ADJUNCTIVE THERAPY FOR DECOMPRESSION ILLNESS

Report of the DCI Adjunctive Therapy Committee of the Undersea and Hyperbaric Medical Society

Including Proceedings of the Fifty-Third Workshop of the Undersea and Hyperbaric Medical Society

REPORT OF THE DECOMPRESSION ILLNESS ADJUNCTIVE THERAPY COMMITTEE OF THE UNDERSEA AND HYPERBARIC MEDICAL SOCIETY

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of the Undersea and Hyperbaric Medical Society

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History of the Decompression Illness Adjunctive Therapy Committee: The Adjunctive Therapy ad hoc Subcommittee was formed in 1998 to investigate and review therapies that could be used in addition to or in lieu of recompression therapy. In 2000 the subcommittee was formally changed to a UHMS standing committee. A grant application had been submitted by Don Chandler on behalf of the UHMS to the US Special Operations Command to (a) Form a standing UHMS committee to review the available literature on treatment of decompression sickness and gas embolism and make recommendations for therapy based on the best clinical series, case reports, and animal studies available; (b) Place special emphasis in this review on the pre-recompression phase of treatment, which may be prolonged in Special Operations; and (c) Make recommendations for specific animal trials that will study the most promising new treatment modalities or otherwise enhance our ability to treat dysbaric disorders.

In line with its mission, a workshop was held at Duke University on January 23 and 24, 2002 to discuss current knowledge about decompression illness in humans, animal models, adjunctive therapies and possibilities for research. Participants are listed below:

Dr. Peter Bennett (Duke University, Divers Alert Network)
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Another meeting was held on June 30th, 2002 in La Jolla, CA to further discuss practical recommendations. The following possible interventions were discussed. Preliminary recommendations using the American Heart Association Criteria were also discussed. The guidelines finalized in December 2002 are appended to this proceedings.

PATHOPHYSIOLOGICAL BASIS OF DECOMPRESSION SICKNESS

Richard D Vann

Bubbles are implicated as the initiating factor in decompression sickness (DCS), but the disease has many forms and may occur secondary to the precipitating event. Some signs and symptoms are attributed to extravascular bubbles and others to intravascular bubbles that originate at remote sites. Moreover, bubbles can have both mechanical and biochemical effects. Multiple mechanisms may lead to the same signs or symptoms, and several mechanisms might contribute to DCS separately or together. The mechanisms are incompletely understood, and what follows is a personal interpretation of existing evidence that is summarized in Figure 1. The numbers that appear below in {braces} refer to the elements of Figure 1.

DCS is caused by a reduction in barometric pressure {1}. The signs and symptoms resulting from counterdiffusion have related mechanisms and are discussed as well {45}. The smallest pressure reduction for which DCS has been reported after a single dive was for an ascent from 20 fsw to sea level[1]. Venous gas emboli (VGE) have been detected after a pressure reduction of 12 fsw[2]. Similarly, the DCS exposure threshold for ascent to altitude from sea level with a 5% DCS incidence was 20,500 ft[3] while VGE were detected at 12,000 ft[4].

Most bubbles originate from preexisting gas cavities known as gas nuclei that expand by the inward diffusion of supersaturated nitrogen or other inert gas {2}. Gas nuclei appear to be extravascular, and bubbles do not form in blood[5], but bubbles have been proposed to form at blood vessel walls[6]. Review of the evidence indicates that many gas nuclei are small spherical bubbles generated continuously by viscous adhesion during exercise or normal activity[7]. These nuclei have limited lifetimes due to the oxygen window and surface tension. It seems likely that extravascular bubbles would damage the microcirculation as they expand, seed the supersaturated blood, and grow by diffusion in the venous circulation {3}.

Cardiopulmonary DCS

The most severe form of DCS, which involves the cardiopulmonary system, is rare today. A massive influx of venous bubbles into the heart {4} can displace the blood rendering the heart ineffective as a pump and causing cardiovascular collapse and asphyxia[8]. Animal studies by Bert[9] and Heller[10] found bubbles in the venous circulation shortly after decompression from elevated pressure. These bubbles caused unconsciousness, shock, and death. Similar effects were not uncommon in humans after severe decompression[11,12]. Modern experiments have confirmed these findings in animals while demonstrating that the responses to bubbles are dose-dependent ranging from negligible to fatal according to the volume of gas released[13-15]. Except in blow-up or missed decompression, cardiopulmonary collapse is unlikely today because restricted depths and bottom times limit inert gas uptake and because decompression stops allow most inert gas to be eliminated in the dissolved state rather than as bubbles.

Pulmonary DCS ('Chokes')

Bubbles are detected by ultrasound in the venous blood and right heart after routine dives, and there is a statistical correlation between DCS and a high incidence of precordial bubbles, but bubbles are often present in the absence of DCS indicating that this correlation is not causal. In small volumes, venous gas emboli (VGE) pass safely through the heart and enter the lungs {5} where they are filtered and exhaled harmlessly {6}[16,17].

Pulmonary DCS is indicated in animals by rapid shallow respiration[18,19]. In humans, mild chokes presents as sore throat and cough upon deep inspiration. Coughing can become paroxysmal and accompanied by severe chest pain, dyspnea, and unconsciousness[18,19]. In the early days of decompression, an attack of severe chokes often forecast a grave clinical outcome[8]. While 'chokes' is usually rapidly reversed by prompt recompression, untreated chokes can be fatal. An excessive gas load entering the lungs can lead to endothelial damage, complement and leukocyte activation, pulmonary hypertension, and respiratory insufficiency {7}. These are manifested as dyspnea, coughing, pulmonary edema, shock, and asphyxia {8}. Pulmonary DCS has contributed to a number of deaths as a result of severe altitude exposure[20] but is infrequent today, probably because exposures are less severe than in the past and, for altitude exposure, preoxygenation is common.

The tracheobronchial tree was often inflamed during 'chokes'[21], which may not be explained by VGE that can be present in great quantity without symptoms. Arterial embolization of the bronchial circulation was thought improbable as arterial emboli would most likely affect the brain and cerebral symptoms and were usually not present in 'chokes.' Ferris and Engle proposed that 'chokes' was a vascular reaction to bubbles in the mucus membranes of the tracheobronchial system not unlike skin mottling.

Arterial Bubbles

VGE are routinely detected by ultrasound in the venous blood and right heart even after dives not considered severe[22]. Bubbles that bypass the lungs through a patent foramen ovale (PFO) or intracardiac shunt[9] will enter the arterial circulation {10} as has been demonstrated in animals[23]. In humans, retrospective studies have indicated a greater incidence of PFO in divers who have had cerebral or spinal DCS symptoms than in a control population or in divers who have had pain-only symptoms[24-26].

Bubbles can also enter the arterial circulation {11} through the pulmonary vasculature if the VGE load exceeds the filtering capacity of the lungs[27], if pulmonary pathology is present[28], or if the pulmonary arterial pressure increases as a result of gaseous obstruction[29]. Bubbles in venous blood withdrawn from dogs after decompression were 19-700μ in diameter[30]. The likelihood that bubbles will enter the arterial circulation increases as larger gas loads enter the lungs[16,23,31] or the bubble size decreases. Ultrasound contrast agents that contained bubbles with diameters of 2-10μ[32] are readily visualized by echocardiography in the left heart of humans after injection into a peripheral vein.

