompression
l) Chamber operator ill
m)Attendant ill
n) Emergency entry of additional attendants
o) Loss of primary pressure gas
p) Loss of primary oxygen supply
q) Rapid increase of chamber pressure
r) Rapid loss of chamber pressure
s) Loss of reserve pressure gas
t) Loss of reserve oxygen
u) Contamination of breathing gas or contamination of the chamber environment
v) Loss of communication

2.5 Training for Emergencies

In most activities with which we are concerned, some training in emergencies is necessary in a simulated form. It is very easy for this training to become a formalised part of the facilities routine training. In doing so it loses much of its value, because it is expected. It becomes an exercise to do, whereas in reality the danger lies in its unexpected. Chamber supervisors need to learn what to do instinctively to unexpected situations.

Emphasis on the unexpected aspects of emergencies should come from the instructor's skill as a teacher, and not from dramatic harassment tactics. It is in the area of emergency skills and decisions that a good instructor will get across the need for awareness, the need for the student to learn more about the system he is operating, and need for reliance upon himself and his own resources to get, and keep, out of trouble. To start with, the instructor has to do all the thinking for the student, but the student has not become an operator in his own right until he is capable of doing all his thinking and decision taking for himself.

3. INCIDENTS AND ACCIDENTS

3.1 Definitions

Even if all a facilities safety policies are adequately planned and implemented, some residual risk will still persists for complex treatment methods like HBO therapy and some negative events may occur. Depending on consequences, we can differentiate between incidents and accidents. An incident is an event that occurs which does not result in loss but may have involved an unsafe condition or unsafe act. An accident is a sudden, unplanned, often violet event that causes loss. Knowledge of the cause may prevent future accidents by removing the cause.

3.2 Monitoring of incidents / accidents

All facilities should develop some form of documented incident reporting procedure. These documents need to be reviewed every 3-6 months and if improvements can be implemented to avoid repeat incidents then this should be considered.

Safety needs to be a culture adopted by all the team not just the safety officer. Boredom and tired staff will do little for your safety record. Only a fool learns from his own mistakes, it is far better to learn from others mistakes. Share safety ideas and insist on high levels of safety. What you don't know leads to a fear of the unknown. Ask, enquire, learn and communicate with other skills. Understand the risk and monitor the risk. Accidents have a habit of developing from a series of small incidents or string of events that may lead in to an incident pit where the accumulate effects of the unchecked or unnoticed incidents leads to a steep or quick string of events that then leads to a major incident or accident. Vigilance may have helped to avoid this scenario.

An incident form needs to be developed for the facility which is easy to fill in and not more than two sides of A4. It may be necessary to write a single page of instructions to ensure all forms are completed correctly.

3.3 Equipment and Chamber Related Incidents

The most reported incidents are likely to be:

- Elevated oxygen levels in the chamber environment
- Prohibited items inside the chamber
- Obscure items installed in chamber systems by non-hyperbaric trained staff

- Facility electrical wiring and fire hazards in the area surrounding the chamber

Safety Formula:

1. Always be alert and safety conscious
2. Insist on high standards
3. Learn from others mishaps
4. Be active in your national hyperbaric association and other international societies and share your ideas
5. Ensure all the team are trained
6. Aim towards an international certification for all the team
7. Be optimistic about the future

3.4 The Hyperbaric Incident Monitoring Study (HIMS)

Though there have been incident monitoring efforts in health care for years, it was not until 1992 that such a programme was specifically developed for hyperbaric medicine. The Hyperbaric Incident Monitoring Study[10] (HIMS) was initially conceived to support the Australian clinical hyperbaric medicine community and was introduced to the international world of hyperbaric medicine in 1996. This anonymous, voluntary incident database has become the undisputed benchmark for our industry and represents an extremely comprehensive and valuable tool for improving the quality of care for hyperbaric patients worldwide.

The Hyperbaric Incident Report (HIR) contains seven incident categories: patient complications, staff problems, incidents related to ventilation, the chamber, equipment, pharmacological, or patient tubing and lines.

Equipment related incidents make up 40% of HIMS reportable events. Of those equipment related incidents reported, the largest category is related to oxygen delivery systems (50%). Primary factors contributing to incidents in oxygen delivery systems are: equipment malfunction (20%), inexperience and/or inadequate training (15%), chance event (15%), failure to follow policy/protocol (12%), inattention (10%) and inexperience with procedure (10%).

HIMS recommends to ensure that all equipment is properly maintained to minimise the chance of malfunction and to institute an aggressive on-the-job training programme to facilitate proper use of equipment, in-depth understanding of policies and procedures, procedural expertise and staff attention to detail and diligence.

4. HAZARDS SPECIFIC FOR HBO THERAPY

4.1 Risk factors

An HBO session requires a number of phases, which must be conducted sequentially. Usually these phases involve both technical and medical procedures, and they may be so complex that they can present an additional hazard when conducted in combination. Potential hazards for any HBO session are naturally divided into a number of sub issues like, environmental, mechanical and human factors and the majority of them are related to:

- Pressure, changes of pressure and pressure differentials. This can affect any part of the hyperbaric system (e.g. chamber walls and piping system), any medical devices inside the chamber (e.g. ventilator, electrical syringes) and body parts exposed (e.g. pneumothorax, drainages).
- Oxygen content inside the chamber atmosphere. This can be related to an oxygen leak from a supply system of the chamber or from an individual breathing unit.
- Breathing mixtures for the patients and the staff. This is mainly related to the partial pressure of oxygen giving risk for pulmonary or central nervous system toxicity.
- Patient clinical condition. Regardless of its therapeutic effects, hyperbaric oxygen can aggravate some pre-existing patient's disorders or can induce potential side effects.
- Personnel health status. Breathing compressed air imposes an occupational hazard of decompression illness and pressure changes can induce dysbaric disorders (barotraumas).
- Prohibited materials within the chamber. This is related to the hazard of putting combustible or ignitable materials or devices in the hyperbaric environment leading to a potential fire hazard.
- Electricity. This is mainly related to the risk of fire ignition, but also of electric shock to the patients and the staff.
- Confined space. This is mainly related to the manual handling of patients on entry exit from chamber and during treatment, as well as the management of body fluids, wastes and infected materials.

4.2 Treatment hazards for patients

The most often event reported from any HBO therapy is middle ear barotraumas of patients[10]. Depending on quality of assessment and diagnostic criteria some degrees of ear discomfort and middle ear barotraumas have been observed in 18 – 69% of patients undergoing HBO

therapy[11]. The prevention or reduction of this hazard can be achieved by proper medical examination of the patient during pre-treatment evaluation, teaching cooperating patients techniques of middle ear equilibration and adaptation of the compression profile to patients' capabilities for middle ear equilibration of pressure. In patients who do not have possibilities to consciously equilibrate pressure the tympanostomy may be indicated.

Oxygen toxicity of patients is the second most often occurring event during HBO therapy[10]. It was observed in 93 cases (19%) of 489 patient related incidents reported to the HIMS[10]. The real incident rate during routine HBO session is reported in 1 of 10,552 of patient session (0.01%) to 1 of 2,844 of patient session (0.04%)[12-14]. Prevention of cerebral oxygen toxicity includes careful examination of the patient toward the predisposing factors (pyrexia, hypoglycaemia, elevated inspired carbon dioxide levels, increased cardiorespiratory workloads and intracerebral pathology) as well as the avoidance of an accumulation of carbon dioxide during breathing. Such procedures will decrease the rate of oxygen convulsions to less than 0.04% which is considered quite acceptable for rationale indications for HBO treatment.

To increase the level of safety for the patient, a careful pre-treatment assessment by the hyperbaric physician should be conducted during reception of a patient for a hyperbaric treatment. This assessment should evaluate the clinical history and actual condition of the patient taking into account hazards related to:

- changing pressure during treatment (compression and decompression) and its influence on closed gas spaces inside the body (pneumothorax, drainage cavities, obstructed sinuses and middle ears)
- high oxygen partial pressure in the breathing mixture with its potential adverse effects like central nervous system or pulmonary toxicity
- use of breathing systems (masks with on-demand system, hoods with free-flow system, mechanical ventilator) and its relation with respiratory workload and transmission of infectious diseases
- medical devices needed for continuation of therapy inside the chamber (monitoring devices, pumps and syringes, mechanical ventilators, pacemakers, etc)
- confined space with problems of entrance and possibility of claustrophobic reactions
- pharmacotherapy used for acute and chronic conditions, especially adrenergic and hypoglycaemic agents, corticosteroids and chemotherapeutic agents known to present potential toxic reactions with hyperbaric oxygen (doxorubicin, bleomycin, disulfram, cis-platinum, mafenide acetate)[15]

4.3 Occupational hazard for personnel

Working under pressure as a medical attendant in the hyperbaric environment presents occupational hazards for staff of the hyperbaric facility[16]. Theses can be sub divided into:

- pre-existing health conditions (pregnancy, infections, etc) giving risks for being influenced by hyperbaric conditions
- changing pressure (compression / decompression) giving risks for barotraumas
- breathing mixtures (air, nitrox, oxygen) giving risks for oxygen toxicity and narcotic effects of nitrogen
- session parameters (maximum depth, exposition time and content of the breathing mixture, number of sessions conducted daily and weekly, intervals between sessions, parameters of sessions) giving risks to decompression illness and
- long term accumulation of negative factors giving risks for chronic health consequences, like aseptic bone necrosis

In order to minimize hazards connected with pre-existing health conditions a medical examination of all hyperbaric medical workers should be performed initially before the first exposure. Future medicals should be repeated periodically according to national regulations (most often annually). Being certified “fit for hyperbaric exposures” does not guarantee that this is valid for every HBO session due to a persons daily changes in health. Therefore daily fitness should be confirmed by the staff themselves just before the start of a session. This includes the possibilities of pregnancy or acute health problems (inability to equilibrate the middle ear pressure). In case of any doubts the exposure of the staff should be abandoned until further clinical investigation and explanation has been obtained.

Attendant staff breathe compressed air during much of a hyperbaric treatment, and therefore they are potentially at risk of dysbaric injuries. The rate of decompression illness in medical attendants depends on the type of session conducted, and it differs between reports in the range of 0.018 to 0.67%[17].

The prevention of decompression illness includes:

- the policy of decompression for hyperbaric workers
- adaptation period for new employers and after long holidays from exposures
- breathing oxygen during decompression
- rotation of attendants to limit exposure to non decompression exposures
- prolonging intervals between exposures and
- restrictions on travel and physical exercise after exposure

Regardless of prevention measures all staff should receive training in the recognition of decompression illness in themselves and attendants. The facility should be ready to conduct the immediate recompression treatment of attendants should it be necessary. This implies the facility has appropriate procedures including an adequate compressed air and treatment gas storage as well as other additional medical attendant to assist the injured worker during their recompression treatment.

5. FIRE PREVENTION AND FIRE FIGHTING STRATEGY

The single most dangerous event usually leading to fatal accidents in any hyperbaric chamber is fire. Although it is true that this type of accident is rare, it nevertheless has to be pointed out that the consequences of a fire in a hyperbaric chamber are almost always fatal for its occupants so special precautions must be taken to avoid this disaster.

There are two types of fire hazards in a hyperbaric centre, i.e., outside and inside the chamber. This section will be restricted to fire hazards inside hyperbaric chambers only.

The results of a study on the causes of fire inside hyperbaric chambers (between 1923 and 1997) have shown that many fires are caused by objects introduced by patients[18]; these included cigarette lighters or combustion hand warmers. Moreover, in the majority of cases oxygen levels inside the hyperbaric chambers exceeded 28%.

Unlike in professional diving, the occupants of hospital hyperbaric chambers are mostly patients, people who have not been trained concerning the specificity of this environment. Patients are not healthy fit persons, but sometimes severely physically disabled.

Furthermore, for many indications, these patients may well be treated in a hyperbaric chamber up to 30 or even 40 times. Even when initially properly informed, patients tend to forget specific recommendations and become careless over time.

Additionally, a large proportion of the work of operators in hyperbaric chambers is composed of repetitive activities, with all the risks entailed by "force of habit". All the factors related to human error are thus in place.

5.1 Study of fire in hyperbaric environment

Before elaborating on prevention of fire, one needs to know and analyse all the involved phenomena and processes.

In a hyperbaric environment, fire behaviour is profoundly modified; all known information about fire behaviour must therefore be reviewed accordingly. Air compressed at 1.5 bars of pressure contains an amount of oxygen equal to that in a normobaric mixture containing 52% of oxygen. Moreover, at this pressure, pure oxygen is distributed to as many as 12 patients simultaneously!

The risk of oxygen leaks is real, and these are by nature concentrated around the patients who "produce" them. Knowing that patients account for approximately 50% of fires reported in the clinical hyperbaric environment[19], this last element is particularly important.

Flammability and ignition

The degree of flammability of any material depends on its behaviour as a combination of ignition, combustion and rate of spread. Tewarson[20] linked the following parameters to ignition: the Critical Heat Flux (CHF), maximum heat flux at or below which a flammable vapour-air mixture is not created and the Thermal Response Parameter (TRP): ease of in-depth penetration of the thermal wave and time delay to reach the ignition temperature.

Filter paper tests (on Whatman paper) demonstrate that the CHF and TRP parameters change depending on the oxygen levels and the pressure. It has been demonstrated that, in air conditions, at 1.5 ata 14% of oxygen is sufficient to accelerate the ignition processes[21].

In the recommendations of the National Fire Protection Association NFPA 53[22], it is interesting to note the difference in the ignition temperature, under oxygen conditions, between treated cotton sheeting (treated with Du Pont™ X – 12 fire retardant) and non-treated cotton. At 1 ata, non-treated cotton ignites at 465°C in air, and at 360°C in oxygen. At 3 ata, these ignition temperatures are 385°C in air and 340°C in oxygen. For fire-retardant treated cotton, these values are 575°C (air 1 ata), 340°C (oxygen 1 ata), 485°C (air 3 ata) and 300°C (oxygen 3 ata). The values at 3 ata are only negligibly lower than at 1 ata, indicating that more studies on the behaviour of fire retardant materials in enriched oxygen conditions are necessary.

Beeson[23] reminds us that the flammability of materials is determined using several test methods developed for specific materials and configurations. So the design and the type of material are taken into consideration for a specific application. He takes into account the complex configuration effects to measures the distance between tests in laboratory and tests *in vivo*. He considers that the configuration effects influence every step, from ignition to flame spread rate and to extinguishing.

But in addition to more rapid ignition, the combustion, the density, the temperature, the partial pressure of gases, and toxicity of gases are also modified.

Combustion

The rate of combustion will be directly related to ambient pressure and the oxygen level in the chamber. Of course, this rate of combustion and spread will accelerate according to the fuel encountered. The NFPA 53 demonstrates the effect of oxygen on flame spread rates over common materials used inside hyperbaric chambers, depending on whether they are in air (160 mmHg oxygen) or in an oxygen-rich environment (258 mmHg Oxygen).

A cotton T-shirt will pass from "no propagation" in air, to 38 mm/s in oxygen; foam cushions from 4.8 mm/s to 315 mm/s; polystyrene from 0.81 mm/s to 30 mm/s. These results demonstrate that materials reckoned to be non-combustible in 21% oxygen at 1 ata will burn very well in an oxygen-rich environment[24].

Fire propagation

The British Standard BS 476 Part 6[25] describes a method of test fire propagation. The test method determines the temperature increase and the rate at which a product will propagate a fire. This index (Fire Propagation Index – FPI) exists to assess the propagation of a fire for different types of materials. Materials with an index lower than or equal to 6 are in the "No fire propagation" category. Materials with an FPI index greater than 20 are rapid acceleration fire propagation materials.

Examples of FPI values of materials (in normobaric conditions, measured in the ASTM E2058 apparatus - so-called Fire Propagation Apparatus) are nylon 26 and PVC power cable 28.

These examples remind us of the need to be conscientious every day we use materials inside the hyperbaric chamber which react very fast already under normal atmospheric conditions. With regard to the power cables, like for the textiles, complementary studies are necessary.

Density and temperature

Immediately following the rate of combustion, a rapid increase in pressure (density) and temperature is observed. In a test chamber pressurised at 4.5 bars and filled with a mixture containing 30% oxygen, the following phenomena were observed: approximately 7 seconds after the first flames, the pressure went up by 1.65 bars while the temperature in the chamber rose to approximately 150°C[26]. This author noted that in hyperbaric and oxygen-rich environments the rates of spread, toxic vapours and heat are increased.

The literature reports that the increase in temperature increases the number of molecules with energy equal to the activation energy and increases the reaction rates[22].

Bettis noted, in his study[27], that the elevated temperature would significantly increase the thermal radiation emitted and increase the distance to which the fire can be safety approached. This immediately makes manual fire fighting, using handheld extinguishers for example, more difficult.

For occupants, this also implies convection burns. In his study[28], Lee recounts a rapid increase in temperature and considers quite rightly that the occupants will suffer severe airway burns.

The release of toxic gases

Fire in a hyperbaric chamber, apart from the aspects of pressure and oxygen are made more dangerous due to the confined environment. No major removal of smoke is possible as the ignition temperature is reduced. The rate of fire spread increases and the combustion product burns more easily. The two major factors that lead to death in confined spaces are failures to recognise and control the hazards associated with confined spaces and inadequate or incorrect emergency responses[29].

David Purser studies the exposure of the occupants of aircraft cabins to smoke toxicity[30]. He noted the following physiological hazards:

> "Impaired vision from the optical opacity of smoke and from the painful effects of irritant smoke products and heat on the eyes.
>
> Respiratory tract pain and breathing difficulties… resulting from the inhalation of irritant smoke…
>
> Pain to exposed skin and the upper respiratory tract followed by burns, or hyperthermia, …"

He stresses the importance of exposure to optically impairing and irritant smoke and the incapacity effects of this exposure. In an aircraft, these effects have as a great consequence due to the limited time to escape.

The aeronautical field is not the only one involved in this type of problem. For example, following the fire tragedies in road tunnels, some countries[31] have undertaken strict safety measures, especially because fire in a tunnel creates unbearable heat conditions due to the enclosed space.

This knowledge clearly indicates that, in the case of a fire in a pressurised and hyper oxygenated chamber, apart from fighting the fire there will be also be a sudden increase of temperature and toxic effects to get under control. Therefore, it is justified to assume that the occupants will rapidly suffer asphyxia that will cause respiratory arrest followed shortly by

cardic arrest. Each minute counts and so the intervention in case of fire may not be merely limited to fire control but simultaneously calls for rapid actions to evacuate the occupants as soon as possible.

To summarise, in case of a fire, three major problems can be identified inside a hyperbaric chamber:

1. the pressure rise; which will render immediate evacuation impossible and which will interact on the fire
2. the oxygen content of the chamber atmosphere; which will completely modify the fire's behaviour by initially increasing the rate of combustion, but will also increase the temperature and thus physically enhance the burning process
3. the confined space; which will render the fire uncontrollable (heat effect) and which will prohibit the escape from the liberated energy and will provoke a high level of exposure to the toxic fumes

Of these three essential components to the danger, only the danger resulting from the accumulation of oxygen inside the chamber can be technically lowered.

5.2 Prevention

Prevention may be achieved by three levels of action: materials, education and procedures:

Materials

If the infrastructure allows it, it is wise to provide changing rooms for the patients, so they change into cotton clothing for the therapeutic session. But even if this procedure lowers the risk, they do not alter the importance of an inside fire. It has been shown that some materials considered to be non combustible (1 ATA), would burn very well in the hyperbaric environment.

Emergency planning, also on the infrastructural level, is important. It has to be reminded that the majority of the victims will, at least, have breathing difficulties (hypoxia, anoxia) and some of them will develop airway burns. Thus, for this type of patient, specific measures need to be in place i.e immediate oxygen, and rapid evacuation by a emergency team needs to be provided.

The essential objectives of the European standards are:

– to harmonise the technical language as a base for common interpretation
– to give common bases for construction, testing and marking of equipment to ensure a harmonised safety level of equipment in order to facilitate cross border trade within Europe
– to define specifications fulfilling the essential safety and health requirements laid down in the European directives

Any Standard will only define the «minimum level required», and, to this day, no Standard seems to provide a conclusive answer to the encountered problems.

As has been shown in the chapter dealing with the Fire Fighting System (FFS), a high-performance system should be present. Certain chamber manufacturers have perceived the necessity to develop and implement a fire fighting system that exceeds the present Standards required of hyperbaric fire fighting systems.

The FFS of the future will integrate passive and active fire fighting means.

Personnel education

Primary education should include a specific chapter about fire in the hyperbaric environment. Also, it would be judicious to assure there is a follow-up training session specific to fire in the hyperbaric environment.

In the specialised literature taking into account the usual standards, it is striking to see that the patient, as a source of danger as well as first victim, is strikingly neglected. In fact these standards and recommendations are taking into account the professional user. What about the "patient"? Of course, there is no need to set up education programs for these people, nevertheless, it would be advisable to develop a double strategy: one, which could lower the source of dangers with the help of technical and informative means; the other one, which could reduce the consequences of the dangers for the patients. These steps are all the more necessary as according to work of Sheffield[18], during the period 1967 – 1996, there were 24 clinical hyperbaric fires, 10 of which were caused by ignition sources that occupants carried into the chamber.

The procedures

The continuing education of personnel is required to ensure that procedures are respected and complied with. The procedures should be clear cut and easily understandable to the chamber staff. It should be emphasised to the staff that the protection of the patients in a vulnerable environment within the chamber is their primary responsibility. Moreover, each new patient needs to be given a full verbal and written explanation on the treatment they will be receiving and on the safety precautions to be respected.