The passage of VGE through the lungs was promoted by repetitive diving in mice and guinea pigs[33], and repetitive diving was found to be a reliable means of producing spinal DCS in

goats[34] and dogs[35]. Another source of arterial bubbles, known as the 'arterial paradox,' is seen in animal studies with rapid decompression where arterial bubbles appear by retrograde growth before VGE {12} are observed[36]. The arterial paradox {12} seems unlikely in divers who make normal ascents.

Neurological DCS has been associated with high VGE scores[37], and there were higher VGE scores and a higher incidence of neurological DCS after helium dives compared to nitrogen dives[38,39]. As helium is exchanged more rapidly than nitrogen[40], the faster uptake of helium might explain why VGE were more common after helium dives[39].

Pulmonary barotrauma during ascent with breath-holding or pulmonary pathology can damage the lungs and release alveolar gas into local tissues and the arterial circulation {13}. The effects of barotrauma can follow any dive independent of dissolved gas content. As there are potentially four sources of arterial bubbles {9, 11, 12, 13}, distinguishing between arterial gas embolism (AGE) and neurological DCS is a difficult differential diagnosis unless pulmonary damage is evident or the exposure clearly favors AGE. This might be the case for a single dive to less than 20 fsw or a very short dive for which inert gas uptake would be slight. As the location of signs or symptoms does not determine their etiology, DCS cases commonly described as "spinal" may actually be of cerebral origin[41].

Whatever their origin {10}, arterial bubbles can cause endothelial damage, lymphocyte activation, coagulation, and infarction {15} leading to the signs and symptoms of AGE or Type 2 DCS {17}[42,43-45]. The brain appears to be the principal target organ {16}, and the spinal cord is rarely affected in other embolic diseases[46] suggesting that arterial gas embolization of the cord is uncommon. In studies of decompressed dogs, however, Francis[47] found several animals with responses consistent with non-dived animals into which arterial bubbles had been infused[48]. A study that infused arterial bubbles into dived animals might help resolve the question of whether arterial emboli routinely precipitate spinal DCS.

The consequences of arterial bubbles {10} are serious by themselves {14} but may become worse if they enter and grow in tissue that is supersaturated from previous diving {18}. This mechanism may be relevant in the severe cerebral and spinal DCI reported after relatively innocuous dives that terminate with pulmonary barotrauma[49]. Cases of this nature have been called Type 3 DCS and may be among the most serious diving accidents that occur today.

Damage to Blood

Bubbles in the blood {20} can cause biochemical damage that triggers thrombosis and activation of the complement, histamine, bradykinin, and prostaglandin systems {21} leading to increased vascular permeability, hemoconcentration, venous stasis, and fat embolism {22}[46,50,51]. These effects might be manifested locally or systemically.

Venous Infarction Hypothesis

Obstruction of the venous drainage of the spinal cord by bubbles has been observed in animal studies and proposed as a mechanism of spinal injury[46]. VGE {3} may have a direct pathway to the epidural vertebral venous plexus (EVVP or Batson's plexus) of the spinal cord {23} through anastomoses such as the azygous vein {24} that connect the systemic venous circulation to the EVVP at various locations[52,53]. These connections are a proposed conduit by which pathogens, tumor cells, and possibly VGE, might reach the EVVP from the systemic circulation[54]. This is the basis for the venous infarction hypothesis of the spinal cord {25} although its active involvement in spinal DCS remains uncertain.

Edema

Extravascular bubbles {2} may enter the lymphatic vessels and pass into the venous circulation {3} or block the lymphatics {26} leading to edema and lymphadenopathy {27}[55]. Local swelling of soft tissue may or may not improve with recompression.

Autochthonous Bubbles and Spinal DCS

Many of the signs and symptoms of DCS appear to result from autochthonous or in situ bubbles {28} that cause tissue distortion and mechanical and biochemical damage {29}. The best evidence for this was bubbles observed in the white matter of dog spinal cords that formed only at depths greater than 85 fsw[56]. Bubbles formed rapidly and were associated with loss of evoked response. Autochthonous bubbles of the spinal cord appeared to be a reasonable explanation for severe rapid onset sensory and motor dysfunction after relatively deep dives {36}.

Autochthonous Bubbles in the Brain

There is less certainty that autochthonous bubbles form in the brain {32} at physiological supersaturations. Most cerebral dysfunction {33} appears to be the result of arterial bubbles {10, 17}.

Limb Pain

Most evidence associating bubbles with limb pain is from altitude studies, but subjects exposed to both hypobaric and hyperbaric decompression had similar occurrences of pain suggesting similar DCS mechanisms and locations for altitude and diving[57]. Existing evidence favors extravascular bubbles as the cause of limb pain {34, 35}.

Radiographs of painful knees at altitude during the Second World War suggested an articular site for joint pain. The relationship of bubbles to pain was addressed in altitude exposures at 35,000 ft in which both knees were radiographed when one knee became painful[21,58,59,60]. There was free gas in the knee joints of all subjects, with or without pain, but bubbles posterior to the femur in the upper posterior fossa and popliteal fat were statistically associated with pain as were streaks of gas which appeared to be along fascial planes or tendons. The severity of pain and size of the gas lesion were associated with bubbles in the popliteal fat.

Acute altitude exposure produced transient pains in the hands and feet accompanied by crepitus in tendon sheaths[21]. Palpation of tendon sheaths revealed bubbles that, when milked away, often relieved the pain. Ferris and Engle concluded the pain was of extravascular origin as: (a) there was no local cyanosis; (b) anoxic pain is usually maximal during the reactive hyperemia of recovery; (c) local recompression sufficient to occlude blood flow relieved rather than intensified the pain; (d) bubbles associated with pain on x-ray had an articular not vascular distribution; and (e) pain relieved by recompression recurred at the same site upon decompression 4-6 hrs later.

Nims proposed that expanding extravascular bubbles might cause pain by mechanically distorting sensory nerve endings[61]. Delayed symptom onset after diving and symptom relief with recompression are consistent with bubble growth by diffusion, but bubble growth by diffusion is incompatible with symptoms that occur hours after descent from altitude when bubbles are resolving[62,63,64] or in cases refractory to recompression therapy[65,66]. Such cases may reflect secondary biochemical damage that accumulates as long as bubbles are present with significant time required for healing[46].

While phantom elbow pain has been reported in a one-armed man[67], neurogenic pain originating at a remote site appears rare, and no apparent brain or spinal cord lesions were found in goats affected only by limb pain[68].

Cutaneous DCS ("Skin Bends")

Rapid ascent to sea level or to a decompression stop after a short, deep dive is often followed by itching (pruritis) and rash (urticaria), commonly known as 'skin bends' {36, 37}[55]. Less frequently, skin bends manifests as a sense of heat. Skin bends usually disappears within an hour, but affected areas are sometimes painful for a day or more. Itching and rash are not generally followed by more serious symptoms and by themselves do not warrant recompression. Itching and rash appear to originate from in situ bubbles. The origin of cutaneous bubbles is uncertain although cavitation at keratinocytes is a potential explanation that requires little supersaturation[69].

Post-dive itching can be prevented by immersion in warm water during and after decompression[70,71]. For hard-hat divers in dry suits, a cold arm itched, but a warm arm did not itch[72]. Poorly perfused cold skin has slow nitrogen elimination and thick diffusion barrier that impedes heat and nitrogen flux. Warm, well-perfused skin has rapid nitrogen elimination and a thin barrier to heat and nitrogen diffusion. Poor nitrogen exchange in the cold tissue would be expected to cause greater supersaturation, increased bubble formation, and more intense itching. Nitrogen eliminated by blood flow appears more important in skin bends than nitrogen absorbed by diffusion.

A more severe form of skin bends, blotchy purple markings known as 'marbling,' 'mottling,' or cutis marmorata, is felt by some to precede serious DCS including chokes[8,21,55]. Recent studies have suggested that arterial bubbles secondary to right to left shunting in the heart may play a role, but the mechanisms are uncertain[73].

Compartment Syndrome

Compartment syndrome leading to ischemia and mechanical damage has been proposed for inner ear DCS {39, 40}[74], spinal DCS {41, 42}, limb pain, and osteonecrosis in bone {43, 44}. Bubbles in the periosteal envelope or medullary cavity were suggested as a source of medullary pain[75], and bubbles that distend the venous sinusoids were suggested as the cause of dull, aching pain[76]. A 'bone compartment syndrome' from intramedullary bubbles has been suggested as responsible for both pain and dysbaric osteonecrosis[75]. Osteonecrosis is statistically associated with DCS after diving and caisson work[77-80], is less common with more conservative military decompression procedures[81], and occurs only rarely at altitude[82].

Audiovestibular (Inner Ear) DCS

Audiovestibular or inner ear DCS {39, 40} may result from diffusion between perilymph, endolymph, and vascular compartments[74]. The vascular compartment exchanges inert gas with its surroundings by perfusion with arterial blood and by diffusion from the perilymph and endolymph compartments. Inert gas also diffuses from the middle ear space through the round window. The round window is small in area, and the diffusion distance through perilymph to the vascular compartment is long, however, so diffusion through the round window appears to have little effect on the overall inert gas exchange kinetics.

Counterdiffusion

Limb pain[83], cutaneous manifestations[84], and audiovestibular signs and symptoms[74] can also be caused by the counterdiffusion of inert gases {45} in the absence of decompression. Bubble formation occurs in the skin by cutaneous counterdiffusion when a slowly diffusing gas such as nitrogen or nitrous oxide is breathed while surrounded by a rapidly diffusing gas such as helium[85]. Helium diffuses from the environment through the skin into tissue more rapidly than nitrogen or nitrous oxide diffuses out. The net inward flux of gas causes subcutaneous supersaturation and extravascular bubble formation without pressure change. When a subject surrounded by and breathing helium-oxygen at 1,200 fsw changed to a breathing gas with 10 atm of nitrogen in a mixture of helium-nitrogen-oxygen, he developed hard, raised, bloodless lesions of the skin with intense itching and severe vestibular dysfunction[84]. Bubble formation was even more severe in pigs immersed in helium while breathing nitrous oxide at 1 ata. Bubbles dissected the subcutaneous tissue causing severe bruising and capillary damage[85]. Continuous counterdiffusion resulted in copious VGE and asphyxia when gas displaced blood from the heart {5, 6}.

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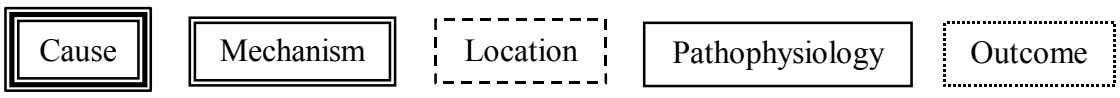
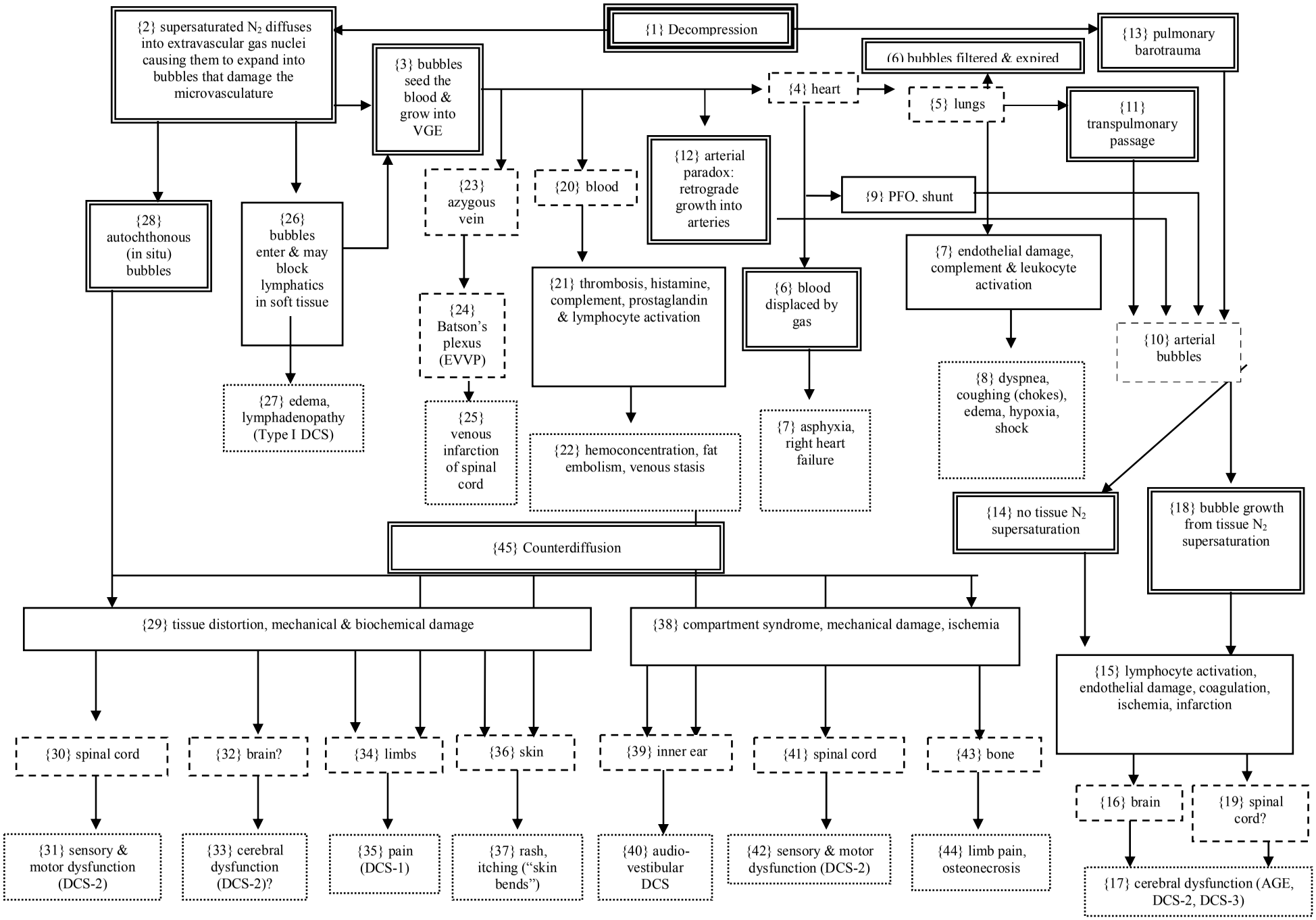
Figure 1. Putative causes, mechanisms, locations, pathophysiology, and outcomes of DCS.