6. CONCLUSION

The scientific study and the recognition of the risks of hyperbaric fires[32,33] are formalising and will in the near future lead to the development of a specific Standard.

Nevertheless, if technical responses to these risks are introduced in this way, they will without a doubt be incomplete as many responses essentially depend on human factors.

So, investments by employers into adequate training of personnel, in order to give them all possible chances of responding appropriately and rapidly to the risks of a fire and its tragic consequences, are to be greatly insisted on.

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3.7. Complications of Hyperbaric Oxygen Therapy

Chapter 3.7.1

BAROTRAUMATISM

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Abstract: Although human tissues is able to withstand significant pressure, tissue injury can occur when a gas-filled space is unable to equilibrate to environmental pressure – whether increasing or decreasing – as described by Boyle's Law. This phenomenon is called barotrauma. Two main conditions must be present for barotrauma to occur: (1) a change in ambient pressure; and (2) transfer of pressure to a non- or partially collapsible gas-filled space. Gas expansion may tear tissue while gas volume reduction may cause vascular engorgement, mucosal swelling and haemorrhage. In particular this may affect the middle ear and sinuses; lung; intestines; teeth; eye, particularly when surrounded by an air space like a face mask; and other physiological or pathological gas spaces

An understanding of these effects and the exclusion of pathology that may introduce risk of disequilibration are best achieved through education and training of divers and the physicians examining them

Keywords: barotrauma; Boyle's law; pressure changes; gas volume; mechanical tissue injury; middle ear; tympanic membrane; eustachian tube; pneumothorax; gas embolism

1. INTRODUCTION

Although human tissues may support great pressure, tissue injury can occur, resulting from the failure of a gas-filled space to equalize its internal pressure with ambient pressure changes, according Boyle's Law. This phenomenon is called barotrauma.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 715–729.

Pressure-related injury or barotrauma may affect all those who participate in diving activities, compressed-air work, aviation and hyperbaric therapy. Injury is most likely when the pressure-volume changes are great or the onset is rapid – as occurs during the initial parts of pressurization or descent from atmospheric pressure.

Two conditions must be present for barotrauma to occur: (1) a change in ambient pressure and (2) transfer of this pressure to a non- or partially collapsible airspace. Gas expansion may tear tissue while gas volume reduction may cause vascular engorgement, mucosal swelling and haemorrhage. In particular this may affect the middle ear and sinuses; lung; intestines; teeth; eye, particularly when surrounded by an air space like a face mask; and other physiological or pathological gas spaces.

The good practice of Hyperbaric Medicine should include education and safety assurance for patients and staff alike to ensure the lowest possible incidence of barotrauma.

2. EAR, NOSE AND THROAT

2.1 Middle ear barotrauma

The middle ear cavity communicates with the nasopharynx through the Eustachian Tube (ET) – a 4 cm long tube. Under normal conditions the tube is opened by chewing, swallowing or yawning due to the action of controlling muscles; this allows equalization to occur between the middle ear and nasopharyngeal air pressure. Closure of ET is a passive process and it is collapsed in its natural state. Passive escape of gas occurs when middle ear pressure is around 4 cm H_2O higher than ambient pressure[1]. However, spontaneous equalization rarely occurs spontaneously during increasing ambient pressure and this is why barotitis media may occur – the most common diving and hyperbaric medical complication. With a pressure differential of 80 cm H_2O (60 mmHg) between the middle ear and the increasing ambient pressure, as would occur upon commencing hyperbaric pressurization in a patient unable to equalize the ears, significant oedema and tympanic membrane congestion would occur -- further narrowing the ET. This adds greater difficulty to equalization and, during conventional hyperbaric treatment to 2.3 to 3 ATA, it usually becomes impossible to equalize voluntarily once a pressure differential of 120 cm H_20 (90 mmHg) it exceeded. Pain and fullness may make way to tympanic membrane rupture and hemorrhage when this reaches 200 to 1000 cm H_2O (150 to 760 mmHg). Warning signs usually develop within the first 2 to 3 meters of compression.[2,3] Otological barotrauma of descent is characterized by an

initial sensation of ear blockage, followed by sharp pain. If swelling, bleeding or perforation occurs this may be accompanied by a conducting hearing loss, mild tinnitus and vertigo. Possible inner ear barotrauma should be suspected whenever there is serious hearing loss and vertigo. Otoscopic examination demonstrates physical signs of traumatic injury; a six grade severity classification has been formulated by Edmonds.[4]

Grade 0 - Symptoms without otoscopic signs
Grade 1 - Diffuse redness and retraction of the tympanic membrane (TM)
Grade 2 - Grade 1 changes plus petechial hemorrhage of the TM
Grade 3 - Grade 1 changes plus confluent / plaque hemorrhage within the TM
Grade 4 - Dark and slightly bulging TM due to free blood or fluid in the middle ear; a meniscus or bubbles may be visible through the TM
Grade 5 - TM perforation with possible blood in our outside the ear canal

The treatment depends on the degree of barotrauma. Further exposure to pressure should be avoided for severities greater than Grade 2 and in all Grades if equalization is impossible. Recovery usually occurs over 3 to 14 days. Topical and systemic nasal decongestants and symptomatic pain relief should be considered. If rupture of the membrane has occurred a systemic broad spectrum antibiotic may be given, particularly if the injury occurred in water. Large perforations, especially those associated with deafness or tinnitus and/or in the proximity of the ossicular chain disruption, should be referred to an otorhinolaryngologist.

In some individuals it is possible for ET dysfunction to cause air trapping in the middle ear during ascent – *barotrauma of ascent – with the TM* bulging outwards. In rare instances this blockage may be severe enough to cause pain, but a pressure difference of more than 60cm H_2O (45 mmHg), may cause asymmetrical stimulation of the vestibular apparatus with *alternobaric vertigo of ascent* (also called Lündgren Syndrome)[5]. This self-limiting form of transient dizziness usually occurs during ascent; it is less common during descent. Although transient, the vertigo, disorientation and nausea – usually lasting less than 10 minutes – may present serious problems for divers, particularly at depth. If possible, further ascent should be avoided until the vertigo is alleviated. If required, a temporary descent may also abort the problem. Usually the onset is sudden and occurs just before or upon surfacing sometimes in combination with pain or fullness in the affected side. Rarely, persistent nystagmus and positive Romberg signs may be observed with a bulging TM visible on otoscopy[6]. Simultaneous ENG recordings of susceptible individuals have shown this to be a true vestibular

nystagmus. However it is rare in conventional hyperbaric practice and the possibility of barotrauma or decompression illness of the inner ear should always be considered when symptoms persist for more than a few minutes.[7]

Another injury described in divers and pilots is a transient unilateral facial paralysis in association with ipsilateral middle ear overpressure, known as *alternobaric facial paralysis*. Several mechanisms have been proposed to explain the facial nerve neuropraxia. Nausea and vertigo may be also be present. Full facial nerve function usually returns to normal within 2 hours of returning to atmospheric pressure.[8-10]. Although recovery is the rule, further diving is not recommended and – for HBO patients – myringotomy is advised.

Rarely, gas expansion during ascent may escape the middle ear and sinus cavities causing pneumocephalus or orbital injuries with surgical emphysema.[11]

2.2 Inner ear barotrauma

Strenuous or prolonged attempts at middle ear equilibrium, particularly when using forceful Valsalva's maneuvers, may elevate intracranial and inner ear hydrostatic pressure sufficiently to cause rupture of inner ear structures: either basement membrane rupture, or round and/or oval windows may be involved[12]. Rupture of the round window leads to a perilymph leak into the middle ear, known as a perilymph fistula. Although extremely rare in hyperbaric medicine practice, it can cause serious consequences if the diagnosis is missed and this should always be considered when any form of ear barotrauma has occurred[13]. Indeed, inner ear barotrauma can occur simultaneously with barotitis media and it may not need to reach the level of a fistula to already cause audiovestibular dysfunction; fortunately this has not been reported in hyperbaric medicine practice.[14]

Diagnosis is supported by the history of serious vertigo; intense tinnitus; a sensation of fullness in the ear; sensory-neural hearing loss; nausea and vomiting; a positive Romberg sign and nystagmus. Although traditionally of sudden onset, the clinical presentation may be delayed for hours if the fistula is small. The clinical hallmark is onset associated with a pressure-related exposure and persistence upon return to atmospheric pressure. Further hyperbaric exposures should be avoided until complete clinical recovery is achieved; if it is essential to continue HBO, a myringotomy should be considered to avoid aggravating the injury.

The differential diagnostic distinctions between inner ear decompression illness and inner ear barotrauma are not necessarily obvious. The time of symptoms onset (e.g., compression); dive characteristics (i.e., rapid ascent, omitted decompression, helium mixtures); difficulty with ear clearing, pre-

existing nasal/sinus/middle ear disease; associated middle ear barotrauma; and absence of other symptoms or signals of decompression illness may favor the one or the other diagnosis.[15] The treatment is based on bed rest with the head elevated to reduce intra-cerebral pressure. The patient must be evaluated with an audiogram, an electronystagmogram and be submitted to a complete otorhinolaryngological and neurological evaluation. Symptoms often resolve spontaneously within 2-3 days, and surgical measures should only be considered for round and oval window ruptures when there is a delay in recovery or progressive deterioration in function[16,17].

2.3 External ear barotrauma

When the external ear canal – which is 3.5 cm long and 1 cm wide – is blocked (e.g., by an ear plug or wax), barotrauma of the canal and eardrum are possible because ambient and outer ear pressures can not be equilibrated. Usually the external ear is filled with water or air at ambient pressure. With a blocked canal, pressure changes during descent and ascent may lead to possible injury of the epithelial lining of the external meatus and the TM, with oedema, hemorrhage and rarely perforation of eardrum. Other causes include an external ear infection, exostoses; foreign bodies; and tight-fitting neoprene diving hoods. The pain is made worse by clearing the ears; mild conductive deafness and vertigo may be present until the pressure is relieved. Otoscopy reveals an ear canal that is swollen with hemorrhagic blistering; bleeding is possible but unusual. Although a relatively common diving problem, it is obscure to hyperbaric medicine.

2.4 Para-nasal sinus barotrauma

This injury is related to inadequate pressure equilibration in the gas volumes of the sinus cavities and it occurs whenever there is ostial obstruction with inadequate gas passage between the nasal cavity and the sinuses. Mucus, nasal polyps, congestion of the nasal mucosa, foreign bodies, nasal structural deformities or mass lesions, may all contribute to such obstruction. When this occurs, sinus barotrauma of descent (sinus squeeze) or ascent (reverse sinus squeeze), may be the result – the frontal and maxillary sinuses being the most commonly affected.

In the presence of a sinus obstruction during descent – the most frequent scenario for sinus barotrauma (i.e., twice more frequent than during ascent[18] – the hydrostatic pressure is transferred throughout the body and, as this is higher than the pressure within the gas space, a relative vacuum phenomenon occurs with blood vessel dilatation, possible rupture and hemorrhage, and eventually haematoma formation in the sinus space.[19] The

main symptom is pain, which may persist for several hours – often associated with a bloody nasal discharge. Paresthesia of the cheek or forehead may occur with maxillary or frontal sinus squeeze respectively due to compression of branches of the fifth cranial nerve.[20] Pain may be referred to the occipital region with sphenoid sinus barotrauma.

Either as a function of pressure, or due to vigorous Valsalva's maneuvers, an over-pressurized sinus cavity may lead to migration of air to the cranium or infra-orbital plate fractures with ophthalmic involvement and – rarely – pneumocephalus[21,22]. Meningitis and blindness rare but have been reported.[23,24] Again there are no known references to these severe complications during HBO therapy.

3. PULMONARY BAROTRAUMA

Pulmonary barotrauma results from pulmonary overexpansion in response to a reduction in ambient pressure; it may occur whenever breathing from a compressed gas source[27]. Near the surface, a pressure differential of 0.12 atmosphere (90 mmHg) is sufficient to cause overexpansion to the point where barotrauma occurs[14,29]. Similarly, overpressure of the lung by 95-110 cm H_2O (70-80 mmHg) initiates damage to the lung[34]. Intra and extravascular intrapulmonary gas migration may follow with various potential complications including cardiovascular collapse due to reduced venous return; arterial gas embolism and pneumothorax.[33]

The gas may exert local pressure effects or cause cerebral and coronary arterial gas embolism, the most dangerous complications.

Usually alveolar gas passively escapes as it expands during decompression; the effects are usually invisible and hidden amidst the dynamics of normal ventilation. However, if there is an obstruction due to closure of the glottis or bronchial constriction, it is possible for the intrapulmonary pressure to reach the threshold where barotrauma occurs. This may be evident by the formation of intraparenchymal gas (i.e., interstitial emphysema) or tracking of gas to the pleural cavity resulting in a *pneumothorax;* to the mediastinum (i.e., *pneumomediastinum*), to the pericardium (i.e., *pneumopericardium*), to the peritoneum (i.e., *pneumoperitoneum*), or to the subcutaneous tissues of the neck (i.e., *subcutaneous emphysema*), all of which may exert pressure on the surrounding structures with resulting impairment of function.[14]

The presence of pneumomediastinum or pneumopericardium, if clinically relevant, can cause cardiac tamponade; this demands immediate pressure release to avoid cardio-respiratory collapse. Pneumoperitoneum is a rare complication of pulmonary barotrauma. The presence of *subcutaneous*

emphysema in the neck may not have particular clinical significance other than indicating an underlying pulmonary injury. Unless the airway or circulation is compromised this can be managed conservatively with 100% normobaric oxygen. Surgical emphysema may complicate 25% of simple pneumothoraces.[14] As such, pneumothorax is a relatively rare complication, appearing only in about 10% of pulmonary barotrauma cases.[27]

The following pulmonary pathological conditions may increase the risk of barotrauma and its consequences during decompression: decreased pulmonary compliance; a previous spontaneous pneumothorax; acute lower respiratory infection; atelectasis; bullous emphysema; pulmonary cysts; blunt chest trauma; sub-pleural blebs; pulmonary fibrosis; and chronic obstructive pulmonary disease with air trapping. Many of these conditions may not be adequately excluded by a chest x-ray. Accordingly – if suspected – a high resolution CT scan is recommended if available when the patients are submitted to HBO or considered for diving. Increased residual volume during body plethysmography lung function testing may be a useful intermediate assessment prompting further investigation.

Chronic obstructive pulmonary disease in its various forms constitutes an added risk for pulmonary barotrauma. The bronchospasm caused by stress or by breathing cold air can lead to air-trapping with alveolar overexpansion proximal to the obstruction leading to gas entry into pulmonary capillaries.[32]

There is also a risk of pulmonary barotrauma in ventilated patients in a hyperbaric environment, especially during the decompression phase if positive pressure exceeds 40 cm of H_2O.[14] A tension pneumothorax may complicate a pre-existent pneumothorax as decompression causes the gas to expand. Cardiac and respiratory failure may occur due to cardiac and/or pulmonary tamponade.

For this reason a pneumothorax should be drained before decompression in a multiplace chamber. If it is only discovered during decompression, further ascent should be stopped until the problem is managed. In a monoplace chamber chest decompression is not possible and every effort should be made to exclude a pneumothorax in suspicious circumstances prior to committing the patient to treatment. In a worst case scenario where the pneumothorax is only discovered during ascent in a monoplace, the patient should be held at a pressure where the cardiopulmonary function is maintained; preparations made for rapid drainage of the pneumothorax with the most highly skilled professional ready and on standby to perform chest decompression. Decompression should then be performed expeditiously and the pneumothorax drained quickly upon arrival at the surface. Barring diving casualties, where rapid decompression may be detrimental and a risk-benefit decision must be made – the abovementioned approach has been shown to be effective with good outcomes.

The clinical picture of pulmonary barotrauma varies with severity. It can show mild overexpansion effects only: dyspnea, tachypnoea with dry cough, chest pain and substernal pressure.

In case of alveolar rupture the following may appear in addition to the above: sudden dyspnea and tachypnoea, haemoptysis, asymmetrical breathing, reduced or absent breath sounds, hyper-resonance, cyanosis, arrhythmia, hemorrhagic pulmonary oedema, and cardiac and respiratory failure. Chest x-ray is essential for determining the presence of intrathoracic or pericardial gas collection. Postero-anterior and lateral views are required to demonstrate retropharyngeal gas.

The differential diagnosis between pulmonary barotrauma and DCI can be complex. The time of onset of symptoms and hyperbaric management considerations offer some distinctions.

Management, depending on severity, includes:

1. 100% O_2 by oronasal mask
2. Emergency drainage of a tension pneumothorax by inserting a large bore intravenous cannula in the second rib space at the level of the mid-clavicular line
3. Definitive management of intrapleural gas or blood is via a formal drainage system at the level of the 4^{th} or 5^{th} intercostals spaces. If HBO is required, a Heimlich one-way valve should be connected to the drainage system. If recompression is not required, regular underwater drainage is appropriate
4. Pericardial drainage for gas tamponade with needle access from the xyphi sternum aiming at the inferior tip of the left scapula[14]

In case of pulmonary barotrauma the risk-benefit of HBO should be considered carefully. In the absence of any decompression illness, pulmonary barotrauma usually does not require recompression unless the expansion of gas within the intrathoracic and cervical areas is severe or no means of external decompression are available. Even then, compression is only aimed at relief of gas expansion symptoms and recompression need not exceed more than a few meters in many cases. This will make subsequent management and removal from the chamber much less complex.

Pulmonary overpressure is the most frequent cause of *arterial gas embolism.* It is relatively common in diving (approximately 10% of diving accidents) whereas it is very rare in hyperbaric medicine practice. Causes include rapid decompression and high positive pressure ventilation.

Paradoxical embolism also needs to be considered with passage of gas from the venous circulation to arterial circulation through pulmonary vessels or a pre-existing patent foramen oval.

Pulmonary barotrauma with gas embolism must always be considered in diving injuries even though it is relatively rare and usually has a very rapid

onset. Arterial gas emboli have a predilection to enter the cerebral circulation where they tend to occlude arteries less than 200μm in diameter, causing ischemic or embolic stroke. However, other areas can be affected also, particularly the coronaries or other organ systems. With the exception of sudden cardiac death due to arrhythmias, these effects are usually more benign.[14,34]

Usually venous gas emboli are filtered by the pulmonary capillaries. However it is possible, either due to a multitude of bubbles or arteriovenous anastomoses for bubbles to cross the pulmonary barrier, allowing them to reach the systemic circulation. Bronchodilators and certain calcium antagonists have a vasodilating effect on pulmonary capillaries and may reduce the effectiveness of the filter.

The gas bubbles act like other embolic phenomena in that they lead to the synthesis of prostaglandins and activate platelets with the associated initiation of the various plasma protein cascades leading to thrombosis, inflammation and even disseminated intravascular coagulation with an increase in free radical production and endothelial vascular injuries.

These effects also occur in the brain with vascular changes, ischaemia-reperfusion, and alteration of the effectiveness of the blood brain barrier with consequent cerebral oedema and an increased intra cerebral pressure (ICP).

The signs and symptoms of gas embolism depend on the amount of gas embolized, the location affected and the concurrent presence of inert gas supersaturation. The signs and symptoms appear during or shortly after decompression. The condition may cause sudden death with no breathing or pulse requiring CPR and advanced life support. Fortunately this only occurs in 4-5% of the cases as the majority of these patients do not respond to resuscitation.[27,30] In many ways acute cerebral arterial gas embolism resembles a stroke, with loss of consciousness, stupor, mental confusion, vertigo, convulsions, headache, hemiparesis and sensory changes.

The condition should be considered a true medical emergency and the patient should be transported to a recompression facility as soon as possible. Other than for the initial assessment; for the purposes of CPR; or where a patient is intubated, they should remain in lateral position to protect the airway. Haemodynamic and ventilatory function should be supported and intravenous access should be established with the administration of isotonic, non-glucose/ dextrose solutions. Hypotonic and dextrose containing solutions should be avoided, as these tend to aggravate cerebral oedema. Crystalloid or colloid solutions are preferred. Steroids are not generally recommended, but may be useful in some cases. Similarly the use of lidocaine / lignocaine may offer some advantages, particularly in non-diabetics and where recompression may be delayed.[26,31] Normobaric 100% O_2 should be administered immediately.[25]

The presence of neurological signs in suspected arterial gas embolism is an indication for HBO; the sooner it can be carried out the better. In the initial stages of arterial gas embolism the effects are largely mechanical. The immediate use of HBO to compress nitrogen (air) bubbles and accelerate the elimination of the nitrogen is clearly advantageous. However, after a delay the consequences of the ischaemia and the pro-inflammatory and pro-coagulation effect of bubbles leads to a myriad of secondary effects for which pressure therapy is only partially helpful. HBO can attenuate some of the peri-ischaemic, inflammatory and pro-edematous effects of the insult, but clearly prevention of these secondary effects is preferred. The choice of recompression therapy is therefore driven by the delay and severity of the clinical manifestations at the time of treatment. During the initial stages when bubble effects predominate, pressure is the single most important ally. Here the use of deep air or mixed gas tables has previously been recommended, although the European Consensus now considers them Level C -- optional. After an uncertain period of time the value of pressure, beyond being an effective means for hyperoxygenation, becomes obscure. In addition, the logistical and safety implications of managing an unstable casualty at great pressure is a disincentive to use elaborate and deep or mixed gas (e.g., Heliox or Nitrox) therapeutic regimens where the value is uncertain and where the facility is not properly equipped to execute the procedure and manage potential complications.