{1} Decompression
{2} supersaturated N_2 diffuses into extravascular gas nuclei causing them to expand into bubbles that damage the microvasculature
{3} bubbles seed the blood & grow into VGE
{4} heart
{5} lungs
{6} bubbles filtered & expired
{7} endothelial damage, complement & leukocyte activation
{8} dyspnea, coughing (chokes), edema, hypoxia, shock
{9} PFO, shunt
{10} arterial bubbles
{11} transpulmonary passage
{12} arterial paradox: retrograde growth into arteries
{13} pulmonary barotrauma
{14} no tissue N_2 supersaturation
{15} lymphocyte activation, endothelial damage, coagulation, ischemia, infarction
{16} brain
{17} cerebral dysfunction (AGE, DCS-2, DCS-3)
{18} bubble growth from tissue N_2 supersaturation
{19} spinal cord?
{20} blood
{21} thrombosis, histamine, complement, prostaglandin & lymphocyte activation
{22} hemoconcentration, fat embolism, venous stasis
{23} azygous vein
{24} Batson's plexus (EVVP)
{25} venous infarction of spinal cord
{26} bubbles enter & may block lymphatics in soft tissue
{27} edema, lymphadenopathy (Type I DCS)
{28} autochthonous (in situ) bubbles
{29} tissue distortion, mechanical & biochemical damage
{30} spinal cord
{31} sensory & motor dysfunction (DCS-2)
{32} brain?
{33} cerebral dysfunction (DCS-2)?
{34} limbs
{35} pain (DCS-1)
{36} skin
{37} rash, itching ("skin bends")
{38} compartment syndrome, mechanical damage, ischemia
{39} inner ear
{40} audio-vestibular DCS
{41} spinal cord
{42} sensory & motor dysfunction (DCS-2)
{43} bone
{44} limb pain, osteonecrosis
{45} Counterdiffusion
{6} blood displaced by gas
{7} asphyxia, right heart failure

DECOMPRESSION ILLNESS AND STROKE: SIMILARITIES AND DIFFERENCES: A DIVING MEDICAL OFFICER'S PERSPECTIVE

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Assistant Medical Director Divers Alert Network

In this talk I am going to take a contrary point of view in dealing with decompression illness (DCI). As this workshop proceeds, you are going to hear all kinds of talks on mechanisms, pathophysiology and bubbles, which is great until you get down to the nitty-gritty. For instance, you could put Dick Vann on the witness stand and query: "Dr. Vann, have you ever seen a bubble cause decompression sickness?" The answer is "No!". All of the evidence is circumstantial. Nobody knows whether bubbles are the primary mechanism or whether they represent a parallel mechanism that doesn't necessarily reflect what is going on in tissue. In particular, what I want to do is talk about whether decompression sickness (DCS), arterial gas embolism (AGE) and stroke can be looked at as models of one another[1]. Why do this? Bends is a rare disease; there isn't a lot of money floating around to study it. In looking through the literature, after developing recompression therapy the second greatest therapeutic advance in treating DCI was giving IV fluids, and after that it has kind of gone downhill. There have been a few drugs studied here and there, but they have rarely gotten past the animal model stage, simply because it's very, very difficult to do any kind of a controlled human study. But there are thousands of cases of stroke every year, and the drug companies are certainly willing to spend a lot of money on therapeutic studies. So, one might be able to look towards the stroke literature to identify potential adjuvants that may be useful in DCI. Why adjuvants? It's pretty much a given that the definitive treatment for DCS and AGE is recompression. The problem arises when you can't administer recompression right away. Two questions arise: (A) Does a long delay before recompression adversely affect the end result? (B) Is there any kind of drug or adjuvant therapy that would either provide complete relief of symptoms at 1 ata before administering recompression or ameliorate any negative effects of a long delay on recompression outcome?

At this point I must admit that all I know about stroke is what I have read in the literature. My clinical experience during most of my career has been with incredibly healthy divers, who don't have a lot of strokes. I'm not going to go through a litany of why and how stroke causes disease. What I want to do is address the question: Can stroke model DCS? That is, is it reasonable to expect a drug that works well in stroke treatment to work well in DCS?

In terms of dysbaric diseases, often now referred to as 'decompression illness' (DCI), one manifestation is musculoskeletal bends, which usually manifests as joint pain. However, nobody dies of joint pain so I'll not include that in my discussions. What we are interested in here are neurological symptoms associated with issues of acute, serious, morbidity and mortality. That is, issues of life and death. Cardiovascular DCS is potentially deadly, but I'm not going to talk about that either, because it has a unique pathophysiology, for which we would need a different conference. In this talk I will confine my remarks to neurological

[1] DCS and AGE are collectively called decompression illness (DCI).

DCS and AGE. I will divide neurological DCS into cerebral and spinal. Cerebral DCS, manifesting as disorders of mentation and other higher function, is rare in diving but is more frequently associated with altitude exposures. What we see in diving, if there is severe neurological injury, are spinal cord manifestations. We call it 'spinal cord DCS' because the spinal cord is the structure that can most reasonably explain the manifestations. The argument is often put forward, "how do you know the damage is in the spinal cord, and not someplace else?" Well, we do and we don't. We have some indirect information from animals and humans with spinal cord manifestations such as trouble walking and urinating. If the spinal cords become available and are examined, lesions are seen.

Distinct from spinal cord DCS is AGE, which seems to be the dysbaric disease that is closest to the stroke mechanism as we envision it. How does gas embolism work? Lung rupture allows gas to enter the arterial circulation directly where it is then transported to the cerebrum. One could imagine that these bubbles could block a blood vessel, and perhaps they do. But there is a lot of experimental evidence that they simply pass through the cerebral circulation without actually staying there. There is also evidence that if they do lodge the bubble begins to be reabsorbed almost right away, because of the gradient for diffusion of gas out of the bubble. That's because of the way tissue metabolizes oxygen to carbon dioxide that results in a net reduction in partial pressure because of the different solubilities of the two gases. In some animal studies it has been suggested that these bubbles may dislodge within minutes and pass on through to the venous side. So the question is, what causes the damage? One suggestion is blockage of a blood vessel, causing anoxia, but there are probably other mechanisms (for details see reference 1).