Hyperbaric therapy should be continued daily or twice daily – depending on severity – until a clinical plateau is achieved. Integrated and continuing rehabilitation is very important as these patients – being younger – often have a far better prognosis than elderly stroke patients.

Based on the jury recommendations of the 7th European Consensus Conference on Hyperbaric Medicine: "*Hyperbaric Oxygen Therapy is strongly recommended, whatever the symptomatology of air embolism*". The minimal treatment pressure must not be lower than 3 ata (Type 1 - recommendation, Level C).[28]

4. OTHER BAROTRAUMA

4.1 Barodontalgia

Tooth or dental barotrauma is characterized by pain or injury during changes in ambient pressure. The mechanism involved may be related to expansion of trapped air in a cavity underneath the crown of the tooth with pain receptor activation; stimulation of nerve endings in a chronic inflamed pulp; or stimulation of the maxillary sinus pain receptors.[35,36] There is

invariably some sort of underlying pathological explanation such as previous dental reconstruction, residual dental cysts, caries, and peri-apical infection.[37,38] Severe pain and implosion or explosion of a tooth or teeth is possible. Upper tooth injury may be confused with maxillary sinus barotrauma. Analgesics and treatment of the underlying dental pathology with appropriate fillings and cavity or root canal treatment are mandatory to manage incidents and prevent future complications. This is an exceptional event in hyperbaric medicine practice.

4.2 Gastrointestinal and ocular barotrauma

Excessive swallowing of gas (i.e., aerophagia) while under pressure may lead to a gastrointestinal barotrauma, during decompression. Although rare, it may occur due to an expansion of air in the stomach and bowel, causing abdominal distension and colicky pain. In extreme cases it may lead to gastric and bowel rupture with a subsequent acute peritonitis and pneumoperitoneum requiring urgent surgical intervention.[39,40]

Individuals who have undergone ophthalmic surgical procedures are known to have gas in the anterior chamber or vitreous cavity. This may be affected by pressure changes with resulting barotrauma including: retinal, uveal or vitreous hemorrhage and possibly a partial globe collapse.[41] Hyperbaric oxygen therapy should be used carefully under ophthalmologic expert advice and diving deferred until ocular complications ruled out. The additional effect of dysbarism related to the face mask should also be considered here.

Any other known pathologic condition where there is a gas filled cavity or space, should be carefully considered.

5. PREVENTION

Patients who need to be treated with HBO should be carefully clinically evaluated in order to prevent barotrauma. Otolaryngological, pulmonary, cardiovascular, neurological and other systems should be screened properly in order to identify any disease state and minimize the potential risk of treatment. Sometimes, in very serious nature of a patient's clinical conditions may make such risk-benefit determinations a complicated matter. Here the experience of others may be particularly helpful.

A careful clinical history, chest x-ray and otoscopy are mandatory parts of the examination. Tympanometry is a very useful tool and should be regularly performed when any doubt exists about tympanic membrane elasticity and ET function. Myringotomy or ventilation tube insertion should

be done whenever there is an inability to equalize middle ear pressure. All medical and paramedical staff of a hyperbaric facility should be educated and trained to quickly identify signs of developing barotrauma. Compression and decompression rates should be slow and carefully controlled. When a relevant symptom is discovered during the compression phase, this should be halted followed by slight depressurization to a point of pain relief. Equalising and decongestion may be attempted to alleviate the problem, but in many cases either the hyperbaric treatment or the underwater excursion will need to be aborted in favour of further medical intervention (myringotomy and tympanostomy) or to allow spontaneous recovery of Eustachian tube function (divers).

Prevention of middle and inner ear barotrauma should be familiar to every person involved in hyperbaric treatments: Where possible, avoid treatments in the presence of significant nasal congestion, discharge or upper respiratory tract infections; if there is a choice have patients sitting rather than lying; nasal or systemic decongestants may be used judiciously; ascent and descent rates should be appropriately slow; and patients should be taught and observed to apply the various equalizing techniques of modified yawning and swallowing; Frenzel and Toynbee techniques; soft palate contraction and gentle Valsalva – avoiding forceful Valsalva at depth.[2,14]

Comatose patients present a special challenge. Some authors propose a routine myringotomy for all intubated and non-cooperative patients, especially neurosurgical ones where the pain may otherwise result in an increase in intracranial pressure.[42,43] Although 25% of United States Centers perform myringotomy on intubated patients, there is no actual standard of care in the literature regarding middle and inner ear barotrauma prophylaxis prior to HBO therapy.[44] With a very low incidence of serious barotrauma, many authorities do not recommended a routine myringotomy in this kind of patient.[45,46] In European practice, this is not a routine procedure. Relaxation of the Eustachian tube muscles appears to permit easier middle ear pressure equilibration in comatose patients, with a corresponding low incidence of barotraumatic injuries.[47] Properly controlled, slow descents and careful surveillance by the medical staff in a multiplace hyperbaric chamber contributes to a reduction in barotrauma incidence risk.

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Chapter 3.7.2

OXYGEN TOXICITY

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Abstract: This chapter will present our current knowledge on the major toxic manifestations of oxygen; the clinical features–descriptions and incidence of symptoms, mechanisms underlying the oxidative insult, the time–duration relationship defining the safety limits, risk factors leading to enhanced toxicity, and strategies for protection

Keywords: Hyperbaric oxygen, hyperoxia, oxygn free radicals, pulmonary oxygen toxicity, nitric oxide, diffuse alveolar damage, pulmonary function, vital capacity, diffusion capacity, latent period, absorption atelectasis, acute tracheobronchitis, ARDS, oxygen tolerance, UPTD, CNS oxygen toxicity, epilepsy, diving, grand mal, generalized seizures, antioxidant, ocular oxygen toxicity, myopia, cataract, tunnel vision

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy
Philipus Aureolus Paracelsus (1493-1541)

More than two hundred years ago Priestley foresaw the toxic nature of oxygen by saying "as a candle burns out much faster in dephogisticated than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve."

The awareness to the toxicity of oxygen had fully emerged with the widespread use of high oxygen pressure in medicine, the accumulated experience in the field of hyperbaric medicine and in military and professional diving. The most dramatic manifestations of HBO (hyperbaric oxygen) are pulmonary oxygen toxicity (Lorraine Smith effect), CNS oxygen toxicity (Paul Bert effect) and ocular oxygen toxicity. Yet the toxic

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effect of oxygen can be found in almost every organ and tissue, and it is only a matter of time until it affects all body tissues and organs.

The following chapter will present our current knowledge on the major toxic manifestations of oxygen; the clinical features–descriptions and incidence of symptoms, mechanisms underlying the oxidative insult, the time–duration relationship defining the safety limits, risk factors leading to enhanced toxicity, and strategies for protection.

1. PULMONARY OXYGEN TOXICITY

The lungs are exposed to higher oxygen tensions than any other organ. At exposures to ambient oxygen pressures around 0.1 MPa (1 ata), the lungs are the first organ to respond adversely to the toxic effects of oxygen. Most of the currently available information on the toxic effects of oxygen on the lungs originates from studies in healthy animals and human beings. Relatively limited amounts of data are available on the effects of hyperoxia in experimentally injured animals and sick human beings.

1.1 Mechanisms of oxygen toxicity

Oxygen toxicity is generally considered to result from the formation of oxygen free radicals (OFR) in excess of the quantity that can be detoxified by the available antioxidant systems in the tissues. Molecular oxygen itself is nontoxic and only modestly active. However, when it is chemically reduced by sequential additions of electrons, it forms highly reactive OFR. The major sources of increased production of OFR during exposure to hyperoxia are the mitochondrial electron transport chain and the cytochrome P450-linked electron transport system of the endoplasmic reticulum. Other possible cellular sources of reactive O_2 metabolites during hyperoxia include microsomes, peroxisomes, membrane and cytosolic oxidases, xanthine oxidase, arachidonic acid metabolism, and autooxidation of iron, hemoglobin, myoglobin, catecholamines and various coenzymes[1-4].

The primary cellular defense mechanisms against oxygen radicals are enzymes that catalyze their removal, namely superoxide dismutases (the cytoplasmic CuZnSOD and the mitochondrial MnSOD), catalase, and the constituents of the glutathione redox cycle (glutathione, glutathione peroxidase and glutathione reductase). Nonenzymatic antioxidants, such as vitamin E, vitamin C, beta-carotene, uric acid, and several other agents also scavenge OFR by reducing them to less toxic substances[2,5,6].

Nitric oxide (NO) is emerging as an additional possible mediator of the toxic effects of oxygen[7]. Presently available data suggest that hyperoxia increases tissue production of NO[8-10]. Both NO and oxygen are hydrophobic

gases that accumulate in cellular membranes where they may interact and produce the potent oxidant peroxinitrite (ONOO-)[11,12]. Reactions among NO, peroxynitrite and a variety of cellular constituents generate a number of potential toxic intermediates capable of mediating at least some of the documented effects of hyperoxia. Furthermore, inhibition of nitric oxide synthase (NOS) was demonstrated to protect against CNS oxygen toxicity[9,13]. The exact mechanisms by which the NO system contributes to the pathophysiology of oxygen toxicity, the mechanism of the protective effects of NOS inhibition in CNS oxygen toxicity and the apparently paradoxical protection conveyed by inhaled NO in pulmonary oxygen toxicity[14], have yet to be clarified.

Tissue damage from OFR basically involves three cellular components: nucleic acids, proteins and enzymes, and membrane lipids. DNA damage results from OFR induced modifications of nucleic acid bases and strand breaks[15,16]. The consequences of these modifications and the activation of their repair mechanisms on cellular functions are reviewed elsewhere in this handbook.

Proteins are another major target of free radical damage. Their susceptibility to reactions with free radicals depends on their level of unsaturation and their content of sulfhydryl (SH) groups. Interaction of proteins with OFR may thus lead to protein sulfhydryl oxidation, conformational changes and cross linking. These alterations may lead to enzyme inactivation, modifications of membrane receptors and ion channels, and affect membrane bound proteins by modifying their lipid environment subsequent to lipid peroxidation. Proteins damaged by OFR are recognized as abnormal by cellular proteolytic systems. When the damage occurs at the outer membrane surface it may activate immune response and induce further delayed injury[17,18].

Lipid damage is yet another central feature of free radical injury. OFR react with cell membrane polyunsaturated fatty acids, generating lipid peroxides and lipid peroxy radicals. The process is potentiated by the presence of metal ions and can become autocatalytic. Peroxidation of membrane fatty acids exerts adverse effects on membrane permeability microviscosity and deformability as well as on ion transport and enzyme activity[2]. Lipid peroxidation was demonstrated during hyperoxia in the CNS, lungs and liver[3].

Although the mechanisms of free radical damage to a large array of cellular systems have already been extensively characterized, large gaps exist in our understanding of the intermediate stages in the pathophysiological cascades that follow such reactions and result in alterations in cell functions. The potential links between OFR and consequent functional deficits (e.g., pulmonary endothelial metabolic dysfunctions and increased endothelial permeability) and clinical

phenomena (e.g., pulmonary inflammatory response) caused by oxygen toxicity are even less clear.

1.2 Morphologic changes in pulmonary oxygen toxicity

The morphologic changes that occur in the lungs in response to inhalation of oxygen at high partial pressures were first described by J. Lorraine Smith in 1897-1899[19,20] as "pneumonia from oxygen". His pioneering observations, mostly of what is currently characterized as the acute exudative phase of pulmonary oxygen toxicity, were later expanded and verified in a variety of animal species and humans[21-24]. It is currently well established that exposure to oxygen at high ambient partial pressures causes alterations throughout the entire respiratory tract including the airway epithelium, microcirculation, alveolar septa and pleural space. A typical pathologic and clinical picture of diffuse alveolar damage (DAD) and/or necrotizing bronchitis (bronchiolitis) occurs within three days to one week of continuous exposure to 0.08-0.1 MPa (0.8-1.0 ata) of oxygen or within shorter periods of time at higher partial pressures, as a result of direct pulmonary oxygen toxicity.

1.2.1 Acute exudative phase

The pathology of oxygen toxicity is nonspecific and shares most morphological features seen in other causes of DAD (toxins, other inhalants, pharmaceutical agents, radiation, and the multiple causes of ARDS including trauma, sepsis and shock). Exposure to a lethal dose of oxygen (e.g., 100% O_2 at 0.1 MPa) is characterized first by an initiation ("latent") phase in which no significant morphological changes are detected. This is soon followed by an acute exudative-inflammatory phase. The capillary endothelium in pulmonary capillaries and venules appears to be the most vulnerable cell type, and the first to react to the toxicity of oxygen. The earliest changes in the acute exudative phase involve microvascular endothelial cells and are associated with sequestration of platelets, and later neutrophils in the pulmonary microvasculature, increased capillary permeability and accumulation of interstitial edema. Neutrophils transmigrate to the interstitial spaces where they seem to augment the already active inflammatory response. In pure pulmonary oxygen toxicity, neutrophils do not accumulate in large numbers in the alveolar spaces. Destruction of pulmonary capillary endothelium with marked decrease in the total mass of endothelial cells and the total capillary surface area indicates significant damage to major portions of the pulmonary capillary bed[21,22].

With continuous exposure to hyperoxia, the destructive phase progresses and is characterized by interstitial, intra-alveolar, and peribronchial edema,

intraalveolar hemorrhage, fibrin deposition, formation of hyaline membrane, destruction and sloughing of the Type I alveolar lining cells with denudation of the alveolar basement membrane and formation of hyaline membranes. Hyaline membranes of oxygen toxicity have been described as lining all or only parts of the terminal airways and air spaces. They arise as a result of extravasation of plasma proteins and necrosis of components of the terminal airway and alveolus. They contain local cellular debris, but their fundamental component appears to be polymerized insoluble form of fibrin. In animals and humans, concurrent hyperplasia of Type II epithelial cells, which eventually leads to replacement of the alveolar epithelial lining with Type II cells, also commences during the acute exudative phase. The pleural surfaces are frequently involved and accumulation of pleural fluid is common[23-26].

1.2.2 Proliferate phase

Healing of the acute exudative phase is termed the proliferative phase. This stage of oxygen induced DAD is an overlapping continuum characterized by proliferation of Type II alveolar epithelial cells and fibroblasts. Type II cells cover the desquamated alveolar membranes and can later differentiate into Type I cells. Proliferation of fibroblasts may induce interstitial fibrosis with extensive deposits of collagen. Another important component of this phase is capillary regeneration. In the terminal bronchiole epithelium, proliferation of nonciliated secretory (Clara) cells is the primary reparative response[21-24].

It should be emphasized that the tracheobronchial tree is also damaged by hyperoxia. Epithelial swelling, degeneration, and desquamation, associated with peribronchial edema and exudation of polymorphonuclear leukocytes and fibrin into bronchial walls and/or lumen have been described. Clara cells as well as ordinary bronchiolar epithelial cells are involved. This hyperoxic-induced bronchitis/bronchiolitis has characteristically been observed in infant animals and humans. The trachea has been less well studied than other airway structures, but it seems that its surface is vulnerable to the same effects that oxygen has on the mucosa of the bronchi[22].

Exposure to oxygen at sub-lethal doses is also characterized by an initial “latent” pathological stage during which significant biochemical and functional alterations involving the lungs do occur, however no substantial overt morphologic changes can be detected. Such sub-lethal exposure delays and blunts the characteristic changes with less sequestration of platelets and leukocytes, a blunted inflammatory response, and a substantially slower loss of capillary endothelial cells. Under sub-lethal exposure to oxygen a proliferative response involving all compartments in the alveolar septum begins near the time of destruction of the pulmonary capillary endothelium and is associated with deposition of collagen and interstitial fibrosis[22-24].

The profound necrotic effects of oxygen-induced DAD on the alveolus and bronchiole as well as the pathological changes that occur during prolonged exposure to sub-lethal doses of oxygen, alongside the destruction of segments of the alveolar septal wall and enlargement of airspaces may ultimately produce emphysema with alveolar disruption and formation of bullas usually accompanied by increased numbers of goblet cells and increased production of mucous. In gross examination, the lungs are over-inflated, pale and covered with extensive bullas – a clinicopathologic combination reminiscent of bronchopulmonary dysplasia of infants[22].

Human data from autopsies of patients dying following hyperoxic treatment are complicated by underlying disease processes for which therapy was initiated. However, the pathologic features described for human pulmonary oxygen toxicity are strikingly similar to those found under well-controlled experimental conditions in laboratory animals[22-24].

1.3 Effects of hyperoxia on pulmonary functions

Impairment of pulmonary functions occurs during exposures to oxygen above a threshold partial pressure of 0.05-0.06 MPa (0.5-0.6 ata). Above this threshold, the nature and rate of development of physiological and clinical manifestations depend on oxygen dose (partial pressure and exposure duration) and individual vulnerability[7]. Most available data on the effects of hyperoxia on pulmonary functions originated from studies on healthy individuals exposed to oxygen at partial pressures of up to 0.35 MPa[27,28]. The data on patients with preexisting lung diseases is patchy and controversial. In general, indices of mechanical function are impaired earlier and more prominently than those of gas exchange. A prolonged exposure to high oxygen partial pressures eventually impairs all indices of pulmonary function.

Acute, progressive reduction in vital capacity is a well documented, consistent manifestation that occurs early in the course of oxygen toxicity and is usually exacerbated later. During the early stages, chest pain and substernal distress limit inspiration and decrease the vital capacity. Later on, absorption atelectasis, pulmonary edema and inflammation and increased alveolar surface tension intensify the collapse of alveoli and small airways, decrease the compliance, reduce tidal volume and the total inspiratory capacity, increase residual volume and functional residual capacity and further decrease the vital capacity[7,27-29].

Data on the effects of hyperoxia on expiratory lung function in humans are inconsistent with some studies showing no change in airway resistance and expiratory flow rates and others reporting a reduction in forced expiratory volume at 1 sec (FEV_1) and in maximum mid expiratory flow rate (FEF_{25-75}) at pressures between 0.2-0.3 MPa[7]. Prolonged exposure to a toxic

level of oxygen eventually produces significant airway obstruction that is attributed at least in part to pulmonary edema[7,29].

Hyperoxia reduces pulmonary diffusion initially as a result of endothelial damage, alveolar capillary destruction and lung edema. Later on, an additional increase in the diffusion barrier due to alveolar edema, formation of hyaline membrane and proliferation of epithelial cells, and eventually, interstitial fibrosis, contribute to a progressive decrease in pulmonary diffusion capacity. It should be emphasized that the demonstration of an early decrease in lung diffusion capacity for carbon monoxide (DL_{CO}) may be biased by the fact that very high concentrations of oxygen may competitively inhibit CO association with hemoglobin and thus alter the measurements[29]. Furthermore, despite a consistent reduction in diffusion capacity for carbon monoxide, alveolar-arterial oxygen differences increase only after prolonged hyperoxia and extreme hypoxemia is certainly a late phenomenon[7].

Static and dynamic lung compliances are decreased during hyperoxia. Initial decrease is attributed to absorption atelectasis and is readily reversible after deep inspiration and hyperinflation of the lung. A subsequent decrease is mostly secondary to an increase in surface elastic recoil and may require prolonged periods of time to reverse. Marked interstitial fibrosis eventually causes irreversible changes in the mechanical properties of the lungs[7,29].

The end result of the oxygen-induced deterioration in pulmonary functions is a progressive ventilation-perfusion mismatch that culminates in increased intrapulmonary shunting that in final stages reduces the oxygen content of the arterial blood.

Studies in healthy humans portrayed kinetics of pulmonary oxygen poisoning over a range of useful oxygen pressures encountered during diving or hyperbaric therapy. Figure 1 illustrates rate of development of pulmonary symptoms and decrements in vital capacity during continuous exposures to oxygen at 0.15-0.3 MPa.

As can be seen in the figure 3.7.2-1 at each oxygen pressure, a decrease in vital capacity started before onset of symptoms and became significant while symptoms were still mild. Rates of symptom development increased progressively at higher levels of inspired oxygen but were characterized by significant individual differences among subjects. Recovery from pulmonary oxygen toxicity is determined by a complex combination of different rates of reversal of the processes that generated the pathophysiological cascades and clinical manifestations of the toxicity. Rates of recovery of vital capacity were generally found to be similar to the rates of its decrease during oxygen exposure and were determined by the magnitude of the decrement[28].

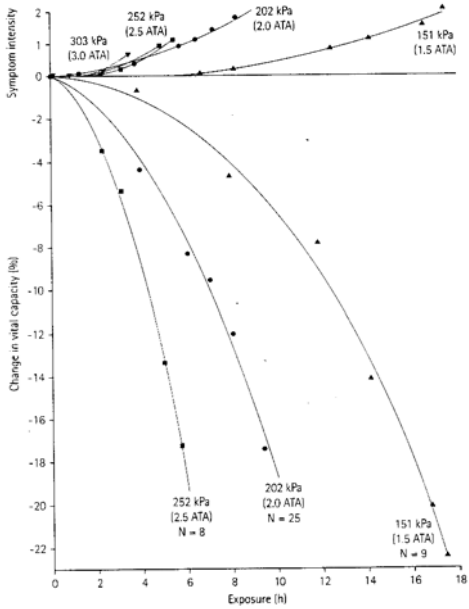

Figure 3.7.2-1. Rates of development of pulmonary symptoms and slow vital capacity (SVC) decrements during continuous HBO exposure. From Clark et al.[28]

Changes in lung diffusion capacity for carbon monoxide (DL_{CO}) are considered a sensitive index of complete recovery from pulmonary oxygen toxicity. Recovery of DL_{CO} occurs slowly and may take several months[7].

1.4 Clinical Features

1.4.1 Latent period

As mentioned above, exposure to toxic levels of oxygen is characterized by an initial period in which no overt clinical manifestations of toxicity can be detected – termed the "latent period". The duration of this "silent" clinical interval is inversely proportional to the level of inspired oxygen [30]. Although it is obvious that mechanisms of the cellular toxicity of oxygen are active during the latent period, recovery from this asymptomatic period is rapid and usually uneventful. The relationship between the inspired oxygen pressure and the duration required for the emergence of clinical manifestations of the toxicity is hyperbolic. Figure 3.7.2-2 depicts a family of hyperbolas representing the pressure-exposure duration relationships for decrements in pulmonary vital capacity and for the occurrence of convulsions that illustrate the duration of the latent period at different oxygen pressures.

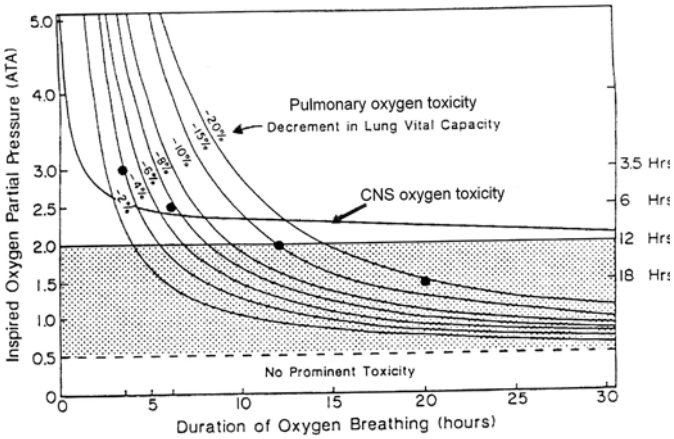

Figure 3.7.2-2. Pulmonary and neurological oxygen tolerance curves for continuous exposures of normal subjects to HBO. Adapted from Lambersten et al.[115]

1.4.2 Absorption atelectasis

During oxygen breathing, absorption atelectasis may occur in lung units with low ventilation/perfusion ratios. In such units the rate of absorption of oxygen from the alveoli to the blood may exceed the rate of replenishment of alveolar gas by respiration thus leading to loss of alveolar gas volume (prompted by the lack of nitrogen in the alveoli). The physiological significance of this phenomenon is increased shunting of venous blood. In contrast to other clinical manifestations of pulmonary oxygen toxicity that occur as a function of inspired PO_2, this potential complication of exposure to oxygen occurs as a function of the fraction of inspired oxygen (FiO_2). Absorption atelectasis usually does not reach clinically relevant proportions in otherwise healthy humans. However, it may be superimposed on the toxic manifestations of pulmonary oxygen toxicity and exacerbate the clinical consequences by increasing shunting and worsening hypoxemia [31].

1.4.3 Acute Tracheobronchitis

Acute tracheobronchitis is the earliest clinical syndrome that results from the toxic effects of oxygen on the respiratory system. It does not develop in humans breathing oxygen at partial pressures below 0.5 ATA. In healthy human subjects breathing more than 95% oxygen at 0.1 MPa (1 ATA), clinical signs of tracheobronchitis develop after a latent period of 4-22 hours and may occur as early as three hours while breathing oxygen at 0.3 MPa (3 ATA)[27,32]. It can start as a mild tickling sensation, later followed by

substernal distress (usually described as tightness on deep inspiration) and inspiratory pain, which may be accompanied by cough, ear discomfort, fatigue and when more severe, by a constant retrosternal burning sensation. Tenacious tracheal secretions may accumulate. Spirometry reveals reduction in vital capacity (as a result of inspiratory pain and/or absorption atelectasis).

Upon termination of hyperoxic exposure the symptoms subside within a few hours, with complete resolution within a few days[27,32,33]. Gross structural changes in the upper respiratory tract consistent with tracheobronchitis (hyperemia, edema and swelling of the mucous membranes of the upper respiratory tract and the airway mucosa) were directly observed by bronchoscopy in healthy human subjects after six hours of exposure to 90-95% O_2 at 0.1 MPa. Tracheobronchitis impairs ciliary function and may thus impair tracheal mucous velocity and clearance of bronchial secretions. It may, therefore, predispose affected subjects to respiratory tract infections[34,35]. The key significance of this relatively benign respiratory disorder is that it may herald full blown pulmonary oxygen toxicity within a relatively short period of time.

1.4.4 Acute respiratory distress syndrome (ARDS)

The clinical symptoms, signs, and laboratory findings of oxygen-induced DAD are not significantly different from those of ARDS from other causes. A steadily worsening dyspnea culminating in labored gasping breathing with bubbling rales and bronchial breath sounds that develop first in the basal posterior lung fields and later spread to involve the entire lung are the clinical hallmarks of the acute exudative phase of pulmonary oxygen toxicity. Production of frothy bloody sputum and utilization of accessory muscles of respiration usually accompany the developing respiratory failure. Typical radiological findings begin as small diffuse bilateral pulmonary densities. These extend and coalesce to opacify most of the lung fields in severe cases. Pleural effusion commonly accompanies the signs and findings of parenchymal involvement. Radiological resolution is slow and in many cases incomplete[29]. Resolution of the acute phase of pulmonary oxygen toxicity or prolonged exposures to oxygen at sublethal concentrations such as during prolonged hyperoxic mechanical ventilation may result in a chronic pulmonary disease characterized by marked residual pulmonary fibrosis and emphysema with tachypnea and progressive hypoxemia[29,36]. The relative contribution of hyperoxia, the underlying clinical condition and mechanical ventilation to the occurrence of chronic pulmonary fibrosis and emphysema in human adults has yet to be clarified.

1.5 Oxygen tolerance

Most information on oxygen tolerance had initially been derived from studies in experimental animals and was based on the theory that oxygen tolerance curves comparing exposure pressure, and the time at which a specific manifestation of the toxicity occurs, have the form of a family of rectangular hyperbolas[37]. Later on, data from human studies substantiated the similarity in tolerance and toxic phenomena to those described in experimental animals[26,28,33.] The expanded data bases originating from such studies provided improved characterization of limits of tolerance – mostly those related to the pulmonary effects of hyperoxia. Among the various indices of pulmonary function, the decrease in vital capacity proved to be the best available sensitive and consistent index for monitoring the development of pulmonary oxygen toxicity both in subclinical and overt symptomatic phases in a clinically and operationally relevant range of ambient pressures[7]. No other single pulmonary function test was found to be satisfactory during the asymptomatic and symptomatic phases of the toxicity. The vital capacity is easily measured both in laboratory settings and field experiments. For these reasons changes in vital capacity serve as an accurate and reliable parameter of the pulmonary toxicity on which current knowledge on tolerance and existing recommendations for permissible exposures to hyperoxia are based. Figure 3.7.2-2 illustrates pulmonary oxygen tolerance curves for continuous exposures by men. The pulmonary limits are based on different levels of changes in vital capacity in 50% of exposed subjects. As stated earlier, out of the various parameters studied after cessation of toxic exposures to oxygen, the diffusing capacity for carbon monoxide (DL_{co}) appears to be a sensitive index of recovery from pulmonary oxygen toxicity[7].

Many factors, clinical conditions, chemicals and potential therapeutic agents have been suggested as enhancing or protecting from oxygen toxicity.

Table 3.7.2-1 provides a partial list of documented protectors and enhancers of the pulmonary toxicity. It has repeatedly been demonstrated that young animals are more resistant than their corresponding adults to the pulmonary effects of oxygen. The prolonged survival of young animals and "spontaneously" resistant adults after oxygen exposure appears to be correlated with lung levels of protective enzymes (e.g., SOD, catalase, glutathione peroxidase, glutathione reductase and G6PD) and especially to the ability to rapidly increase levels of protective enzymes in response to hyperoxia (38).

Exposure to sublethal levels of oxygen (80-85% for prolonged periods of time or intermittent exposure to 100% at 0.1 MPa), chronic exposure to hypoxia, prior exposure to bacterial endotoxin, and pre-exposure or early treatment with the cytokines tumor necrosis factor α (TNFα), or interleukin 1 (IL-1) provide a protective effect against lethality of exposure to hyperoxia.

Table 3.7.2-1. Factors, agents and treatments that protect or enhance pulmonary oxygen toxicity

Factors protecting against pulmonary oxygen toxicity	**Factors enhancing pulmonary oxygen toxicity**
• Pre-exposure to sublethal doses of oxygen (80-85% O_2 or intermittent exposure to 100% O_2 at 0.1 MPa)[32,53] • Chronic hypoxia[54] • Young age[55] • Adrenalectomy or adrenergic blocking agents[56] • Hypophysectomy[57] • Thyroidectomy[58] • Hypothermia and hibernation[9] • Vitamin E[60] • Pretreatment with IL-1, IL-6, IL-11[42,61,62] • Pre-treatment with TNFα & post-treatment with anti-TNFα antibodies[43] • Endotoxin[39] • Superoxide dismutase (SOD), PEG-SOD, & PEG-SOD/Catalase [63,64] • Glutathione[65] • Diethyldithiocarbamate (250 mg/kg) [66] • Anti-intercellular adhesion molecule–1(ICAM-1) antibodies[48] • Iloprost (Prostacyclin analog)[49] • Surfactant[44,47] • Inhaled Nitric Oxide (NO)[50] • Exogenous administration of heme oxygenase-1 (HO-1) by gene transfer[51]	• Premature birth[67] • Viral pneumonia[60] • Humidified environment[68] • Fever[29] • Vitamin E deficiency[60] • Adrenocortical hormones & ACTH[60] • Epinephrine and norepinephrine[60] • Hyperthyroidism, thyroid extracts & thyroid hormones[58,60] • Paraquat[69] • Diethyldithiocarbamate (>250 mg/kg)[70] • Disulfiram (>10 mg/kg)[38]

It has been demonstrated that these protective effects are associated with the induction and increased activity of protective antioxidant enzymes[38-43]. It has also been suggested that other mechanisms may account for the protection afforded by these interventions because in some studies enzyme induction occurred after periods of time longer than that required for death of most control animals. In this regard, it has been demonstrated that increased levels of endogenous surfactant[44] and characteristic cellular changes (e.g., thickening of the interstitial spaces and proliferation of Type II alveolar cells) make the lungs more resistant to the toxic effects of oxygen[47,48]. The relative importance of each of these mechanisms to induction of increased pulmonary tolerance has yet to be determined. In this regard, It has been found, that exogenous administration of surfactant ameliorated hyperoxic lung injury and decreased mortality from respiratory

failure. It has been suggested that surfactant exerts its protective effect by promoting alveolar stability, scavenging extracellularly generated oxygen radicals, and by enhancing intracellular antioxidant enzyme content[44,49].

A steadily growing list of metabolic, nutritional factors, and potential drugs has been shown in animal studies to affect sensitivity to oxygen toxicity. These include thyroid function, adrenal function, hypothermia or fever, starvation, protein deprivation, vitamin deficiencies, deficiencies in essential minerals, and changes in dietary composition of fatty acids. Tentative mechanisms by which these factors exert their effects upon oxygen toxicity include changes in metabolic rate, cellular respiration, and rate of OFR production (e.g., increased sensitivity by hyperthyroidism and thyroid hormones, epinephrine, norepinephrine, and paraquat), quenching of radicals (e.g., increased tolerance by administration of SOD, catalase, vitamin E and vitamin C), increased lipid peroxidation (e.g., by large doses of vitamin C), and effects on protective enzymes (e.g., selenium deficiency, copper depleted diets, and diets that increase the content of unsaturated fatty acids in cellular membranes and enhance toxicity)[29,38]. Interventions that modify the inflammatory response (e.g., anti ICAM-1 antibodies, the prostacyclin analogue Iloprost, inhaled nitric oxide, exogenous administration of heme oxygenase-1 by gene transfer) have been shown to increase pulmonary tolerance to oxygen toxicity[48-51]. In contrast to increased tolerance at a young age, prematurity increases susceptibility to pulmonary toxicity and so does vitamin E deficiency, which is more frequent in premature infants. The picture is complicated by the fact that compounds protective under hyperbaric conditions may be toxic at 0.1 MPa oxygen (e.g., disulfiram), and that different doses of the same agent may exert a completely opposite effect on the tolerance (e.g., vitamin C, Diethyldithiocarbamate)[38].

In general, the large body of data that originated from studies of enhancers and protectors of oxygen toxicity supplied us with valuable information on mechanisms of the toxicity but has not yet provided useful, clinically relevant tools to prevent or at least postpone the toxicity. Currently, increased awareness of preventable or treatable factors as well as increased caution in the use of hyperoxia in the presence of factors that may enhance the toxicity can improve the rational use of hyperoxia for clinical and operational purposes.

1.6 Quantification of pulmonary oxygen toxicity – the UPTD concept

In many situations in which hyperoxia is utilized in diving and in clinical practice, the exposure protocol is composed of a sequence of different combinations of oxygen pressures and durations (e.g., treatment protocols for decompression sickness). The risk of oxygen toxicity involved with such

"irregular" exposures cannot be estimated by the standard dose-time curves that are based on single pressure/duration combinations.

The unit pulmonary toxic dose (UPTD) concept represents an attempt to create a practical tool for calculations of the total risk of pulmonary oxygen toxicity involved in any exposure protocol. It is based on vital capacity measurements that describe the rate of development of pulmonary intoxication at oxygen pressures above 0.05 MPa. The reference standard for UPTD calculations is duration of oxygen breathing at 0.1 MPa expressed in minutes (i.e., exposure to oxygen at 0.1 MPa for 1 minute equals 1 unit). The total number of units for a given exposure protocol is calculated from the sum of individual UPTD values computed for every combination of pressure and time at the different steps of the designed protocol [52]. The total amount of UPTDs allowed for a given exposure protocol depends on the indication for its use. An oxygen dose, equivalent to a small reduction in vital capacity, would be allowed for decompression from diving whereas a calculation based on the allowance of a significantly larger decrement would be considered for a clinical condition in which oxygen may be a life-saving drug. The UPTD system has been used widely for construction of guidelines for safe diving.

Limitations of the UPTD approach are related to the marked individual variability in sensitivity to oxygen toxicity. Furthermore, the calculations do not take into consideration "recovery" periods between exposures to oxygen at toxic levels and are, therefore, overly conservative. On the other hand, the lack of knowledge about rates of recovery from the toxic effects of oxygen, and especially the significance of chronic, long term effects of repeated exposure to subclinical or mild degrees of pulmonary intoxication, represent another serious limitation of the approach[7].

2. CNS OXYGEN TOXICITY

CNS oxygen toxicity was first described by Paul Bert (and, therefore, named after him), in his book "*La Pression Barometrique*" (1878)[71]. In this monumental book of more than 1000 pages, Bert described in detail the effect of exposure to elevated oxygen pressures in a variety of species.

CNS oxygen toxicity is expressed in humans in much higher oxygen pressures than pulmonary toxicity and is the main limitation for the use of HBO in diving and hyperabaric treatments. Most of the data available on CNS oxygen toxicity is drawn from studies on healthy humans in dry and wet oxygen exposures.

2.1 Clinical Features

The most dramatic manifestations of CNS oxygen toxicity are seizures. The classical description was given by Lambertsen[72]:

> "The convulsion is usually, but not always, preceded by the occurrence of localized muscular twitching, especially about the eyes, mouth and forehead. Small muscles of the hands may be involved and incoordination of diaphragm activity in respiration may occur.…..Eventually an abrupt spread of excitation occurs and the rigid "tonic" phase of the convulsions begins…Vigorous clonic contractions of the muscle groups of head and neck, trunk and limbs then occur becoming progressively less violent over 1 minute"

Hyperoxia-induced convulsions are defined and classified as generalized, tonic-clonic (grand mal) seizures[72]. Figure 3.7.2-3 shows a typical electroencephalogram of HBO seizures consisting of spike and wave discharges from both hemispheres starting simultaneously or at random in cortical and subcortical areas[73,74]. The hyperoxia-induced discharges are believed to be reversible, causing no residual neurological damage, and disappearing upon reduction of the inspired oxygen partial pressure[72].

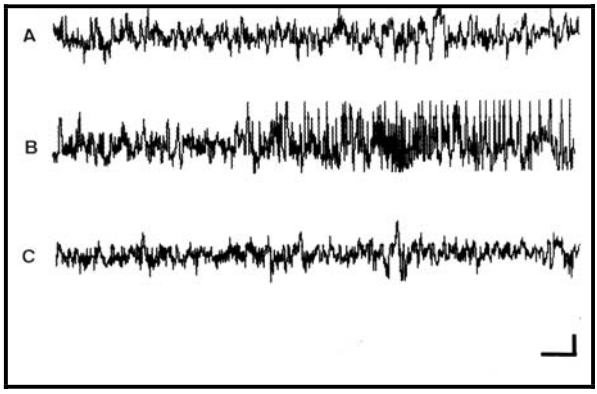

Figure 3.7.2-3. Typical EEG from rat exposed to to 0.5 MPa oxygen. A: Air at atmospheric pressure. B: appearance of typical spike and wave electrical discharges at 0.5 MPa oxygen (arrow). C: On return to atmospheric pressure. Calibration: 1 sec/50 V. From Bitterman, 2004[74]

HBO-induced seizures are accepted to be generalized, although several studies suggested specific susceptible areas for the initiation of the epileptic activity. The local sensitivity may be correlated with variations in cerebral blood flow between different brain areas[75-77], regional changes in amino

acids and ammonia levels[78], variations in lipid peroxide distribution[79] and local alterations in distribution of antioxidant enzymes in different brain areas during exposure to HBO[80].

Early abnormal changes in cortical electrical activity were reportedly seen on exposure to HBO a few minutes prior to the full development of the electrical discharges [81,82] .Unfortunately, no real-time, on-line definition of the pre-seizure EEG activity that could serve as an early EEG indicator of CNS oxygen toxicity is available, in spite of extensive research activity[7,83-85]. An early on-line, real-time EEG indicator could be a useful tool for forewarning the patient or the diver of the potential seizures when exposed to HBO.

Few large scale human studies describing the clinical symptoms of CNS oxygen toxicity are available in the literature[86-91]. The list of symptoms, described in these studies, includes probable and definite symptoms; the probable symptoms are minor signs such as: nausea, dizziness, sensations of abnormality, headache, disorientation, light-headedness and apprehension. The definite symptoms are blurred vision, tunnel vision, tinnitus, respiratory disturbances, eye twitching, twitching of lips, mouth, and forehead, and the development of convulsions. There is no consistency in the pattern of appearance of symptoms, and no typical gradual sequence of minor signs appearing prior to the full development of the seizures, which would help serve as warning signs. Despite prolonged experience with experimental and accidental CNS oxygen toxicity episodes, there is no consensus about the frequency and the incidence of the different symptoms.

Table 3.7.2-2 compiles oxygen toxicity symptoms from about 550 human exposures to HBO (the data were derived from Donald in 1947[87], Leitch in 1984[88], and three series of experiments conducted by Butler and Thalmann[89-91]. The symptoms of CNS oxygen toxicity are presented in a declining order of their incidence of appearance. As can be seen from the table, there are inconsistencies in the frequency of the appearance of the symptoms in the different HBO series, and even between series, which were performed at the same experimental diving unit (e.g. [89-91]). This versatility in symptoms reflects the impact and importance of environmental and personal factors on the development of CNS oxygen toxicity.

Table 3.7.2-2. Symptoms of CNS oxygen toxicity presented in declining order of their incidence (data from: Donald, 1947[87], Leitch, 1984[88] and Butler and Thalmann[89-91]. From Bitterman[74]

Donald	**Leitch**	**Butler and Thalmann (NEDU)**		
1947	1984	1984	1986	1986
Convulsion	Convulsion	Lightheaded-ness	Nausea	Muscle twitching
Twitching of lips	Unconscious-ness	Convulsion	Muscle twitching	Dizziness
Vertigo	Cyanosis	Tinnitus	Dizziness	Blurred vision
Nausea	Limb shaking	Apprehension	Tinnitus	Dysphoria
Respiratory Disturbances	Dizziness	Dysphoria	Dysphoria	Convulsion
Twitching of parts other than lips	Strenuous breathing	Blurred vision	Confusion	Aphasiaia
Sensations of abnormality	Auditory aura	Tunnel vision	Convulsion	Dyspnea
Visual Disturbances	Breathing disturbance	Disorientation	Decreased auditory Acuity	Paresthesias
Acoustic Hallucinations	Nausea	Lethargy	Aphasia	Nausea
Paraesthesiae	Dissociation	Dysphasia	Tingling	Lightheaded-ness
	Apnoea	Aphasia	Numbness	Air hunger
	Loud cry/groan	Eye twitching	Choking sensation	Tinnitus
	Malaise	Nystagmus	Amnesia	Confusion
	Headache/ pulsation	Incoordination	Muscular rigidity	Muscular rigidity
	Apprehension		Lightheadednes s	Irritability
	Amnesia		Poor concentration	Hypoacusis
	Facial twitch		Visual disturbances	Hyperacusis
	Lip tremor		Decreased mental alertness	Poor concentration
	Disorientation		Increased respiratory rate	Tunnel vision
N=388	N=35	N=28	N=33	N=59

2.2 Mechanisms

Although hyperoxia-induced seizures have been well described, the effects of HBO on neural elements remains poorly understood. Studies on vertebrate nerves demonstrated decreased excitability and blockage of impulse conduction[92,93], while increased axonal excitability and an increase in membrane time constant were demonstrated in the isolated nervous system of the cockroach on exposure to HBO[94]. The synaptic mechanisms

seem to play an important role in the development of HBO-induced seizures. Among the main electrophysiological findings, we list an increase in spontaneous synaptic transmitter release[95] and a reduction in inhibitory transmission together with enhancement of evoked excitability activity at the neuromuscular junction of the lobster[96].