This is a scenario depicting a classical presentation for gas embolism. There is usually a rapid, uncontrolled ascent. This is not essential, but during ascent there is some mechanism for pulmonary barotrauma that allows gas to get into the circulation. Classically, shortly after surfacing there is a cerebral event. By a 'cerebral event' I mean a disorder of consciousness. These were the kinds of symptoms that were described in individuals doing submarine escape training, where they lock in to the bottom of a 30 or 40-foot tower of water and then do a free ascent to the surface as if they were escaping from a submarine. Once there is a cerebral event there may be a transient recovery and then there can be a relapse. If the case is serious enough, and the individual is not recompressed rapidly, death can occur, seemingly due to involvement of the respiratory center: people just stop breathing. I have only seen two cases of decompression sickness where the respiratory center was involved, requiring mechanical ventilation, and they both eventually died.

The recompression protocols that were developed for treatment of AGE were really developed around submarine escape. This is a situation where the recompression chamber is right there at the surface of the escape training tank where the embolism may occur. The scenario was: someone arrives at the surface, has a cerebral event, is immediately picked up and thrown into a chamber and recompressed. The history of that process is that it seems to work pretty well. So what kind of pathophysiology are we talking about here: blood vessel blockage, endothelial damage, neutrophil clumping or other biochemical cascades? These are reasonable to think about, but in the case of gas embolism it's hard to imagine that the mechanism is not much different from embolic stroke. But there is one difference: a

thromboembolus takes a lot longer to be lysed by the body's fibrinolytic system than the reabsorption of a gas phase. The gas phase is much more transient. One hypothesis is that if you look at untreated AGE, what you are looking at is the best outcome that could be observed in an untreated thromboembolic stroke. Things are happening rapidly, the gas phase will eventually be reabsorbed, and at least in animal models, if the original event doesn't kill them they tend to get better. Thus, in arterial gas embolism, recompression is the ultimate 'thrombolytic'. If the diver is treated quickly, which we like to think of as within 6 hours, the gas phase is reduced in volume so that its passing through the capillary network would be hastened, if it hadn't already. The high oxygen partial pressure from breathing a high O_2 treatment gas may preserve function and hasten repair as blood flow is restored. The question is; how could elimination of blood vessel blockage and restoration of flow and adequate tissue oxygenation get better than that?

There is overwhelming animal evidence that lidocaine improves the rate of recovery from experimental gas embolism, but I will state a caveat: most of the studies have used a model where intra-arterial gas is injected at 1 atmosphere. Maybe this mimics what is going on in diving, and maybe it doesn't. Certainly in diving there can be a supersaturation of inert gas in tissues, and maybe this results in a gas phase growing in a way that cannot be mimicked in 1 ata models. There is one human study of lidocaine in cardiopulmonary bypass[2], and a follow up study is going on at Duke, but there doesn't seem to be much interest in lidocaine among people studying stroke. This is perhaps because lidocaine is too cheap; there is no money in marketing it for a new indication. But really, the evidence for lidocaine being neuroprotective in AGE models is pretty impressive in animal studies[3,4]. Why are there no studies in humans with decompression diseases? Bends and AGE are rare diseases. Simon Mitchell, who did the human lidocaine study in cardiopulmonary bypass, initially started out to look at DCI, and when he looked at the number of cases he could study, even including Australia and New Zealand, with their relatively large diving population, there weren't enough cases for him to obtain meaningful results within the time he had to do his study. He therefore chose cardiopulmonary bypass patients. His data do not stand up and beat you over the head to indicate that lidocaine is definitely better but certainly the indications are that people pre-treated with lidocaine before cardiopulmonary bypass seem to have less of a psychomotor deficit than people who do not receive lidocaine. So here we have an adjuvant which has demonstrated efficacy in animal models and which also seems effective in human studies. Does the AGE model mimic embolic stroke? The results of the human trial suggest it does. If so, why is lidocaine not finding routine use in treating AGE? What further evidence is needed?

As far as AGE goes, if something works in stroke it might also work in AGE. AGE is not the biggest problem that we have though. In terms of occurrence, it's down on the list. What we have is a lot of DCS. However, the fact is, we do not know what causes the damage. We can look at the tissues after the damage has occurred. James Francis applied the term 'autochthonous' to bubbles that form in the spinal cord, which means bubbles that, after they form, stay put[5]. When I asked him whether he thought these were the lesions that spinal cord cause decompression sickness he responded "maybe not". The lesions are there, but the spinal cord may not be all that sensitive to gas phase. We can certainly put gas in the spinal canal, producing only a headache. If you slip a needle into the tracts and inject gas you can

push the axons apart, but the question is, is this going to cause enough compression to interrupt transmission of action potentials? The answer is completely unknown. It has been observed in decompression sickness models that there is gas phase within the myelin sheaths[6]. It may be that even a micron change in distance at the myelin sheath can result in large changes in action potential. So, is the damage mechanical, biochemical or both? If these gas phases form, do they form in areas that cause mechanical damage, pushing structures apart, or do they cause some kind of biochemical cascade to occur, as you might expect in embolic stroke? The problem is that the embolic stroke models are cerebral models, not spinal cord models. In the literature there seems to be a dichotomy between spinal injury and stroke injury, and spinal injury by and large is traumatic. Embolism or thrombosis of spinal vessels is incredibly rare. Most of the spinal cord injury models are designed to simulate trauma, for example by dropping weights on the spinal cord. So what is the scenario for spinal cord DCS? The diver surfaces from a dive and first notices some paresthesias in the extremities followed by weakness in the lower extremity or upper extremity, bilateral or unilateral, ascending paralysis, but in most cases when the motor system is involved, it is confined to the voluntary motor system. If you do an MRI after a week or so, sometimes you can see edema in the spinal cord, often in a location you would expect from the neurological exam. But what is really going on; is this just plain old edema? Is there neuronal compression, causing interruption of action potentials, or is the damage within the myelin sheath, perhaps causing membrane damage. The bottom line is, we really don't know. One of the difficulties in studying spinal cord bends in humans is that recompression is almost never denied if it's available, so there isn't a good control population. People have looked at indigenous diving populations, for example in Central America, as a source of cases of untreated bends, but there is no medical follow up. It's very difficult to establish the history of some of these individuals, except to say that a disability is present. One of the things that we can say about bends, is that the recovery is usually much better than in other forms of neurological disease. In decompression sickness the presentation may be extremely severe, but there is a high probability that therapy can make most of it go away in a pretty short period of time. If the case is severe, and the diver is recompressed in a chamber, he doesn't immediately jump up and start walking around. But if you are persistent and you administer follow up treatments for a week or so the patient will probably start to get better. After 12-16 weeks only a careful exam can sometimes determine that there is any residual damage.