HBO is known to affect most neurotransmitters and their related enzymes: GABA, Acetlycholine, Glutamate, Dopamine, Ammonia, Norepinepherine and Aspartate[94-104], and even neuromudulators such as Nitric Oxide (NO)[105].

Membrane bound active transport systems are also impaired on exposure to hyperbaric oxygen[7,85,98,99,106,107], with implications on neural activity. From the different studies performed in different nerve preparations and synapse models, using direct physiological techniques and indirect biochemical methods, it is evident that HBO affects almost all neural elements. However, the primary, major neural target for the oxidative insult that is responsible for the development of the hyperoxic-induced seizures is still an issue to be explored.

It is well accepted that oxygen free radicals species (OFR) produced in excess on exposure to HBO, overwhelming the body's normal antioxidant defense system, mediate the hyperoxic insult[108].

A lot of work has been done to prove the role of OFR in development of CNS oxygen toxicity. A few of the findings that should be mentioned are: an increase in free radicals generation in the brain preceding HBO-induced convulsions (demonstrated in brain extracts)[109], an elevation in H_2O_2 in various brain areas on exposure to HBO[80,110,111], and a rise in free radical levels in the blood of humans exposed to HBO (studied with the use of ESR)[112]. Nevertheless, a recent study, which was done with conscious animals using a microdialysis probe, failed to detect any increase in hydroxyl radicals in exposure to HBO prior or during the convulsions[113]. Currently, the available experimental data does not allow us to decide whether OFR are the primary cause for the hyperoxic-induced seizure activity via a direct effect on essential neural elements (such as membrane, transmitters, receptors), or alternatively, that ROS are acting indirectly on neural elements via secondary messengers such as small inorganic molecules or proteins, to elicit the epileptic activity. The exact mechanism will hopefully be clarified in the near future.

Study of the Blood-Brain Barrier integrity using horseradish peroxidase as a cytochemical marker in chronically EEG implanted rats revealed that CNS oxygen toxicity at its early stages (onset of electrical discharges) is not associated with altered permeability of the cerebral microvessels[114].

2.3 Dose-response curves

The relationship between inspired oxygen partial pressures (in a dry hyperbaric chamber) and time duration until the appearance of symptoms of pulmonary and CNS oxygen toxicity (seizures) is presented in the classical work of Lambertsen and his colleagues at the University of Pennsylvania (Figure 3.7.2-2).

Figure 3.7.2-4 displays the depth-time limits for wet (immersed) oxygen diving[90], setting the lower limit for oxygen diving at about 15 msw (50 fsw, 0.25 MPa absolute pressure) for a period of 10 minutes, and enabling safe prolonged oxygen diving for about 4 hours at a fairly shallow depths around 7 meters (20 fsw, 0.17 MPa absolute pressure) (threshold depth).

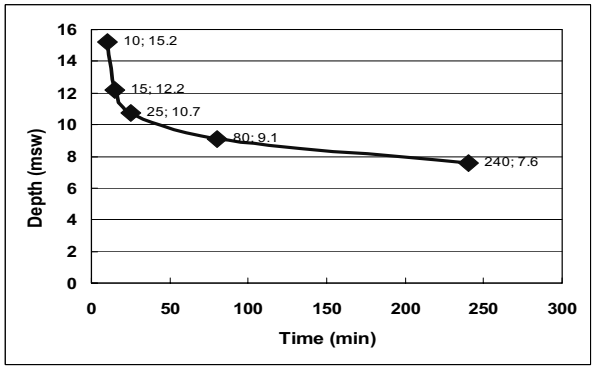

Figure 3.7.2-4. Time–depth limits for oxygen diving. From Butler & Thalmann, 1986[90]

2.3.1 Incidence of hyperoia-induced seizures in HBO treatments

In contrast to the well controlled, methodologically constructed wet and dry limits for HBO exposure in diving, the limits for safe use of oxygen in clinical settings have been gathered from various retrospective studies and case reports reviewing incidence of CNS oxygen toxicity occurring in patients during treatments. Table 3.7.2-3 summarizes the main reports on incidence of seizures during HBO treatments and calculated seizure rates.

Table 3.7.2-3. Summary of main reports about incidence of CNS oxygen toxicity during HBO therapy (adapted from Hampton and Atik, 2003[122]). M=mask, H=hood; MO=monoplace. *CO intoxication, **dysbarism treatment

Report	Oxygen pressure	Patient treatments	Seizures	Seizure rate
Hart & Strauss, 1987[116]	0.2-0.3 Mpa ***MO***	3,160	44	1:12,253
Davis et al., 1988[117]	0.24 MPa			1:7,692
Davis,1989 [118]	0.2.4 MPa	52,758	5	1; 7,692
Welslau & Almeling, 1996 [119]	0 .24- 0.3 MPa	107,264	16	1: 6,704
Hampton et al., 1996 * [120]	2.45 MPa	300	1	1;300
	0.28 MPa	300	9	1:33.3
	0.30 MPa ***H***	300	6	1:50
Plafki et al., 2000[121]	0.24-0.25 MPa	37,611	4	1: 2,844
Hampton & Atik 2003 [122]	0.236 MPa	20,328	6	1 : 3,388
Smerz, 2004 ** [123]	0.24-0.29 MPa	2,166	45 (5 seizures)	1:48 (1:433)
Yildiz et al., 2004[124]	0.24 MPa ***H***	80, 679	2	1:40,339
Yildiz et al.,2004 [125]	0.23 MPa ***H,M***	36,500	3	1;12,166

There are great variations between the different studies presenting incidence of CNS oxygen-induced seizure. It is difficult to compare the different studies using various protocols of exposure (oxygen pressures, air brakes, duration of exposures and number of HBO sessions), assorted techniques for oxygen delivery (hood, mask, monoplace), changeable HBO chamber settings (carbon dioxide removal, equipment resistance), and assorted indications and status of the patients (including medications, smoking etc.). Every one of these factors can contribute to the large dispersion in seizure rate. This issue has recently been discussed in a mini forum[126].

2.4 Risk factors

Various environmental and personal factors may modify the sensitivity to CNS oxygen toxicity, thus shortening the duration of the latent period, and lowering the threshold pressure for the development of seizures.

The most dramatic increase in oxygen toxicity is observed under the effect of elevated inspired carbon dioxide concentrations[2,7,85,87,127-131]. Elevated CO_2 is a common situation in closed-circuit oxygen diving and clinical settings. Hypercapnia is frequently present in patients due to

hypoventilation, chronic obstructive pulmonary disease, effects of analgesics and narcotics, anesthesia, CO_2 retention, and drugs such as carbonic anhydrase inhibitors.

Exposure to HBO in wet environments increases sensitivity to CNS oxygen toxicity compared to a dry hyperbaric chamber at the same inspired partial pressure of oxygen[72,87]. Physical activity (exercise) is another potent factor dramatically decreasing the duration of the latent period for hyperoxia-induced seizures[72,87,128]. The latent period for the appearance of electrical discharges in the EEG is significantly shorter in darkness than in light[132] suggesting the importance of visual input in the modulation of sensitivity to CNS oxygen toxicity. The risk of CNS oxygen toxicity is not determined solely by the partial pressure of the inspired oxygen, and even relatively low partial pressures of inert gases contribute to the imminence of HBO-induced seizures[133]. The increased sensitivity caused by inert gases could be explained by the involvement of free radical production[134]. Circadian rhythm[135], various drugs, age[136], sex[137], interspecies differences and individual day-to-day alteration[87] may contribute to wide-ranging physiological variability in the sensitivity to CNS oxygen toxicity. Figure 3.7.2-5 presents data from a unique study carried out by Donald about 50 years ago,[87] in which he exposed a single diver 20 times to the same profile of HBO within a three-month period, until the appearance of neurological symptoms of oxygen toxicity[87]. As can be seen from the figure, there are large day-to-day variations in time duration until onset of symptoms, suggesting that there is no fixed personal predetermined threshold of tolerance to oxygen toxicity, a finding that supports the ineffectiveness of using the oxygen test as a screening tool for oxygen divers' selection.

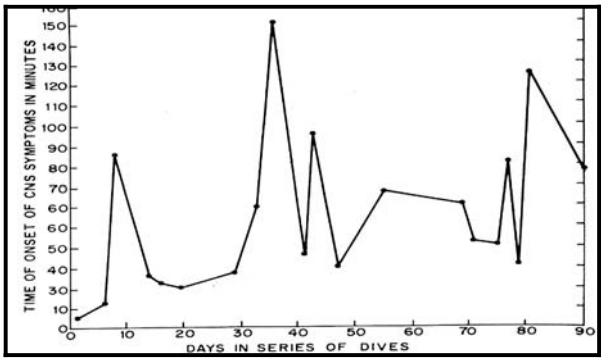

Figure 3.7.2-5. Day to day variations in time duration until onset of CNS oxygen toxicity symptoms of a single diver. From Donald, 1947[87]

2.5 Protection

Intermittent exposure to breathing of HBO with air breaks at the same pressure is a technical approach for increasing the total time of exposure to hyperoxia[7,85]. This procedure is routinely used in the clinical setup with different protocols and ratios between the time duration of oxygen and air breathing periods.

Various pharmacological strategies were tested in animal models for postponing hyperoxic-induced seizures:

1. Cerebral vascular modulation. Exposure to HBO results in cerebral vasoconstriction leading to decrease in CBF[72,75,76], which is subsequently followed by cerebral vasodilatation. It has been suggested that the breakpoint in cerebral vasoconstriction is correlated with the development of hyperoxia-induced seizures[75]. Therefore, any pharmacological agent inducing cerebral vasoconstriction may have the potential to protect or at least postpone the development of the seizures. Caffeine, a well known cerebral vasoconstrictor widely consumed in tea, coffee, chocolate and cola drinks, when given in physiological concentration significantly postponed the hyperoxic-induced seizures in a dose related manner[138]. Two nitric oxide synthase inhibitors, L- NAME and 7-nitroindazole (7-NI), significantly prolonged the latent period for onset of seizures on exposure to both HBO and to a hypercapnic-hyperoxic mixture[13,139,140], supporting the involvement of the L-arginine-NO pathway in the pathophysiology of hyperoxia-induced seizures.
2. Neural activity modulation. On the basis of the clinical manifestation of hyperoxic seizures, several antiepileptic drugs were studied. A significant prolongation of the latent period for seizures was demonstrated using Carbamazepine (Tegretol)[141]. The most promising agent for protection was Vigabatrin (Gama vinyl GABA), an irreversible inhibitor of GABA transaminase. It successfully protected against hyperoxic seizures in a dose related manner for prolonged periods of 24 hours and more after a single administration of the drug[142].
3. Enhancement of the anti-oxidant state. Extensive research was directed toward defining agents that will help protect against oxidative stress, avoiding its development, and increasing the potential for neutralizing or scavenging the OFR.

The results up to now are not very promising, and the literature contains contradictory reports on the potential of various antioxidants to protect against CNS oxygen toxicity. For example, two of the most studied antioxidant enzymes – superoxide dismutase (SOD) and catalayse (CAT) – were found to be protective by Puglia and Loeb[143], yet according to Block et al.[144], these same antioxidants failed to exhibit protective effect. When entrapped in liposomes, SOD and CAT inhibited hyperoxia-induced

seizures[145]. No protection was found in transgenic animals over-expressing SOD[146] and no effect was seen in knockout animals regarding pulmonary oxygen toxicity[147]. Harabin et al.[148] have shown no correlation between symptoms of oxygen toxicity and the levels of antioxidant enzymes on intermittent exposures to HBO.

Metal ion chelators (such as Deferoxamine) were not proved to protect against hyperoxic seizure[149]. A variety of OFR scavengers and natural and synthetic antioxidants have been tested, showing different levels of protection in animal models[149-154]. OFR "Trappers" from the nitroxide stable radicals group (Tempo and Tempol) were effective for prevention of CNS oxygen toxicity in correlation to their lypophilic properties[152,153].

Natural origin beta carotene (*Dunaliella bardawil*) was demonstrated to be among the most effective antioxidants after a one-week diet[154]. The lack of evidence about dramatic protection of antioxidants in CNS oxygen toxicity was supported in a recent review article by two pioneers in the area of OFR: "It was soon clear to many researchers that free radicals did not cause a plethora of diseases, neither were "spoonfuls" of SOD or vitamins going to modify them, let alone cure them"[155].

Deprivation of food or water prior to exposure to HBO significantly prolonged the latent period before the onset of hyperoxia-induced seizure in a dose related manner[156].

Most of these drugs have not yet been tested in humans, and therefore, cannot be recommended for use in oxygen diving or HBO treatments.

3. OCULAR OXYGEN TOXICITY

Exposure to HBO results in physiological and pathological ocular manifestations. Physiological effects include constriction of retinal vessels and narrowing of the peripheral visual field, which occur immediately on exposure to HBO and reverse on return to normal atmosphere[157]. Pathological effects are not reversible and are expressed in histological, biochemical and physiological changes. Most of the pathological ocular effects were observed in animals and in cell culture but have rarely be seen in humans, probably because exposure pressures and durations in the latter are much lower than in experimental protocols for animals[157].

3.1 Effect of HBO on peripheral vision (single exposure)

Breathing oxygen at high pressures causes retinal vasoconstriction and a decrease in peripheral visual fields. The initial observations were made by Behnke et al. (1936)[158] in a healthy subject exposed continuously to oxygen at 0.3 MPa for 3.5 hours. A progressive loss of peripheral vision, almost to

the point of total blindness and diminution of visual acuity were documented. The ocular effect known as “tunnel vision” was reversible and recovery was measured in less than 1 hour after termination of HBO exposure. About 50 years after the initial study, a series of comprehensive experiments were performed in Pennsylvania, summarized under the title of “Predictive Studies V” [7]. Healthy volunteers were exposed to various oxygen pressures, between 0.15 and 0.3 MPa oxygen, and organ specific oxygen tolerance was evaluated, including visual functions. Significant changes were measured in the peripheral field during and after breathing oxygen at high pressures as can be seen in Figure 3.7.2-6. The narrowing of the visual field is possibly attributed to retinal hyperoxia-induced vasoconstriction[157,159].

Single exposure to HBO does not seem to affect dark adaptation, as shown in 5 healthy subjects exposed to 0.2-0.3 MPa for 20 minutes[160], and in 13 subjects exposed to 0.22MPa for 65 minutes[161]. Yet, Kent[162] showed a decrease in rod sensitivity associated with breathing HBO at 0.28 MPa for 20 minutes in two out of four subjects studied.

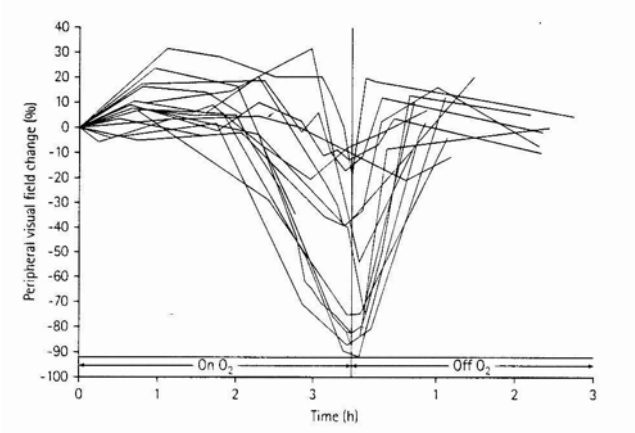

Figure 3.7.2-6. Peripheral visual field changes in man during and after oxygen exposure at 3.0 ATA. From Lambertsen et al.[115]

Various pathologic changes were demonstrated in animal studies including enzymatic derangements, visual-cell death, retinal detachment, cytoid-body formation and retrolental fibroplasia[157,163,164]. The animals were exposed to higher pressures and extended durations compared to human exposures, and therefore, these findings are mostly not relevant for typical HBO treatments or diving protocols. Moreover, most single HBO exposures were carried out on healthy rather than diseased animal and human models.

3.2 Effect of HBO on ocular function (repetitive exposures)

Symptoms of ocular dysfunction are rarely reported in diving[165]. A case report by Butler et al. (1999), described a temporary myopic shift of -1.5D in a diver using a closed-circuit mixed gas underwater breathing apparatus, adjusted to provide a constant partial pressure of 1.3 ata oxygen in nitrogen-oxygen mixture. The symptoms of blurred distance-vision with intact near-vision acuity appeared after 18 days of diving and became progressively worse over the next days. The diver had a total of 84.8 hours diving with a mean dive time of 4.04 hours each day and about three dives a day, at an average depth of 21.3 m. Visual recovery was completed one month after termination of diving. There are no published reports on the occurrence of cataracts in divers.

Several reports describe ocular manifestations in patients exposed to repetitive treatment protocols of HBO. Table 3.7.2-4 summarizes the main reports documenting ocular effects in patients. Not all the information is available for each report, and detailed information on the indications treated and the criteria for excluding patients is partly lacking. As can be seen from Table 3.7.2-4, there are differences between HBO protocols expressed in parameters of pressure, duration of exposure, number of sessions, and oxygen delivery techniques (e.g., monoplace, hood, mask). Patients were treated for a variety of indications, which might have different side effects and potential modifications of ocular functions. It is, therefore, difficult to combine the available studies in order to draw conclusions on safety limits, and to construct a dose-response curve for ocular toxicity and recovery process.

Table 3.7.2-4. Summary of the main reports on the effect of HBO treatment protocols on visual function. **M**=mask, **H**=hood; **MO**=monoplace

	Oxygen Pressure; Delivery	Dur-ation	Total time, exposures	Subjects Number & Ages	Ocular Findings	Cataract
Anderson & Farmer, 1978[167]	0.2 MPa ***H***	120 min	80 hr= 40 expos.	n=10 51-69 yr	Transient Myopia -1.6 D (-0.5-2.5 D)	(–)
Lyne, 1978[168]	0.25 MPa ***MO***	120 min	4-52 weeks	n=26 36-80 yr	Transient Myopia - 0.5-5.5 D (18/26)	(—)
Palmquist et al., 1984[169]	0.2-0.25 MPa ***MO***	65 min	850-150 sessions	n=25 23-68 yr	-3.0 D (25/25)	(+) 7/25

	Oxygen Pressure; Delivery	Dur-ation	Total time, exposures	Subjects Number & Ages	Ocular Findings	Cataract
Ross et al., 1996[170]	0.2 MPa ***MO***	120 min	20 sessions	n=8 31-68 yr	Transient Myopia (8/2)	(—)
Fledelius, Jansen, Thorn, 2002[171]	0.25 MPa ***M***	95 min	30 sessions	n=17 24-72 yr	Transient Myopia 0.5 D after 20 sessions	(—)
Evanger et al., 2004[172]	0.24 MPa ***M+H***	90 min	21 sessions	20 Mask 12 Hood	Transient Myopia, - 0.5 D ***M*** - 1.-0.5 ***H***	(—)
Onoo et al., 2005[174]	0.13-0.15 MPa O_2 ***M*** 4-5 MPa pressure)	60-120 min	34-64 sessions	n=12 22-57 yr	Transient Myopia	(—)

Evanger et al.[172] showed that the myopic shift after HBO therapy was more pronounced using a hood compared to oronasal mask supporting previous findings[173]. It was explained that the oxygen tensions of aqueous and lens tissue are much higher when both the corneal surface and arterial blood are exposed to increased oxygen pressures[173].

A recent report demonstrates transient myopia in workers in pneumatic caisson, which is similar to patients treated in hyperbaric chambers[174]. The workers were exposed to partial pressures of 0.13-0.15 MPa oxygen (the total pressure was 0.4-0.5 MPa).

It is probable that temporary myopic shift episodes observed in HBO treatment protocols are more frequent than reported in the literature, due to the transient nature of the myopia and unawareness of the patients to this phenomenon. Additionally, there are several reports on improved transient presbyopia during HBO treatments[175]. Several studies have suggested that younger patients show less of a tendency to refractive change than older aged groups[168,176], while others could not find a correlation with age[169].

Based on human and animal models, it has been suggested that the myopic shift does not result from corneal power changes, changes in axial length or accommodative tonus but from alteration in the structure of the crystalline lens[167,168, 170,171,173,175] .

Cataract formation was reported by Palmquist et al.[169] in patients undergoing a prolonged course of daily HBO exposures at 0.2-0.25 MPa oxygen (a total of 300-850 hours). On the other hand, experience from various hyperbaric centers indicates that new cataracts do not develop within

the series of 20-50 therapies that are used in most chronic disease states[171,175-177].

Animal studies, in vitro preparations and lenses in organ culture experiments support oxidative damage to the lens as the underlying mechanism for the catarctogenic effect[163,177-179]. Treatment of bovine cultured lenses with HBO demonstrated a significant toxic effect, including decreased lenticular transparency, enzymatic activity and structural changes. The effects were cumulative depending upon the oxygen pressure[179].

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Chapter 3.8

ORGANIZATION OF HYPERBARIC MEDICINE IN EUROPE

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Abstract: Important and independent organizations are involved in the orgization of HBO in Europe: namely the ECHM, the European College of Baromedicine (ECB), the European Underwater and Baromedical Society (EUBS), the group of European Specialists who brought forward the action of the U.E. COST B14 Action, the European Diving Technology Committee (EDTC) and, more recently, the European Baromedical Association for nurses, operators and technicians (EBASS). Finally, regarding recreational diving safety and medicine, the DAN Europe Foundation

Keywords: Education, HBO Standards, Medical Management, HBO Procedures

1. INTRODUCTION

It is now over 25 years after the Constitution of the European Underwater and Baromedical Society, 15 years since the constitution of the European Committee for Hyperbaric Medicine and 10 years since the first European Handbook on Hyperbaric Medicine (Oriani, Marroni and Wattel Eds. Springer, 1996) was published. During this period many positive things have happened in Europe and the European Hyperbaric Medicine Community.

This has shown uncommon coordination capability and the ability to build consensus, rather than develop controversies, really anticipating the European Union action and dream, at least in specific medical discipline of Hyperbaric Medicine.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 767–778.

It must be acknowledged that this is essentially due to the continuous and successful action of the European Committee for Hyperbaric Medicine, from which many other very successful initiatives and actions have stemmed.

Ten year after the first European Handbook and the First European Consensus Conference on Hyperbaric Medicine, organized in Lille by the ECHM, the time was indeed right to produce a New European Handbook on Hyperbaric Medicine, to represent both a new edition of the former one and a "state-of-the-art" update and report on the many successful actions conducted in Europe since 1994, which greatly contributed to the development of Hyperbaric Medicine into a full-fledged and highly specialize medical discipline today.

Important and independent organizations have been the players in this: namely the ECHM, the European College of Baromedicine (ECB), the European Underwater and Baromedical Society (EUBS), the group of European Specialists who brought forward the action of the U.E. COST B14 Action, the European Diving Technology Committee (EDTC) and, more recently, the European Baromedical Association for nurses, operators and technicians (EBASS). Finally, regarding recreational diving safety and medicine, the DAN Europe Foundation

2. THE ECHM

The European Committee for Hyperbaric Medicine has, during the last decade, become a common referral for state-of-the-art hyperbaric medicine practice and guidelines in Europe as well as internationally, with special reference to the European scene. The action of the ECHM, since its inception, has been characterized by a pragmatic and direct approach to the many problems connected to the development and acceptance of hyperbaric medicine in a multifaceted, multilingual, and extremely variegated reality, such as the European one.

This has been done thanks to the enthusiastic action—and devotion—of a small group of dedicated individuals who represented the best of hyperbaric medicine in many European countries and were the clinical and/or academic reference persons in their respective countries, either acting as single recognized specialists or representatives of national scientific societies. Over the past fifteen years the European hyperbaric community, with the coordination of the European Committee for Hyperbaric Medicine, has worked cohesively and effectively to define best practice standards in this highly specialized field of Medicine.

The production of the ECHM during this period has been indeed remarkable, with 7 European Consensus Conferences, 3 Thematic

Workshops, 2 ECHM Reports, all of which are now published in specifically dedicated volumes.

The ECHM was founded in 1989, following an informal and friendly discussion between some distinguished gentlemen involved in diving and hyperbaric medicine with a common vision about the necessity of founding a committee to improve the level of quality and acknowledgement of Hyperbaric Medicine in Europe.

All presidents of the national or international societies devoted to Hyperbaric or Diving medicine in Europe were invited to be ex-officio members of the committee. For the European countries where there was no organized Hyperbaric Medicine Scientific Body, the leading authorities in Hyperbaric Medicine were invited to be members of the committee.

All the western and eastern European countries, included Turkey, Iceland, Cyprus and Malta were thus represented.

The scope and goals of the Committee were defined as follows :

* *Studying and defining common indications for hyperbaric therapy, research and therapy protocols, common standards for therapeutical and technical procedures, equipment and personnel, cost-benefit and cost-effectiveness criteria*
* *Acting as a representative body with the European Health Authorities*
* *Promoting further cooperation among existing scientific organizations involved in the field of Diving and Hyperbaric Medicine*

An effective cooperation between the ECHM and numerous scientific medical or technical organizations was promoted and organized particularly with the European Underwater and Baromedical Society (EUBS), The Medical Subcommittee on the European Diving Technical Committee (EDTC), DAN Europe, and an official presentation of the ECHM was done to the General Direction for Health and Safety and General Direction for Science, Research and Development, European Community, Brussels.

But the most important action of the Committee was to define European standards for Hyperbaric Medicine Practice regarding indications, patient care and quality assurance, equipment and quality control, personnel and training policies, and research.

All this was successfully achieved through the organization of 7 European Consensus Conferences on Hyperbaric Medicine, covering different and challenging themes, plus a number of special workshops and seminars.

2.1 History of the ECHM

After its constitution the action of the ECHM has been constant and outstandingly productive.

All the presidents of the national or international societies devoted to Hyperbaric or Diving medicine in Europe were invited to be ex-officio members of the committee. For the European countries where there is no organized Hyperbaric Medicine Scientific Body, the leading authorities in Hyperbaric Medicine were invited. All the western and eastern European countries, included Turkey, Iceland, Cyprus and Malta became thus represented in the ECHM. The Undersea and Hyperbaric Medical Society (UHMS, USA) and the International Congress on Hyperbaric Medicine (ICHM) were also invited to nominate a Representative and liaise with the ECHM, in order to assure maximal international coordination.

Since then, the most important action of the Committee has been – and still is - to define European standards for Hyperbaric Medicine Practice regarding indications, patient care and quality assurance, equipment and quality control, personnel and training policies, and research.

An initial draft document was prepared as a synthesis of the current international indications for HBO.

The document, named "European Standards for Hyperbaric Medicine" was composed of the following sections :

I. Indications
II. Patient Management
III. Safe and efficient use of hyperbaric chambers and medical equipment under hyperbaric conditions
IV. Personnel and training policies
V. Research Section Editors

In order to allow for the validation of the proposed European Standards for Hyperbaric Medicine and to obtain the best possible consensus within the medical community, the ECHM organized the ***First European Consensus Conference on Hyperbaric Medicine***.

More than 350 specialists from 21 different countries participated at the conference that was held in September 1994 at the Medical university of Lille, France. An international jury : E. Camporesi, New York (Usa), A. Gasparetto, Roma (Italy), M. Goulon, Paris (France), Lj. Greenbaum, Bethesda (Usa), E.P. Kindwall, Milwaukee (Usa), M. Lamy, Liège (Belgium), D. Linnarsson, Stockholm (Sweden), JM. Mantz, Strasbourg (France), C. Perret, Lausanne (Switzerland), President Of The Jury, P. Pietropaoli, Ancona (Italy), H. Takahashi, Nagoya (Japan), C. Voisin, Lille (France), with the support of a panel of 62 conference experts and rapporteurs was called to formulate recommendations that could answer to

the 6 following questions after each one of them has been discussed and debated during monothematic workshop.

** Which treatment for decompression illness ?*
** Which acute indications for hyperbaric oxygen therapy ?*
** Which chronic diseases need adjunctive hyperbaric oxygen therapy ?*
** Which design and safety requirements for chambers and medical equipment for hyperbaric use ?*
** Which initial training and which continuing education for clinical hyperbaric medicine ?*
** Which research to expect and plane for the next five years period ?*

Considering the heterogeneous nature of the different conditions grouped under the definition "Decompression Illness", and in view of the significant development of recreational diving which, the ECHM Committee organized the 2nd European Consensus Conference in Marseille, on May 1996 devoted to "The treatment of decompression accidents in recreational diving" with the goal to reach a European consensus about first aid and treatment procedures.

Then, in view of the fact that HBO constitutes an important adjunctive part of a complex treatment requiring a multidisciplinary approach, and in order to inform and convince the concerned specialists for the best benefit of the patient, the ECHM started a series of ad-hoc consensus conferences.

The 3rd European Consensus Conference (Milano, September 1996) was dedicated to the role of HBO in acute musculoskeletal trauma

The 4th European Consensus Conference (London, December 1998) dealt with the use of hyperbaric oxygen in the treatment of foot lesions in diabetic patients

The 5th European Consensus Conference (Lisbon, October 2001) was dedicated to the use of HBO in Radionecrotic Lesions,

The 6th European Consensus Conference (Geneva , Ocober 2003) was again dedicated to diving related issues and covered the Prevention of Dysbaric Injuries in diving and hyperbaric work.

Finally, 10 years after the first one, the ECHM organized the 7th European Consensus Conference on Hyperbaric Medicine (Lille, December 2004), which focused once again on the indications, treatment protocols, patient managements and safety issues in Hyperbaric Medicine practice.

This last conference also coincided with the conclusive meeting of the European Union COST Action B14, another remarkable achievement of the same scientific and academic groups (and individuals) constituting the ECHM.

During its 15 year of life and activity, the ECHM also organized a number of ad-hoc workshops, with the aim to prepare the basis for discussion at future consensus conferences and/or specific operational guidelines. Three workshops were organized:

I. Wound healing, safety, cost-effectiveness of HBO (Beograd, May 1998)
II. New-Methods of fire fighting in hyperbaric chambers - theory and life tests (Lübeck, 1999)
III. New indications for HBO (Malta, September 2000)

2.2 Structure of the ECHM

The members of the European Committee for Hyperbaric Medicine (ECHM) are individuals who are either members in their capacity of the current Presidents of the Diving and Hyperbaric Medicine Scientific Societies existing in the represented countries and/or invited individuals particularly experienced and active in the baromedical field in their countries.

The ECHM is governed by the *ECHM Board of Representatives*, which is formed by individuals who are members in their capacity of the current Presidents of the Diving and Hyperbaric Medicine Scientific Societies existing in the represented countries.

The founding members of the ECHM are permanent members of the *ECHM Board of Representatives*. Any decision of the BD must be approved by at least two thirds of the professionally active founding members.

Those individuals who are serving as the Immediate Past and the Past Presidents of the Diving and Hyperbaric Medicine Societies existing in the represented countries, invited distinguished baromedical scientists and clinician nominated and elected by majority vote of the ECHM Executive Board or Board of Representatives, and the Past Presidents of the ECHM are members of the ECHM and form the *ECHM College of Advisors*.

The ECHM Board of Representatives, upon nomination by the ECHM members, elects the *ECHM Executive Board*, which is composed of 9-12 members who will serve for a 4 year term, renewed by 1/2 every 2 years, without limit to re-election. The minimum number of the ECHM Countries represented in the EB should be at least 1/2 + 1 of the number of the EB members. The first interim members of the ECHM Executive Board are the current ECHM Executive Committee members, for a period of two years and with the task to implement the present variations to the ECHM regulations, to prepare voting regulations and procedures and to call the next ECHM general business meeting and elections.

The President of the ECHM is nominated by the members of the ECHM EB and elected/ratified by the BR. The President serves for a two year term and can be re-elected for one further term only.

The President of the ECHM is the Chairman of the Executive Board.

All invited members of the ECHM are nominated by the ECHM members, approved by the ECHM Board of Representatives and invited by the ECHM Executive Board in the person of its Chairman and President of the ECHM.

The Executive Board periodically calls for nominations of the new ECHM officers and members, as appropriate.

2.3 On-going actions of the ECHM

4 relevant actions have been so far and successfully conducted.

1. The definition of European standards for HBOT indications
2. ECHM recommendations for safety in multiplace medical hyperbaric chambers
3. Propositions for personnel education and training policies to be used by the European College of Baromedicine (ECBM), created in 1999, together with the Dan Europe Foundation and with the support of the university of Malta, with the following general principles for application: Common syllabus, Common Faculty, Regional organization for theory teaching, Practical training in agreed Centres, Agreement and mutual recognition of final examination, Common graduation
4. Creation of a research network by inclusion of HBOT evaluation in the COST B 14 program of the European Union

All the proceedings of the ECHM Consensus Conferences and Workshops, the safety recommendations for the practice of HBOT and the education program are published "in extenso" in the “ECHM Collection”, Volumes I and II, published by Best Publishing Co. and covering all the ECHM action until the Lille 2004 Conference.

3. THE EUROPEAN COLLEGE OF BAROMEDICINE (ECB)

The action of the ECHM continued, after 2003, with many other initiatives, among which it is important to mention the creation of a satellite body, the European College of Baromedicine, which has the scope and intent

to be a European Accreditation Body for Education in Diving and Hyperbaric Medicine, according to the standards set forth by the ECHM.

In 2004 this action officially introduced to and approved by the European Hyperbaric Medicine Community during the 7th ECHM Consensus Conference on Hyperbaric Medicine, which took place, again in Lille, 10 years after the First “hystorical” one in 1994, and coincided with the closure of the European Union COST B-14 Action’s aimed at the harmonization of Hyperbaric Medical Research and Education in Europe.

3.1 Nature and Scopes of the ECB

The European College of Baromedicine (ECB) is a medical speciality organisation set up to establish and maintain reciprocal recognition of qualifications in the Diving and Hyperbaric Medicine fields between the academic and training institutions in Europe.

It is intended to become the Accreditation Body for Baromedicine in the European Union

The ECB was an initiative of a number of the leading specialists and academics in Diving and Hyperbaric Medicine who, together with the European Committee for Hyperbaric Medicine (ECHM) and the Divers Alert Network Europe (DAN Europe), set up the structures necessary for the College to exist and function.

This was the result of initiatives in the late nineties in Europe in response to a growing demand for better practice of Baromedicine through formal and standardised training and specialisation, and a need to harmonize certification in this area for better consumer information.

The ECB aims at the improvement and promotion of:

1. the quality of health care, by making available specialized knowledge and skills in Baromedicine to the benefit of the patients and of working and recreational divers
2. The quality of the general practice of Diving and Hyperbaric Medicine through the contact of trainees and general practitioners with registered specialists
3. The quality of the service to the public by, among other things, the protection of the public against nonqualified "specialists"
4. The professional satisfaction of qualified practitioners in Baromedicine
5. The structure of health care for patients who may require hyperbaric care, thereby improving its perception and understanding by health care funders and managers (including military and commercial-diving treatment centre administrators), medical practitioners in other specialities and those interested in health insurance

6. The medical support of diving activities, particularly the occupational health of divers at work, and including the management of non-decompression diving accidents
7. The provision of expert advice on the physiological and medical aspects of all categories of diving as may be required by diving employers, military and police diving authorities, commercial diving companies and their client companies, diving scientists and archaeologists, other professional diving bodies and by recreational training agencies
8. The quality of medical personnel in hyperbaric clinics and associated with the diving industries
9. The further development of the speciality of Baromedicine

The primary objectives of the ECB are to advance Baromedicine in Europe and increase the competence of those who practice in this field by:

1. establishing guidelines in collaboration with the ECHM and the European Diving Technology Committee (EDTC) for post-graduate education and training prerequisite to becoming a specialist in diving, in hyperbaric oxygen therapy or in a combination of both of these two aspects of Baromedicine
2. Examining and authenticating medical practitioners as specialists in Baromedicine in order to better serve the patients, their health care funder, the recreational and working diver, the diving industry and the public in general
3. Encouraging research and other contributions to knowledge relating to pathogenesis, diagnosis, therapy, prevention and control of diseases relevant to Baromedicine, the health and safety of fit persons exposed to the hyperbaric environment, and promoting the communication and dissemination of this knowledge.

4. THE COST B-14 ACTION

A logical and effective consequence of the action of the ECHM and its contacts with the European Union Health Authorities, was the start of a specific EU sponsored and coordinated action aimed at the harmonization of Hyperbaric Medical Research, Practice and Education within the EU Countries and those who belong the European Cooperation Area

The main objective of the Action has been to improve the knowledge required for a rational use of HBOT, to a level making it possible to set out specific guidelines for the implementation and development of clinical HBO centres and to provide scientifically sound recommendations for HBO treatment of various diseases and conditions.

The COST B14 Action has been implemented through 3 working groups devoted to the development of:

1. An "Information Network" consisting in an Internet Website, allowing the easy retrieval of information, the participation to discussion groups and the consultation of a bibliographic database pertinent to HBO
2. A "Research Guidance Document" specifying the quality criteria desired for any new and ongoing research projects on HBO, based on the analysis of existing research data and of the weight of the available scientific data
3. A "Research Priority Report", defining areas needing further clarification urgently, that will serve as a basis for directed clinical and experimental research

After having completed its task, this working group has launched 5 specific research teams devoted to one of the selected topics:

1. Sudden deafness
2. Femoral head necrosis
3. Oncology
4. Diabetic foot lesions
5. Technical aspects of HBO, subsequently renamed "Safety aspects of HBO", which eventually produced a document, the "European Code of Good Practice in Hyperbaric Oxygen Therapy", which has been circulated internationally and has become the referral standard in most European Countries and elsewhere.

A reflection about the future cooperation in the field of Hyperbaric oxygen Therapy once the COST action B14 finished, was then initiated. Two main topics emerged: education and hyperbaric oxygen therapy in intensive care patient. In order to pursue the reflection, 2 new working groups were implemented: the first one "Education" with a project of a European Educational Network in hyperbaric medicine, the second "HBO and Intensive Care" with a research project on the specificities in physiologic and pathophysiologic responses of intensive care patient in HBO.

The "Education and Training Working Group" based its work on the ECHM/EDTC Standards on Education and elaborated a document defining the level of education and training in order to reach the target level of competencies as well as modular syllabus for educational courses. Allocation of credits for each module makes possible the mutual recognition of diplomas throughout Europe as well as the possibility for students to have multi-site education and training.

The "Intensive Care in HBO" evaluated the problems raised by the care of a critically ill patient during HBO in order to prioritise the actions to be done. Two main actions were identified: the availability of medical devices to be brought in hyperbaric chambers and the frequency of incidents/accidents occurring during the clinical practice.

Concerning the first problem, a network was proposed to coordinate actions and have more impact on manufacturers to require an extension of the CE marking to hyperbaric chambers and facilities.

Concerning the second problem, the risk analysis done by the WG "technical aspects" was adapted and extended to the Intensive Care setting, and a survey on the incidents occurring during HBO according to the level of care required by the patient (Intensive care or not) was implemented.

5. THE EUBS

Over the past 25 years the EUBS has represented the scientific meeting point of the European Diving and Hyperbaric Medical Community. Although its action has essentially regarded the organization of Annual Scientific Meetings, more than the definition of standards for diving and hyperbaric medicine research and practice, the role of the EUBS has been essential, as it has represented the "common home" where most of the key players could meet and exchange their views and opinions and it was actually the site where the initial ideas which subsequently gave birth to the ECHM first met and developed.

6. THE EDTC

This Committee has worked effectively over the past 30 years and produced essential referral documents and guidelines about the safety and technology of commercial diving work, which has been officially adopted in great part by the EU Health and Safety Authorities and have become a common referral standards for underwater contractors in Europe, The EDTC has a specific Sub-Committee for the Medical Aspects of Commercial Diving, including matters regarding Fitness to Dive Standards and the related Medical Education. This Sub-Committee has effectively worked, since the mid 90s, with the ECHM, and this cooperation generated the current Educational Standards for Diving and Hyperbaric Medicine post-graduate Education, which form the basis of the Educational project implemented by the COST B-14 Action Education Working Group and the operational referral of the European College of Baromedicine for the European Accreditation of Diving and Hyperbaric Medicine Courses.

7. THE EBASS

EBAss (European Baromedical Association for nurses, operators and technicians) started its action with a steering and planning meeting held during the Annual EUBS Conference in Bruges, Belgium, in 2002 and was

officially constituted at the following EUBS Annual Conference, in Copenhagen in 2003.

The main purpose of the association is to encourage coordination and cooperation between nurses, operators and technicians working in European Baromedical Centres with special regard to:

- Developing working and study groups
- Developing interprofessional communications
- Harmonizing education programs for baromedical teams
- Representing its members within other baromedical associations
- Conduct studies related to the baromedical field
- Develop international baromedical personnel exchange programs
- The organisation of conferences either independently or in conjunction with other organizations
- The publication of technical and scientific papers related to the baromedical field

An important action of the EBAss has been conducted within the COST B14 Action with special regard to the safety of Hyperbaric Chambers management and the Education of Hyperbaric Nurses and Technicians.

8. THE DAN EUROPE FOUNDATION

DAN Europe is an international non profit Foundation whose main mission, besides medically assisting divers in distress worldwide, is to foster diving medical research and education about recreational diving safety worldwide.

As such DAN Europe participated, together with the ECHM, in the Foundation of the ECB, of which it is, until now, the sole financial sponsor.
Many of the research protocols conducted by DAN Europe in the field of recreational diving, and their results, have become common referrals for researchers and medical doctors interested in recreational diving safety and medicine and have been included in the documents produced by the ECHM during its Consensus Conferences of 1994, 1996 and 2003.

9. CONCLUSION

The development of Hyperbaric Medicine in Europe, which is condensed in this book, represents the rewarding result of a uniquely wide international cooperation and effort; it also represents the real spirit of unprejudiced, broad-minded and far-sighted international scientific cooperation among a unique multinational group of passionately dedicated individuals, who, with time, became close friends and not only colleagues.