One of the questions we have is: if someone has never been bent, would you get full recovery after the very first case of untreated DCS? This is not an unreasonable question to ask. In other words, is the residual damage the result of cumulative damage? One of the reasons that I ask this question is that the Navy has funded a lot of studies on large animal models, and some preliminary data has been presented at program reviews. The bottom line is, if the 'chokes' don't kill them, no matter how severe the spinal bends is, they get better without treatment. It will be interesting to see how this pans out after completion and publication of these studies. So you begin to wonder, does this mean that we shouldn't treat divers? No, it doesn't. We certainly know that recompression seems to hasten recovery. Certainly if we go back and look at the old tunnel worker data we know that if there is no recompression eventually there will be a problem. But is that outcome really from 'one-off' event that isn't treated or is it cumulative damage in individuals who have experienced DCS time after time,

and now you are looking at the result of a whole lot of damage that accrued incrementally? One scenario where this is important is in submarine rescue, where you may not have recompression facilities available to treat everybody. So, if you had a good solid model and showed that (a) if you don't recompress they will eventually get better and (b) if there is some adjuvant you could give that would hasten recovery, it would certainly make the triage and handling of large numbers of rescued submariners a lot easier.

For spinal cord DCS are thrombotic models applicable? Unlike cerebral thromboembolism, there are not a whole lot of thrombotic models in spinal cord disease. Are trauma models, in which weights are dropped on the spinal cord, applicable? We don't know, because we really don't know what causes the injury in spinal cord bends. So, if we don't have a better understanding it's hard to identify potential adjuvants. What that would mean is that one would be hard pressed to say that if a treatment modality works in spinal cord trauma it will work in spinal cord bends. It would first have to be tried in a model of spinal cord decompression sickness. Even lidocaine, which has been pretty well investigated in animal models of AGE, has not been investigated very much in DCS. So we don't even know how well that drug applies to DCS vs. AGE. In the AGE models, at least for animals, we have to say that the index of recovery is evoked potentials, not a clinical or functional outcome. Most of the studies have been done in anesthetized animals that are not allowed to wake up. Are return of evoked potentials a useful model of human recovery or is the injury so severe that it doesn't mimic well what goes on in human AGE?

In conclusion, AGE would seem most likely to benefit from treatments that have been demonstrated to work in embolic stroke. If a treatment works well in embolic stroke it would probably be worthwhile to try it in an AGE model, and one might hypothesize that it should work as well. Spinal DCS is a weird disease, in that it can present with a very severe neurological injury, yet in most cases there is full recovery. Certainly we recompress everybody, so the question of what happens without recompression goes begging. It would be nice if we could have a follow up in native populations who could be identified as having one single severe case of spinal bends and compare them to individuals who have had several cases. This would provide evidence to answer the question of whether only one case causes the injury or whether several cases are necessary. We haven't identified the mechanism. We can look at the initiating mechanisms and the slides, but we really don't know what is going on as the disease evolves. It's all conjecture. Certainly the models of spinal cord trauma that are currently being used to investigate adjuvant effectiveness may not apply to spinal DCS. In contrast to AGE, spinal cord DCS may be a unique disease will require its own model and its own investigations in order to identify adjuvant therapies.

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DISCUSSION 1:

Dr. Bove: I don't agree with the fact that as clinicians we can't work toward understanding mechanisms. I think in all other clinical approaches to patients we do try to understand mechanisms and sometimes give up because we can't figure them out, but I think that in the broad list of cases that have to do with bubble disease, in the majority of them we can figure out the mechanism. I would not start the meeting saying that we can't figure out the mechanisms, because that's the whole reason for the meeting. I would much rather be able to see a patient sometime in the future and say this occurred from pulmonary barotrauma or this occurred from new bubble growth from Henry's law principles or a combination of the two. I think we should be aiming towards trying to figure it out even though sometimes we can't.

Dr. Thalmann: There are three possible mechanisms: venous, arterial or local injury and no matter what the injury is, we can get people who can argue vehemently and support their own view regarding which of those three mechanisms there are. The point is there is no overwhelming evidence to support one over the other right now. The venous blockage theory may have fallen out of favor a bit. The arterial mechanism may seem unlikely, yet we do see evidence that maybe the spinal cord is affected. So we should try to understand mechanisms and I think that's reasonable. My point is that we really don't know what the primary event is, if this gas phase exists or where exactly it is acting to cause the clinical symptoms that we see at the cellular or membrane level. We can put it at the spinal cord or at the brain, and maybe we can pin its location down to a specific tract, but then trying to specify why it causes that injury leads to problems.

Dr. Bove: I was interested in Dr. Vann's comments about the fact that a lot of patients with spinal cord decompression sickness leave the chamber with some residual, and later on are better. I have had the same experience, but I don't think that we have done the long-term studies to understand how many of those people do fully recover. That's the difference between significant strokes and significant bubble injury: most of the patients who suffer strokes have lost enough neurologic tissue that five years later they have deficits, whereas many of the bubble injured patients seem to recover. You are saying that the same thing, and it would be interesting to see a long term study showing that kind of recovery.

Dr. Thalmann: We get anecdotal long term studies in the sense a lot of our patients will go back and see us in six months and we can see that they are normal. We'll examine them and send them to get a neurological work-up. It is certainly is not 100% of the cases, but by and large one marvels at how sick they were and how well they had. We treated a commercial airline pilot that was initially quadriplegic due to decompression illness but 12-16 weeks later his disability was limited to trouble with his foot extensors. Eventually he seemed to fully recover. We had another individual who had cerebral decompression sickness, but a couple of months later his main problem was that when skiing his turns were off a bit. This is the kind of thing we are talking about, certainly not something that you would expect from a stroke patient.

Dr. Massey: The trouble with extension of the foot, is that normal? I think that point is that there are patients who leave the chamber or have had therapy and in two weeks there is still a residual, they probably have residual in a year, just like stroke patients. I have stroke patients who don't have a residual as often and that just depends on where it is and the amount of disease that's involved. So I think there are deficits in these people. The ones that can go skiing certainly have minimal dysfunction, and they may get a lot better. But there is significant residual.

Dr. Thalmann: Some of these symptoms are in a dynamic presentation: I think his foot drop actually got better too. We don't know if there are residual lesions left, in which we just can't see anything clinically. I don't think there has been 100% agreement on that yet.

Dr. Massey: Some of our patients have been treated for spasticity two years out, and they may not return to normal.

Dr. Moon: Can you comment on the differences between embolic or traumatic spinal cord injury and decompression illness.

Dr. Massey: Embolic spinal cord disease is really rare. I am not convinced that I have seen an embolic event in the spinal cord. Usually we

consider infarction of the spinal cord to be thrombotic, usually in the artery of Adamkiewicz. Those patients do not do well, and are usually paraplegic a year after the event. Certainly they have a prognosis worse than divers who are paraplegic in the first few hours. Embolic disease of the brain is markedly different from thrombotic disease. Embolic disease tends to cause branch occlusions of the middle cerebral artery, whereas thrombotic disease affects predominantly the deep white matter, lesions of the lenticulostriate.