Chapter 3.9

RESEARCH IN HYPERBARIC MEDICINE

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Abstract: Hyperbaric oxygen therapy is a relatively recent development in the field of human medicine, and is in many aspects "unproven", because based on animal and laboratory evidence. An overview is given of the recent developments in research effort, made by the European hyperbaric "community" to work towards this final goal: to stand the test of Evidence-Based Medicine. It appears that financial and human resources are lacking, but also that more attention should be paid to the formal scientific teaching and training of hyperbaric staff

Keywords: Research, Evidence-Based Medicine, Randomised Clinical Trial, Multicentric Clinical Trial, Quality Research, COST Action B14, Oxynet, Internet portal site, Education and training, Consensus Conference, European Committee for Hyperbaric Medicine

1. INTRODUCTION

Hyperbaric Oxygen Therapy (HBO) clinicians are well aware of the potential beneficial effects this treatment can exert in a variety of diseases. A list of "accepted" publications for HBO therapy has been published by national and international Scientific Societies for Hyperbaric Medicine (ECHM[1], UHMS[2]), endorsed (often partially) by social security or governmental organisations[3] and is regularly revised.

For many other diseases, classical medical treatment is not possible or satisfactory, increasing external pressure on HBO clinicians for allowing or "trying" a hyperbaric oxygen treatment, even if no clear scientific proof is available of it's possible efficacy.

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 779–792.

However, even for very few of the "accepted" indications, conclusive scientific evidence is available in the medical literature. Although this situation may be slowly improving, HBO therapy is still regarded as "experimental" and "awaiting validation" by many.

Key players in conducting the necessary research to change this situation are the HBO clinicians themselves, as there appears to be little or no interest from major medical equipment manufacturers or pharmaceutical companies to stimulate research in hyperbaric oxygen.

2. GOALS AND OBJECTIVES SET OUT FOR HBO RESEARCH

In 1994, at the issue of the First European Consensus Conference on Hyperbaric Medicine, several Jury Recommendations were made regarding research in hyperbaric medicine[1].

Question 6: which research to expect and plan for the next five year period?

- It is strongly recommended that quality research protocols are put in place to assure and reinforce the credibility of hyperbaric oxygen therapy (Type 1 recommendation).
- It is strongly recommended that doctors operating in hyperbaric centres are trained to basic and clinical research methods (Type 1 recommendation).
- It is strongly recommended that hyperbaric facilities and specialists associate into multidisciplinary teams (Type 1 recommendation).
- It is strongly recommended that information and personnel exchange policies between hyperbaric facilities are implemented (Type 1 recommendation).
- It is strongly recommended that a network of multicentre clinical research is implemented (Type 1 recommendation).
- It is strongly recommended that a structure for coordination and information is created (Type 1 recommendation).
- It is strongly recommended that Reference Centres as well as a European Ethical and Research Commission are constituted, within the European Committee for Hyperbaric Medicine (Type 1 recommendation).

The implementation of these recommendations suggest the need to create a European Ethical and Research Commission as well as of a Coordination and Information Structure with the following primary goals:

- establishment of a directory of centres and teams involved in Hyperbaric Medicine Research

- establishment of a network of consultants (epidemiologists, methodologists, engineers, etc.)
- organisation of seminars and workshops dedicated to clinical research training
- coordination of Reference Centres, after approval of the same by the European Ethical and Research commission (EERC)
- monitoring and assuring the achievement of the planned goals, as defined by the EERC

In 2002, a new analysis of the status of hyperbaric research was made, following up on the literature analysis made in 1994[4], and a recommendation was made for research efforts to be directed towards 4 main areas[5]:

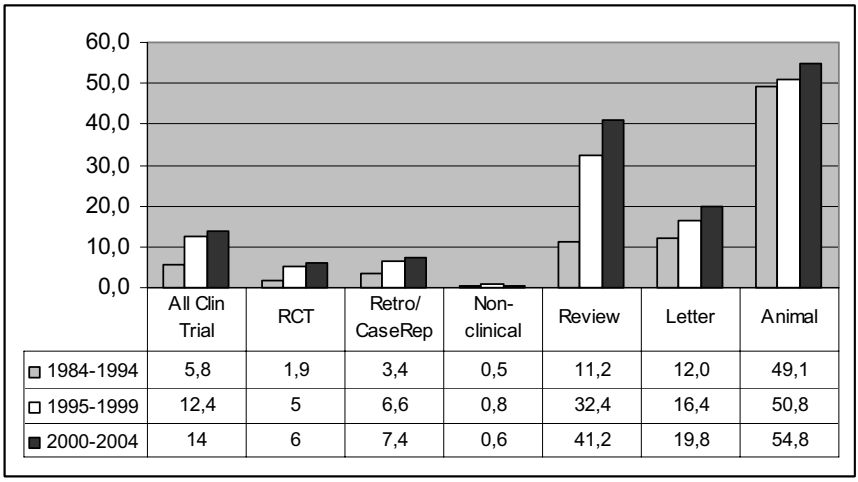
1. Determining the precise physiopathological basis of Hyperbaric Oxygen therapy (HBO).
2. Validating methods allowing assessment of HBO effects in patients.
3. Evaluation of clinical efficacy of HBO.
4. Evaluation of the quality and pertinence of including HBO in the general care of the patient.

Although in an ideal setting, the sequence of these last recommendations should allow a logical evolution from "idea" to "proof", in practice, this is never the case; instead, several research efforts are conducted simultaneously, in a random order, by separate research groups. This is inevitable in most fields of research, and should be accepted in a widely dispersed speciality as HBO therapy.

3. PROGRESS AND ACHIEVEMENTS IN HBO RESEARCH OVER THE PAST 10 YEARS

Since the initial recommendations were made, ten years have passed. Although it is beyond the scope of this chapter to give a complete and exhaustive overview of all the actions that were undertaken, the following observations can be made:

3.1 Summary of publications in the field of hyperbaric oxygen



	All Clin Trial	RCT	Retro/ CaseRep	Non-clinical	Review	Letter	Animal
1984-1994	5,8	1,9	3,4	0,5	11,2	12,0	49,1
1995-1999	12,4	5	6,6	0,8	32,4	16,4	50,8
2000-2004	14	6	7,4	0,6	41,2	19,8	54,8

Figure 3.9-1. Annual number of scientific publications in hyperbaric oxygen therapy (Medline survey Oct 2, 2004 - 2004 number extrapolated from first 6 months)

In medical research, the trend towards an "evidence-based approach" has consolidated, and hyperbaric medicine research should comply with this requirement if it is to be taken seriously by the medical scientific community in general[6]. The number of randomised controlled clinical trials (RCT's), published in international peer-reviewed medical literature, seems, after an increase in the period 1994-2000, to have relatively stabilised at a higher level than previously.

The difficulties of conducting RCTs in hyperbaric medicine have been outlined by several authors[5-8], and will be summarized and briefly discussed below. These difficulties are most likely responsible for the fact that, when RCT's are available, they are not always of optimal quality, either by their design or by their sample size[9-11].

The golden standard for clinical research is the randomised controlled trial; however, in case this type of studies is not possible, other types of research can provide a reasonable level of scientific proof, provided they are of sufficient quality and number.

The levels of publications of retrospective clinical trials in HBO therapy have been continuously increasing since 1994. Their numbers are not so high as one might expect – in fact, it is only slightly higher than the number of

RCT's published, although in HBO-related Conference Proceedings they are much more numerous. This reflects a clear difficulty to have these retrospective studies accepted for publication. The elements making this type of research less "publishable" reside essentially in fragmentary and non-standardized data collection. This may be caused by factors of an economical or a practical nature (impossibility to obtain for each treated patient a full set of laboratory and imaging data before, during and upon completion of the HBO treatment), variability in treatment protocols (both hyperbaric and medical / surgical treatment for any given disease may differ significantly between HBO centres and even within a single HBO centre, making comparisons between patients difficult), and the lack of a control patient population.

Two other types of scientific publication, Case Reports and Reviews, have increased substantially, by approximately 200%, in the years after 1994 and seem to have stabilised at that level. Although this kind of report serves well to increase awareness about the usefulness of HBO therapy for certain indications and may provide valuable ideas and suggestions towards "new" indications, it should be kept in mind that these provide far from conclusive evidence about the efficacy of HBO therapy. It is the easiest and fastest kind of scientific publication; although it should not be discouraged, for the greater benefit of the HBO medical community in general, it should definitely not be stimulated above prospective and retrospective clinical research!

There is a remarkable stability in the number of fundamental scientific research publications and animal studies with HBO therapy. As little of this basic research actually seems to be translated in evidence for clinical applications for HBO therapy, there appears to be quite a large gap between clinical HBO centres and institutions / centres for fundamental research.

3.2 Workshops and Consensus Conferences

The European Committee for Hyperbaric Medicine (ECHM) has performed a steady and well-directed job towards organising regular Workshops and Consensus Conferences[12], and the organisational effort going into these must not be underestimated. These Conferences and Workshops strive to summarize recent and older knowledge and thus provide essential milestones in the process obtaining an increasing body of evidence. They also serve to validate the accumulated evidence by an independent evaluation jury, making their conclusions acceptable to the non-HBO medical community[8,13].

3.3 Multicentre coordination of research

In December 1998, a European Commission funded programme has been initiated, the COST (European Cooperation in the field of Scientific and Technical Research) Action B14 "Hyperbaric Oxygen Therapy". The aims and goals of this Action were defined as "(…) to improve the knowledge required for a rational use of Hyperbaric Oxygen Therapy (HBO), to a level making it possible to set out specific guidelines for the implantation and development of clinical HBO centres and to provide scientifically sound recommendations for HBO treatment of various diseases and conditions."

By the end of June 1999, 15 European countries had already signed the Memorandum of Understanding (MoU); finally, 19 countries (including Israel and Cyprus) have participated in the meetings and working groups of the COST B14 Action.

In a stepwise approach, important objectives of this COST Action have been realised:

- The creation of a European Website for HBO therapy (www.oxynet.org) which serves as a "portal site" and provides objective information on HBO, as well as serving as a contact site between European HBO centres and the COST B14 Action.
- Publication of a "Research Quality Guidelines" document, which lists the minimum required quality criteria for HBO research. This concise document, which is also published on the Oxynet website, addresses several difficult issues in HBO research, such as the variability in oxygen delivery pressures and systems, and the need (or not) for blinding the patients towards the treatment received. Furthermore, the document stresses the importance of HBO centres being able to provide or ensure optimal "conventional treatment" aside from HBO therapy.
- Publication of an Risk Analysis Document in HBO therapy, which served as a basis for the work of the specific Working Group "Safety", within the same COST B14 Action.
- The publication of a "European Code of Good Practice in HBO Therapy", by the WG Safety, which covers the safety of patients, staff, third parties and the infrastructure including the organisation of the facility, staff education, standard and emergency procedures.
- The initiation of a number of randomised clinical trials in HBO therapy, who, if not all have been actually running and including patients, have succeeded in opening the discussion within the HBO medical community and exposing practical difficulties in setting up, managing and following up such multicentre studies.

3.4 Education and training

Existing training and research resources have been stable over the past 10 years:

- University-level training in hyperbaric medicine is available only in some countries. The curriculum of this training provides for some form of scientific work, but does not in itself provide training or education in scientific research.
- At the level of national scientific societies in diving- and hyperbaric medicine, courses and training in (mostly diving-) medicine are organised on a regular basis. Either these are coordinated centrally, or a "reference curriculum" is provided as a basis for accreditation.
- On a limited scale, research efforts are stimulated through the attribution of scholarships or prizes by national scientific societies in diving- and hyperbaric medicine.

In 2001, the "European College of Baromedicine" (ECB) was created, in order to provide a European education organism, following general principles for application of a common syllabus, common faculty, regional organization for theory teaching, practical training in agreed centres, agreement and mutual recognition of final examination, common graduation. This ECB has been conceptualised and founded, and its first officers and board members have been installed.

Within the framework of the COST B14 Action, a Working Group "Education" has been set up, which, in close collaboration with ECHM and EDTC (European Diving Technical Committee), will propose a European training curriculum for diving and hyperbaric physicians.

The COST program provides for funding for "Short-Term Scientific Missions" (STSM), allowing exchange of young staff between HBO centres and research institutions. No such exchange was realised in the running period of the COST B14 Action.

4. FACTORS AFFECTING THE LIKELINESS OF CONDUCTING / PARTICIPATING IN HBO RESEARCH

As can be observed, in many of these Recommendations, progress has been made. However, this seems to have only partially resulted in an increase in scientific publications complying with the evidence-based paradigmata. Research in hyperbaric medicine remains a difficult to achieve goal. Next, let us examine which factors play a role in these difficulties.

Few HBO clinicians see themselves as researchers, for a variety of reasons. Lack of manpower is one of the most frequently cited; by far, most of the HBO treatment facilities are already just sufficiently or even understaffed for the day-to-day clinical work. In most European countries, HBO therapy is insufficiently remunerated; HBO clinicians therefore seldom practice HBO therapy as an exclusive medical speciality, but most often as a "secondary" occupation.

In-hospital financial resources are lacking for hiring extra dedicated nurses or research assistants to organise and follow up on research projects. External funding requires an active and time-consuming search, the difficulty of this task and the required importance (scope) of the research for which funding is sought being most often beyond the possibilities of one individual HBO clinician or HBO centre. This is by no means an exclusive HBO problem[14].

Research institutes and research departments of universities have slightly less problems in obtaining funding for their (mostly animal or basic) research projects, because the necessity of obtaining funds is fully inherent to their main activity. However, economical constraints and a more "results-oriented" governmental policy are responsible for a certain decline in governmental basic research funds being made available, and a greater reliance on privately sponsored research funding[15]. This inherently carries the risk that when research does not seem to be or become economically promising, it is easily cancelled[16].

The basic mechanisms described in animal and fundamental research are not easily extrapolated to the human situation, where many other factors play a (not always properly understood) role. It is therefore difficult to evaluate how strong a given observed effect or mechanism needs to be, in order to warrant extrapolation to a clinical situation in human pathology[17]. These effects need to be verified in the human setting in appropriate trials – which brings us back to the previous point.

The lack of standardisation of hyperbaric as well as "classical" medical or surgical treatment of diseases has been cited above. In order to achieve an acceptance of HBO as an adjunctive treatment for a given disease, an evaluation must be made of the extra benefit that HBO offers when added to the chosen "classical" treatment. Not only must this "classical" treatment be chosen in such a way that it represents the "state of the art" or "best available" treatment for this disease (which in turn – if this is not achievable or desired by the collaborating non-HBO physicians – may limit the participation rate of clinical studies), but it needs to be highly standardised if a multicentre study design is adopted – something which, for the majority of clinical studies on HBO therapy, seems inevitable[18].

A somewhat troubling observation is, that the HBO treatments themselves seem to be insufficiently standardised and evaluated[19]. Differences in treatment pressures, the application of air breaks of various duration, the total duration of the treatment, the administration methods (type of HBO chamber – mono- or multiplace, type of breathing system – mask or hood, type and fixation of mask, delivered flow and type of delivery system – demand or free-flow), and lack of uniformly accepted or widespread use of oxygen delivery control systems (such as transcutaneous oxygen pressure measurement or continuous in-mask oxygen concentration measurement), are responsible for not only possible differences in observed effects or side-effects of HBO therapy, but also for a (be it unjustified) undesirable impression by the medical non-HBO community that HBO clinicians are unable to reach a proper agreement on how to perform a HBO session[20].

Given the wide range of reported incidences of side effects of HBO therapy related to excess dose of oxygen (predominantly, the acute neurological and subacute and reversible ophthalmologic side effects of hyperoxia)[21,22], the (lack of) differences using all these variants do not seem to justify a stubborn adherence to any given treatment protocol. It might add a great deal of credibility to research protocols in HBO, if a single given HBO protocol, although it maybe slightly different from the "usual" protocol in each participating centre, would be used.

We have proposed during discussions in COST B14 Working Group, that a single protocol could be "distilled" from the habitual protocols, with the administration of 70 minutes of oxygen at 2.5 ATA (no air breaks), preceded by a 10-15 minutes compression on air and 10-15 minutes decompression on air. This protocol could serve as a uniform HBO session to replace all different "wound healing", "sudden deafness", "carbon monoxide", "infection", "diabetic foot lesion" types of sessions currently used in European centres. Unfortunately, to date, only a few centres have actually taken the step to change their long-time habits.

An often heard comment of HBO clinicians is "that since it doesn't make that much difference, we should only define a minimum treatment pressure and minimum duration"; this attitude could be compared to a study protocol describing the use of a new antibiotic in a dose anywhere above 20mg per day for two or three times, orally or intravenously, for a given infection. Even if the effect of HBO session standardisation would be largely psychological, it is a goal that should be pursued.

Once a study protocol has been agreed on and Ethics Committee approval has been obtained, the next step is to include patients. Recent experience in the course of the COST B14 clinical studies, has shown that this is often not so easy as it may seem. It has to be kept in mind that most of

the patients treated in a HBO therapy facility have actually been referred by a "third party" – individual physician – who has reasons to choose HBO for his/her patient[23].

Therefore, many patients refuse participation if this implies that they might be randomised into the "non-HBO" group, because they fear that the standard of care will be less than what their treating physician had in mind. A possible solution could be to design if possible, studies in a "cross-over" protocol, where patients would be treated with HBO regardless of the randomisation group they fall into. This however often represents a too long time frame, either for the patient, or for the pathology. It is an undeniable observation that the average rate of inclusion in a clinical HBO study lies at less than 10% of the eligible patients. For study protocols with strict inclusion criteria, where the number of eligible patients is not very high, this may represent the final hurdle upon which the study fails[10].

Relaxing the inclusion criteria may mean a larger number of patients possible to include – it may also mean that the study results become less clear or unequivocal to interpret, and that the study protocol by itself may be subject to severe (and perhaps justified) criticism, jeopardizing possibly the prospects of publication in an international, peer-reviewed scientific journal. The decision to relax the study protocol must therefore not be taken light-heartedly, and the possible consequences must be weighed against the possible benefits[9].

Another possibility to overcome the low inclusion rate of patients, is to enlarge the number of participating HBO centres. Here again, the COST B14 Action has taught us some interesting lessons. In order for a study to be conducted in a multicentre setting, adherence to the study protocol must be strictly controlled.

This requires a constant attention to all aspects of the protocol: inclusion, exclusion, treatment arm, data gathering, follow-up. In an ideal setting, this would be the task of a dedicated "research nurse"[23]. Furthermore, a multicentre design requires central monitoring capabilities in order to ensure a constant awareness and recruitment of patients, as well as a verification of the proper execution of the study protocol[7]. Neither of these seem to be realistically feasible at the moment.

Finally, in the setting of Evidence-Based Medicine, HBO clinical research by necessity has to encompass an evaluation of the cost-benefit ratio of HBO[5,6]. Therefore, it is highly desirable that all clinical study protocols provide space for collection of both complications and side effects of the HBO treatment and the extra financial costs involved in the treatment. Cost-effectiveness studies that have been published to date, in estimating the cost of treatment, have had to refer to rather generalised data available from the literature, coupled to a crude estimation of "HBO costs incurred by the

patient". These costs do not necessarily reflect in all cases the "real" cost of HBO therapy. Likewise, efforts should be made to collect the direct and indirect financial costs of the "classical" medical/surgical treatment of the pathology studied[5].

5. DISCUSSION

The difficulties encountered in conducting research are by no means specific to hyperbaric oxygen therapy alone. Many smaller medical specialities or subspecialities face the same type and degree of difficulties [14,24], and even large specialities like surgery are suffering from administrative and other hindrances in research[25].

These difficulties can be partly attributed to a financial problem:

- lack of explicit funding
- lack of availability of dedicated HBO research in research institutions (only a limited number of such institutions actually carry out HBO research)
- lack of an independent organisation of research coordinators

Two options are open here: either a closer collaboration of clinical HBO centres with existing research structures (university-based, government or private) in order to achieve mutual benefit, or the establishment of a specific professionally run research coordinating body (as exists for other specialities, such a radiotherapy).

However, when evaluating the factors outlined above, another striking conclusion arises: it appears evident that HBO clinicians are not sufficiently trained in order to achieve some of the basic tasks in clinical research:

- Formulation of hypotheses
- Literature search and analysis
- Awareness of scientific methods in design and analysis of trials
- Awareness of the importance of the quality of data collection and analysis
- Knowledge and skills in presenting the results of research

As HBO research, owing to the relative scarcity of includable patients in each HBO centre, will have to be conducted in a multi-centre setting, the necessity of this research education becomes all the more evident and urgent[26]. At this moment, no such training, specific to hyperbaric medicine is available. A specific Working Group of COST B-14 (WG Education), in close collaboration with ECHM (European Committee for Hyperbaric Medicine) and EDTC (European Diving Technical Committee), is drafting European standards for education of diving and hyperbaric medical

specialists; it is to be recommended that formal and practical research is made an important part of this future curriculum.

6. CONCLUSION

Over the course of the past 5 to 10 years, a constant number of scientific papers of EBM standards have been published, resulting in a progressively increasing acceptance of Hyperbaric Oxygen Therapy as a valuable adjunctive medical treatment in a given number of diseases. Also, as basic knowledge on oxygen radicals and their effects increases, the possible benefits of HBO are recognised in a number of other disease states and it's application is justified on a more scientific basis than before.

However, the absolute number of these publications is still to be considered too low, and the general quality of research is still to be improved[9,27]. Failing this, the scientific proof of cost-effectiveness for even "evident" indications for HBO therapy will never reach the standards of Evidence-Based Medicine, and, as healthcare costs in general tend to rise and savings are sought in many areas, this might eventually lead to a reduction of the acceptance of HBO therapy as a whole, as has happened in Germany some years ago[28].

Although worthwhile efforts have been undertaken, there still appears to be a major lack of formal training in basic and clinical research methodology for HBO specialists. This might well be a key factor in the success of a (still to be created) dedicated Coordination and Information Structure for HBO research.