Dr. Goodman: I agree completely with Dr. Massey that the prognosis of spinal cord infarction is really bad. I will say that as a person who has been working in the design of clinical trials, one would have to have a well-designed follow up study. In spinal cord trauma we are tracking down felons and drug dealers, so it can be done.

Dr. Latson: I just have a comment that possibly differences in recovery between diving injuries versus stroke may be because diving injury happens typically in younger people that have more resilience. There's time for the younger body to regenerate versus a stroke in an older person. That certainly wouldn't explain it all, but it may be a factor.

Dr. Mitchell: I would disagree with the notion that musculoskeletal decompression illness and those cases that present with very minor neurological symptoms like tingling are interesting but they have no real significance. Knowing what to do with those cases is one of the most challenging issues for a hyperbaric physician, who may be faced with the decision as to whether to ask for a major evacuation to get a diver to a hyperbaric facility. Many of those cases can develop medicolegal issues if they are not treated properly. I think in a symposium on adjunctive treatment it is important to keep those cases in mind. Certainly it would be a great thing for me to have an alternative treatment for some of the minor cases.

Dr. Thalmann: Looking at the DAN literature, overwhelmingly the most common clinical neurological symptom is tingling and paresthesias. It would be great to get out of this meeting from our neurological colleagues to come up with a set of criteria that you could apply to determine whether the symptoms were due to a peripheral nerve, that is, a nerve outside the spinal cord vs. a lesion within the spinal cord. A lot of the stuff that I see now, I am convinced is due to peripheral nerve lesions, but there's absolutely no way to prove it.

Dr. Massey: There is a way to prove it, by clinical history and examination. This is similar to the argument about using the term 'decompression illness', allegedly because of the inability to differentiate between spinal cord and brain involvement. That's baloney, in my opinion. We can tell by clinical exam 100% of the time whether there is brain or spinal cord injury. There may of course be both, and those are the difficult ones. The majority of the time if there is involvement of the peripheral nerve we should be able to tell. The problem with a drug study is that we have to be very careful about what we are treating. For example, we can't treat numbness in the face by simple assuming that the cause is a lesion in the cortex, unless we are absolutely sure that it is not due to a lesion of the trigeminal nerve.

Dr. Thalmann: For 'mushy' paresthesias it is very difficult to distinguish between spinal cord and peripheral nerve lesions, when there is no motor involvement and no other lesions. These are the most common neurological presentations we see that we end up treating. If a guy walks in and says "my forearm feels funny, or I don't feel quite right", it turns out that they are all very subjective.

Dr. Dietrich: I would like to follow up on a comment about cumulative damage with repetitive insults. Actually you don't necessarily have to damage the endothelium but affect the ability of the endothelial cell to elaborate vasoactive substances, which predisposes the vasculature to secondary insults. I think there is a possibility that for a diver who is experiencing repetitive diving episodes to be treated between those episodes, and thus protect the microvasculature from embolic insults. I think there is a lot of information available from the study of embolic stroke that could help this field.

Dr. Moon: We've heard from our speakers that we don't really know what's going on, we don't know what the pathophysiology is and we don't know where the lesions are all the time. Dr. Dietrich, could you comment on the importance of pathophysiology, particularly with regard to vascular obstruction, for the development of new treatments.

Dr. Dietrich: Being a basic scientist, I come from the perspective that you have to understand the pathophysiology in order to come up with new

treatments. The more we understand about the pathophysiology of brain and spinal cord injury the more we have realized that it is multifactorial, and that there are numerous structural, biochemical and molecular events going on. So combination therapy is what we are turning to. Maybe the best strategy is to use drugs that target acute pathophysiological mechanisms. Then there are other drugs that target events that occur a few days later. So right now we are ready to talk about what types of combination therapy can target multiple pathophysiological mechanisms, not just one. I think one of the most exciting areas right now is apoptotic cell injury, or programmed cell death. In spinal cord injury this process can target oligodendrocytes, leading to demyelination that can lead to some of the functional changes that we have heard about this morning. Anti-apoptotic drugs are being developed to affect delayed injury. The point about age being critical in stroke vs. diving is very important. A blossoming area of research has to do with endogenous reparative strategies. There appear to be stem cells in our bone marrow that may actually migrate to the brain or spinal cord after injury and actually replace damaged cells, probably an age-dependent event. There is a lot of excitement in the field. I think we have to understand the basic pathophysiology and then do drug studies in well-designed animal models.

Dr. Thalmann: One of the things I think is important to keep in mind is the time course of spinal bends versus stroke. In spinal patients we tend to see patients with rather severe neurological bends who get better When you talk about these mechanisms of demyelination, do these fit in with something that in fact could be reversed in 8-10 weeks with treatment? There are certainly a lot of mechanisms that could be postulated but they have to be examined in the context of the time frame of decompression sickness, how the disease develops, the speed at which it develops and the speed at which it resolves, to decide whether these mechanisms are reasonable. Certainly a lot of decompression injuries seem to be reversible if they are treated early enough.

Dr. Hardman: When I got involved in this area I came at it not from a diving officer's perspective. One of the things to remember is that in all of the organ systems in the body it is possible to lose a fair amount of function before it causes symptoms or signs. That's true of stroke as well as a number of other conditions. So, having a clinically normal patient might tell you that there is a lesser degree of injury but it doesn't tell you that there is no injury.

Dr. Thalmann: In some papers presented at the UHMS meeting, which looked at spinal cords of divers who died for other reasons, divers were supposedly normal (although maybe they weren't) but despite their spinal lesions they seemed to be okay. If you have somebody like a submariner who doesn't dive but he has to make the one big escape and he gets spinal bends. If you don't treat him is it likely that he will recover? Because he doesn't have any cumulative residual injury is there a chance he will recover? Certainly animal studies seem to indicate that it is possible. However, I don't think that examination of the spinal cords from these animals a year or two later has been done yet. I think acutely they don't seem to have injury but I'd have to go back and ask the investigators again because they haven't really written this up yet. Most of it is word of mouth.

EXPERIMENTAL DECOMPRESSION ILLNESS
AN ANIMAL MODEL OF FOCAL BRAIN INJURY

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A consistent model of focal brain injury would facilitate controlled studies of necrosis, inflammation and repair of the central nervous system. I believe that our studies of decompression illness (DCI) using a saturation animal model could be adapted for such research. In the following brief report I summarize the key pathophysiologic and pathologic features of the animal models that we have used. We originally switched from a dog model to a porcine model in the late 1980s to comply with the concerns of animal rights groups that we not do experimental studies on any animal that is revered as a pet. In addition we were precluded from doing experiments that might cause prolonged pain and suffering of the experimental animal.

Our saturation model of DCI in dogs[1] produces a disease so severe that bubbles occur in the pulmonary artery within five minutes after the animal reaches sea level pressure. In both dogs and pigs, the disease is sufficiently severe to cause signs of disease (e.g., loss of function of limbs and/or respiratory disturbance) within 10-30 minutes of reaching sea level pressure. The dogs weighed 20-30 kg and shoats 50-60 kg.