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Annex

LIST OF HYPERBARIC THERAPEUTIC CENTRES IN EUROPE

OXYNET List

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Abstract: This chapter contains a list of therapeutic centres for hyperbaric medicine located in Europe. Each centre was added to the list based on the voluntarily request for inclusion by the centre with verification by the members of the Working Group of the COST Action B14. The detailed database is presented on the Oxynet website (www.oxynet.org)

Keywords: hyperbaric oxygen therapy; hyperbaric centre

The COST Action B14 "Hyperbaric Oxygen Therapy", in its first phase comprised three Working Groups, one of which was dedicated to the development of an internet information and communication tool. The work of this group led to the elaboration of a portal internet site for hyperbaric oxygen therapy, called "Oxynet".

One of the essential parts of this website is a contact list of hyperbaric centres in Europe and immediate adjacent countries, even if it was acknowledged that it would be difficult to obtain a complete and verified list. Therefore, it was decided to allow inclusion on the list on the basis of a voluntary submission of data by each centre, and to have an appropriate disclaimer text on the page. At the term of the COST B14 Action, 180 HBO Centres from 24 different countries had registered for inclusion on the website. Website statistics showed that monthly, over 1500 visits and more than 20.000 "page hits" were counted. In December 2004, it was decided that

D. Mathieu (ed.), Handbook on Hyperbaric Medicine, 793–803.

the Oxynet website would be maintained and linked to the official website of the European Committee for Hyperbaric Medicine.

The following is an overview table of the HBO Centres registered as of May 20th, 2005. The complete list with details including treatment possibilities and full contact information can be consulted at the Oxynet website (www.oxynet.org).

Table Annex-1. List of European HBO centers registered in the Oxynet database

City	*Center name*	*Chamber type*	*Associated with:*
AUSTRIA			
Graz	Dept. for Thoracic Surgery & Hyperbaric Surgery	Multi	County Hospital, University Medical School, Graz
Wien	Hyperbarmedizin Dept.	Multi	Hyperbarmedizin Anesthesia & Intensive Care Medical University Vienna
BELGIUM			
Aalst	Hyperbaric Center Aalst	Multi	Onze Lieve Vrouw Ziekenhuis Aalst
Antwerpen	Hyperbaric Therapy Unit	Multi	AZ Stuivenberg Antwerpen
Arlon	Service Anesthesie-Réanimation	Mono	Cliniques du Sud Luxembourg
Brugge	Hyperbaric Therapy Unit	Multi	AZ St.Jan Brugge
Brussels	Center for Hyperbaric Oxygen Therapy	Multi	Military Hospital "Queen Astrid"
Brussels	Centre Hyperbare	Mono	University Hospital St Pierre Brussels
Brussels	Hyperbaric Chamber	Mono	University Hospital V.U.B
Charleroi	Hyperbaric Chamber	Mono Multi in 2005	University Hospital Charleroi
Edegem	Hyperbaric Medicine Unit	Multi	Universitair Ziekenhuis Antwerpen
Genk	Centrum voor Hyperbare Zuurstoftherapie ZOL	Multi	Ziekenhuis Oost-Limburg - Genk
Liege	Hyperbaric Center	Multi	CHR La Citadelle
Liege	Hyperbaric Chamber	Mono	University Hospital Sart Tilman Liege
Zeebrugge	Naval Hyperbaric Medicine Center	Multi	
BULGARIA			
Varna	Hyperbaric Medical Centre	Multi	St. Marina University Hospital of Varna

City	*Center name*	*Chamber type*	*Associated with:*
CROATIA			
Pula	Poliklinika za Baromedicinu Oxy	Multi	Opca Bolnica Pula General Hospital Pula
Zagreb	Poliklinika za Baromedicinu Oxy	Multi	KB Dubrava (Clinical Hospital Dubrava)
CYPRUS			
Larnaka	Larnaka General Hospital - Hyperbaric Center	Multi	Larnaka General Hospital
CZECH REPUBLIC			
Chrudim	Pharmavit Private Sanatorium	Mono	
Hronov	Prajzko Private Sanatorium	Mono	
Kladno	HBOx Kladno	Multi	
Most	Ambulance Hyperbaric Oxygenotherapy	Multi	Hospital Most
Olomouc	Hyperbaric Center	Mono	
Ostrava	Hospital Ostrava Fifejdy - ICU	Multi	Hospital Ostrava Fifejdy
Plzen	1st Medical Clinic - Hyperbaric Chamber	Multi	Faculty Hospital
Plzen	Dpt. of Clinical Pharmacology - Faculty Hospital	Multi	Faculty Hospital
Praha	4th Medical Clinic - Hyperbaric Chamber, General Faculty Hospital	Multi	General faculty hospital
Praha	Army Hospital ICU	Mono	Army Hospital
Praha	Hospital "Na Homolce" - ICU	Mono	Hospital "Na Homolce"
Praha	Institute of Aviation Medicine	Multi	Army Hospital
Teplice	Hyperbaric Center	Mono	
DENMARK			
Aarhus C	Dept. of Anaesthesia	Mono	Kommunehospital Aarhus
Copenhagen	The Hyperbaric Oxygen Treatment Unit	Multi	Department of Anaesthesia Rigshospitalet Copenhagen University Hospital
FINLAND			
Helsinki	Helsinki Ear Institute, H.E.I. Happihoitokeskus	Multi	
Helsinki	Medioxygen	Multi	

City	*Center name*	*Chamber type*	*Associated with:*
Helsinki	Research Institute of Military Med., Dept of Naval Medicine	Multi	Central Military Hospital
Turku	National HBO-Center	Multi	Turku University Hospital
Upinniemi	Gulf of Finland Naval Command	Multi	Upinniemi Garrison Hospital
FRANCE			
Ajaccio	Service de Medecine Hyperbare	Multi	Centre Hospitalier de la Miséricorde
Angers	Service de Réanimation et Médecine Hyperbare	Multi	Centre Hospitalier et Universitaire d'Angers
Bordeaux	Unité de Médecine Hyperbare	Multi	C.H.U. Bordeaux - Groupe Hospitalier Pellegrin
Brest	Unité de Soins Hyperbares	Multi	Hôpital de la Cavale Blanche, Brest, Centre Hospitalo-Universitaire
Fort De France - Martinique	Service de Réanimation, des Brûlés et d'Oxygénothérapie Hyperbare	Multi	Centre Hospitalier Universitaire, de Fort De France
Garches	Service de Réanimation Médicale	Multi	Hôpital Raymond Poincaré
Lille	Centre Regional d'Oxygénothérapie Hyperbare	Multi	Hôpital Calmette - CHRU Lille- Centre Hospitalier Régional et Universitaire
Lyon	Centre Hyperbare	Multi	Unité de Soins Intensifs Hôpital Edouard Herriot
Marseille	Centre Hyperbare	Multi	Hôpital Sainte Marguerite
Metz Armées	Service d'Oxygénothérapie Hyperbare	Multi	Hôpital d'Instruction des Armées Legouest
Nice	Centre Hyperbare	Multi	Hopital Pasteur. CHU Nice
Papeete	Service des Urgences - Smur - Evasan - Caisson - SAMU 987	Multi	Centre Hospitalier Territorial de Tahiti
Paris	Caisson Hyperbare	Multi	Centre Medico-Chirurgical de la Porte de Pantin, Paris
Paris	Hôpital d' Instruction des Armées du Val de Grâce	Multi	Hôpital du Val de Grâce, Paris
Perpignan	Centre de medicine hyperbare	Multi	Clinique Saint-Pierre, Perpignan
Reims	Service d'Aide Médicale Urgente, Unité d'Hyperbarie Médicale	Multi	Centre Hospitalier Universitaire de Reims

City	*Center name*	*Chamber type*	*Associated with:*
Strasbourg	Service de Réanimation Médicale	Multi	Hôpital de Hautepierre, CHU Strasbourg
Toulon	Centre Hyperbare	Multi	Hôpital Font-Pré, Centre Hospitalier Intercommunal Toulon la Seyne/mer, (CHITS)
GERMANY			
Aachen	HBO-Zentrum Euregio Aachen	Multi	University Clinic / Technical University Aachen
Berlin	Berliner Zentrum für Überdruck- und Tauchmedizin	Multi	VIVANTES Krankenhaus im Friedrichshain
Braunschweig	Zentrum für hyperbare Sauerstofftherapie Braunschweig	Multi	
Bremen	ZETÜM - Zentrum für Tauch- und Überdruckmedizin	Multi	
Duesseldorf	Sauerstoff-Therapiezentrum Duesseldorf, ORL-VITALMED GMBH & CO KG	Multi	
Duesseldorf	Unit of Hyperbaric Medicine, Institute Of Diagnostic Radiology	Multi	Universitatsklinikum Duesseldorf
Duisburg	Zentrum für Hyperbare Medizin	Multi	St. Joseph-Hospital
Frankfurt am Main	Zentrum für Sauerstoffüberdrucktherapie, Tauch- und Höhenmed an der Orthop. Univ. Klinik	Multi	Orthopädische Universitätsklinik Frankfurt
Freiburg im Breisgau	Druckkammerzentrum Freiburg GmbH, Freiburg im Breisgau	Multi	St. Josefskrankenhaus Freiburg
Halle	Klinik für Anästhesiologie und Operative Intensivmedizin	Multi	Martin-Luther-Universität Halle-Wittenberg
Heidelberg	Druckkammerzentrum Heidelberg GmbH, Zentrum für Tauch- und Überdruckmedizin	Multi	St. Josefskrankenhaus Heidelberg
Jena	Hypermed - Zentrum fur Uberdruckmedizin Jena GmbH	Multi	
Kassel	Druckkammerzentrum Kassel	Multi	Hospital Rotes-Kreuz-Krankenhaus Kassel
Kiel	Schiffahrtmedizinsches Institut der Marine, Naval Medical Insitute	Multi	University Hospital of Kiel
Krefeld	Sauerstoff-Therapiezentrum	Multi	
Leipzig	Zentrum für Hyperbarmedizin	Multi	St. Georg Leipzig

City	*Center name*	*Chamber type*	*Associated with:*
Mannheim	HBO-Zentrum Rhein-Neckar	Multi	Diakoniekrankenhaus Mannheim
Murnau	Druckkammerzentrum	Multi	Berufsgenossenschaftliche Unfallkinik Murnau
Offenbach	Druckkammerzentrum Offenbach GmbH	Multi	Städtische Kliniken Offenbach
Osnabrueck	HBO-Center Osnabrueck, Druckkammerzentrum	Multi	Klinikum Osnabrueck / Marienhospital
Papenburg	Oxymed Centre for Diving and Hyperbaric Medicine	Multi	
Ramstein	Oxymed, Privatinstitut für Hyperbare Medizin	Multi	German-American-Hospital
Regensburg	Institut fur Uberdruck-Medizin	Multi	Klinikum of the University of Regensburg
Stuttgart	Druckkammer Centrum Stuttgart GmbH & Co	Multi	Marienhospital Stuttgart, Katharinenhospital Stuttgart
Stuttgart	HBO-Zentrum Stuttgart	Multi	Rot-Kreuz-Krankenhaus Stuttgart
Traunstein	Druckkammerzentrum Traunstein	Multi	Kreiskrankenhaus Traunstein
GREECE			
Athens	Department of Hyperbaric Medicine	Multi	Athens Naval Hospital
Kifisia	Hyperbaric Oxygen Unit, Athens University, Faculty of Nursing	Mono	'KAT' General Hospital of Kifisia, Athens
Thessaloniki	Hyperbaric Department	Multi	"Saint Paul" General Hospital - Thessaloniki
ISRAEL			
Eilat	Yosftal Hospital Hyperbaric Center	Multi	Yosftal Hospital, Eilat
Haifa	HBOT Center Rambam	Multi	Rambam and Elisah Hospitals, Haifa
Haifa	Israel Naval Medical Institute	Multi	Rambam Hospitals, Haifa
Tzrifin	Hyperbaric Medical Center	Multi	Asaf Harofe Hospital
ITALY			
Augusta (SR)	Centro Medicina Iperbarica, Istituto Ortopedico "Villa Salus"	Multi	
Avellino (AV)	Servizio di Terapia Iperbarica	Mono	Azienda Ospedaliera di Avellino

City	*Center name*	*Chamber type*	*Associated with:*
Bari	A.U.S.L. BA/4, O/C S. Paolo, Unit Operativa di Medicina Iperbarica	Multi	A.U.S.L. BA/4, O/C S. Paolo
Benevento	Benevento, A.O. gaetano Rummo	Multi	Ao G. Rummo
Bologna	Poliambulatorio Day Hospital MPM	Multi	
Bolzano	Iperbarico di Bolzano	Multi	
Brescia (BS)	Servizio OTI - Istituto Clinico Citt di Brescia	Multi	
Cagliari	Centro di Medicina Iperbarica "G.Boero"	Multi	Presidio Ospedale Marino
Caserta (CE)	Azienda Ospedaliera di Caserta	Mono	Azienda Ospedaliera di Caserta
Catania (CT)	S.O.T.I.S.	Multi	
Fano (PS)	Iperbarica Adriatica	Multi	
Fara Novarese	Centro Iperbarico "I Cedri"	Multi	Casa di Cura I Cedri
Fidenza (PR)	Centro Iperbarico	Multi	Ospedale Fidenza
Firenze (FI)	Centro OTI "Nautilus"	Multi	
Gallipoli (LE)	Centro Iperbarico	Multi	Ospedale di Gallipoli
Gazzi di Messina (ME)	Unit Operativa di Medicina Iperbarica	Multi	
Grosseto (GR)	Servizio di Medicina Subacquea ed Iperbarica	Multi	P.O. Misericordia
La Maddalena (SS)	Ospedale La Maddalena	Multi	Ospedale La Maddalena
Larino (CB)	Ospedale "G. Vietri"	Multi	Ospedale "G. Vietri"
Lecce (LE)	Nike srl	Multi	
Lecce (LE)	Ospedale "V. Fazzi"	Multi	Ospedale "V. Fazzi"
Lipari (ME)	Ospedale "S. Anna"	Multi	Ospedale "S. Anna"
Marghera (VE)	OTI Services	Multi	
Massa (MS)	CE.M.I.S.	Multi	
Milano	Istituto Lombardo di Medicina Iperbarica	Multi	
Napoli	Azienda Ospedaliera Santobono-Pausilipon	Multi	Azienda Ospedaliera Santobono-Pausilipon
Nocera Inferiore (SA)	Ospedale "Umberto I"	Multi	Ospedale "Umberto I"
Palmi (RC)	Ospedale Pontimalli	Multi	Ospedale Pontimalli
Partinico	Centro Hiperbarico, Ospedal Civico Partinico	Multi	Civoco Partinico
Pisa	Azienda Ospedaliera Pisa	Multi	Azienda Ospedaliera Pisa
Pozzuoli (NA)	Iper srl	Multi	
Ravenna (RA)	Centro Iperbarico srl	Multi	
Roma (RM)	Centro di Medicina Iperbarica	Multi	Istituto di Anestesia e Rianimazione-Universit

City	*Center name*	*Chamber type*	*Associated with:*
			"La Sapienza"
Salerno (SA)	Centro di Medicina Subacquea ed Iperbarica (CE.M.S.I.)	Multi	
Siracusa	A.O. Umberto I UOC di Anestesia Rianimazione e Medicina Iperbarica	Multi	A.O. Umberto I
Torino	Servizio di Anestesia e Rianimazione	Multi	Azienda Ospedaliera San Giovanni Battista
Torino	O.T.I.P.	Multi	
Torri di Quartesolo (VI)	OTI Medicale Vicenza srl	Multi	
Villafranca di Verona (VR)	Istituto Iperbarico SpA	Multi	
Zingonia (BG)	Istituto Fisiochinesiterapico	Multi	
LUXEMBURG			
Esch/Alzette	Centre national d'oxygenotherapie hyperbare	Multi	Hopital de la Ville d'Esch-sur-Alzette
POLAND			
Gdynia	National Center for Hyperbaric Medicine	Multi	Institute of Maritime and Tropical Medicine in Gdynia, Medical University of Gdansk
PORTUGAL			
Lisboa	Centro de Medicina Hiperbarica	Multi	Hospital da Marinha
SLOVAKIA			
Kosice	Centrum hyperbarickej oxygenoterapie	Mono	
SLOVENIA			
Ljubljana	Department of Automation, Biocybernetics and Robotics	Multi	Institute Jozef Stefan, Ljubljana
SPAIN			
Alicante	MEDIBAROX, Unidad de Medicina Hiperbarica	Multi	Sanatorio Perpetuo Socorro - Hospital
Barcelona	CRIS-UTH (Unitad de Terapeutica Hiperbarica)	Multi	Hospital Creu Roja
Castellon	Unidad de Terapeutica Hiperbarica	Multi	Hospital General de Castellon
La Laguna	Hosital Universitario de Canarias	Multi	Hospital Universitario de Canarias

City	*Center name*	*Chamber type*	*Associated with:*
Mahon (Menorca)			
Malaga	Centro Hiperbarico	Multi	Clinica El Angel
Murcia	Servicio de Medicina Hiperbarica	Multi	Santo y Real Hospital de Caridad
Palma de Mallorca	MEDISUB Institut de Recerca Hiperbarica	Multi	Clinica Juaneda Hospital
San Fernando (Cadiz)	Diving & Hyperbaric Medical Service	Multi	Hospital General de la Defensa
Santander	Unidad de Terapia Hiperbarica Valdecilla	Multi	Hospital Universitario Marques de Valdecilla
SWEDEN			
Gothenburg	Department of Hyperbaric Medicine	Multi	Sahlgrenska University Hospital / East Hospital
Helsingborg	Hyperbaric Unit, Department of Anesthesiology & Intensive Care	Multi	Helsingborg Hospital
Karlskrona	Department of Anesthesiology & Intensive Care		Blekingelans Sjukhus Karlskrona
Lule	Hyperbaric Unit, Department of Anesthesiology & Intensive Care	Multi	Sunderby Hospital
Stockholm	Department of Anaesthesiology and Intensive care - Division of Hyperbaric Medicine	Multi	Karolinska Hospital
Uddevalla	Uddevalla Hospital	Multi	Uddevalla Hospital
SWITZERLAND			
Basel	Druckkammerlabor Basel	Multi	Associated with Universitätsspital Basel
Geneva	Chambre Hyperbare, Division des Urgences Médicales et Chirurgicales	Multi	Geneva University Hospital
Zürich	Druckkammerlabor am USZ	Multi	Universitätsspital Zürich
THE NETHERLANDS			
Amsterdam	Hyperbaric Medicine AMC	Multi	Academic Medical Center
Den Helder	Diving Medical Centre, Royal Netherlands Navy	Multi	Gemini Hospital
Hoogeveen	Institute for Hyperbaric Medicine, Hoogeveen	Multi	Academic Hospital Groningen - The Netherlands
Rotterdam	Institute for Hyperbaric Medicine, Rotterdam	Multi	Academic Hospital Rotterdam - Erasmus MC

City	*Center name*	*Chamber type*	*Associated with:*
TURKEY			
Ankara	Ankara Hiperbarik Okisjen ve Yara Tedavi Merkezi	Multi	
Ankara	BAROMED	Multi	Ozel Sevgi Hospital
Ankara	GATA Department of Underwater and Hyperbaric Medicine	Mono	Gulhane Askeri Tip Akademisi
Eskisehir	Gulhane Military Medical Academy	Multi	Hava Hastanesi
Istanbul	Department of Underwater and Hyperbaric Medicine	Multi	GATA Haydarpasa Egitim Hastanesi
Istanbul	Department of Underwater and Hyperbaric Medicine, Istanbul Tip Fakültesi	Mono	Istanbul Tip Fakültesi
Istanbul	Hiperbarik Oksijen Tedavi Merkezi	Multi	
Istanbul	Hipermer HBO	Multi	
Istanbul	MED-OK, Hiperbaric Oksijen Tedavi Merkezi	Multi	
Istanbul	Oksimer HBO	Multi	
UNITED KINGDOM			
Aberdeen	Hyperbaric Medicine Unit, Grampian University Hospitals NHS Trust	Multi	Aberdeen Royal Infirmary
Gosport	Hyperbaric Medicine Unit	Multi	Royal Hospital Haslar and Queen Alexandra Hospital, Cosham
Hull	North of England Medical and Hyperbaric Services (NEMHS)	Multi	East Riding Hospital, Hull
Isle of Cumbrae, Scotland	Millport Hyperbaric Unit, Isle of Cumbrae	Multi	The Lady Margaret Hospital
Isle of Man	Isle of Man Hyperbaric Facility	Multi	Nobles Isle of Man Hospital, Douglas Isle of Man
London	London Diving Chamber	Multi	Hospital of St John and St Elizabeth
London	London Hyperbaric Medicine	Multi	Whipps Cross NHS University Hospital
Oban	Dunstaffnage Hyperbaric Unit, Oban	Multi	Lorn and Islands District General Hospital
Plymouth	Diving Diseases Research Centre	Multi	Plymouth Hospitals NHS Trust (Derriford)
Poole, Dorset	Poole Hyperbaric Centre	Multi	Poole Hospital

City	*Center name*	*Chamber type*	*Associated with:*
Upper Forest Way	The National Hyperbaric Unit of Wales, Seansea	Multi	
Wirral	North West Emergency Recompression Unit (NWERU)	Multi	Murrayfield Hospital, Holmwood Drive, Wirral

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