Porcine Model

Healthy young adult shoats weighing 50-60 kg are placed in a dry dive chamber breathing air and compressed to 100 feet sea water (fsw) for 12-18 hours. The shoats are rapidly decompressed to sea level and observed for 30 minutes. The animals were immediately euthanized with ketamine and then given intravenous potassium chloride to cause cardiac arrest. A complete post mortem examination was performed within one to two hours of death. All tissues were immersed in buffered 10 per cent formaldehyde and later sectioned and processed for standard hematoxylin and eosin-stained sections for review by light microscopy.

Pathophysiology: Once bubbles form, we need to understand how they cause disease. The pathological effects of bubbles formed in DCI are primarily due to autochthonous bubble formation in the tissues[2] (see Table 1). After rapid decompression dissolved nitrogen in the tissues forms bubbles *in situ* (so-called autochthonous bubbles) in all tissues and organs, but lipid-rich tissues accumulate more dissolved nitrogen than do non-lipid rich tissues. In large animals including man the organs most affected include blood, lungs, bone and the central and peripheral nervous systems.

As autochthonous bubbles grow in a tissue, they exert pressure on the surrounding tissue and compress adjacent capillaries and stop blood flow. Such altered blood flow will cause local ischemia and necrosis. Similarly, a bubble formed in the blood can flow with the blood until stopped by a vessel smaller then the bubble, typically the capillary loops of the pulmonary

alveoli. Arterial bubbles may embolize to small vessels of the brain, spinal cord, kidneys, heart, lungs or bone.

Pathology: Our animal model is useful for both clinical and pathologic studies. Round to oval Space Occupying Lesions (SOLS), so-called autochthonous bubbles, and/or petechial hemorrhages were found principally in white matter of the spinal cord and adipose tissue of the trunk and viscera of the animals[3]. Hemorrhages are often eccentric to or fill the SOLS. SOLS remain up to six hours. By 8-12 hours, tiny (1 mm) oval to round foci of necrosis appear in the spinal white matter in a distribution pattern comparable to SOLS and hemorrhages. In animals surviving 12-24 hours infiltrates of neutrophils appear in and around the necroses. After 24 hours macrophages appear and reactive axonal swelling follows. With resolution of the necroses, glial scars and degeneration attributed to Wallerian degeneration remain. These pathological events are comparable in dogs and shoats.

Without treatment by recompression 78% (7 of 9) of the shoats developed demonstrable hemorrhages and SOLS in the spinal cord white matter within 30 minutes of being decompressed[4]. Hemorrhages occurred as soon as 10 minutes after reaching sea level pressure.

Summary

Experimental decompression illness of young shoats may be used as a model of focal necrosis, inflammation and repair of the central nervous system. Tiny hemorrhagic and necrotic lesions of the spinal white matter are produced without surgical manipulation of the animal. These lesions could serve as a model for the study of the pathophysiologic mechanisms and pharmacologic manipulation of the cellular processes involved in injury and repair of the central nervous system.

Table 1: Space Occupying Lesions (SOLs) in spinal cords of dogs ventilated with air at different ambient pressures (From Francis et al[2]). After 4 hours of exposure cardiac arrest was induced with intravenous KCl prior to decompression. The cords were removed after decompression, fixed by immersion in 10% buffered neutral formalin. Blocks from lumbosacral, thoracic and cervical levels were embedded in paraffin, sectioned, stained with H&E and examined by light microscopy by two observers blinded to the history of each animal. A few small (<100 ÿm) extravascular SOLs were found in all experimental and control animals. The number of large (>100 ÿm) lesions in the sections examined are shown.

Pressure (ATA)	**1.0**	**1.5**	**2.0**	**2.8**	**3.0**	**3.3**	**3.6**	**4.0**	**5.0**
Dogs (n)	3	1	2	1	2	2	4	2	1
Sections (n)	60	16	40	21	33	47	86	40	18
Bubbles (>100 ÿm) per section (mean)	0.05	0.06	0.05	0.14	0.12	0.15	0.33	4.93	6.61

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DISCUSSION 2:

Dr. Thalmann: On some of the slides it looked like the space occupying lesions seemed to be distributed around the gray-white junction. Do you see that as a consistent pattern?

Dr. Hardman: Based on blood flow studies that's where the interface zone might be; the lowest tissue face might be at that level.

Dr. Thalmann: As I understand it there's very little anastomosis across the gray-white region, there are mostly end vessels that penetrate. Is that correct?

Dr. Hardman: I haven't seen very many studies that really answer that question well at all, but maybe I have missed them.

Dr. Thalmann: What causes the symptoms, is it hemorrhage?

Dr. Hardman: I think that the symptoms have to be due to axonal impairment.

Dr. Thalmann: Do you think that's because of the hemorrhage or because some kind of disruption of the myelin?

Dr. Hardman: I think that the hemorrhage is a manifestation of that, probably due to the pressure from the bubble.

Dr. Thalmann: Do you really think that in the spinal cord, there's enough rigidity that gas phase would actually cause compression, because in your slides you seem to see that the tissue has moved away from the bubble, but it didn't seem that it was compressing the neurons locally.

Dr. Hardman: The only way I can answer you is when you follow the animals out two or three days from the injury, there is real necrosis around each of those areas, so there is actual destruction of tissues. Acutely you see hemorrhage; two or three days later you will actually see necrosis in that same area, around where the bubble is so in that sense there really is injury to the tissue. How the injury occurred, whether by pressure or obstructing a vessel I'm not sure we can answer that question.

Dr. Warner: Could you associate the neurologic function of the animal with the pathology? Did it improve as the people have been discussing earlier or did they stay paraplegic?

Dr. Hardman: They did improve. The best marker we had for their clinical state was paralysis. When they were paralyzed it was obvious. Their paralysis might not have been completely gone but they could move much better within a few minutes. They weren't necessarily back to normal but they were close. We didn't follow any of these animals long term because we weren't allowed to do that. Once they were hurt we had to put them to sleep.

Dr. Piantadosi: I want to ask a little more about the hemorrhage: it's very interesting and extensive in some places and I'm curious about your thoughts in terms of the contribution of the hemorrhage to the pathophysiology. Is this an extensive capillary injury that you are seeing so you are seeing leakage of these red blood cells into the parenchyma? Then you load up those tissues with iron and heme. What happens after that in terms of pathophysiology? Any thoughts or any data?

Dr. Hardman: It seems like if it were all intracapillary then we would see more sausage shaped lesions, which we didn't find. It seems as if the capillary that's injured is right at that site. Frequently the hemorrhage would be on one pole of the bubble; it wasn't necessarily all around the bubble, but I found all different patterns so it wasn't possible to say that one was more dominant than the other.

Dr. Piantadosi: Was it obstruction of the capillary, is that what you think?

Dr. Hardman: The capillary is obstructed in that area.

Dr. Piantadosi: Is the capillary stretched and destroyed?

Dr. Hardman: It doesn't look like it, but I don't know that for sure, and I don't know how to prove that for sure. For the person who is adamant that it has to be intracapillary, it's very hard to disprove it. If I could find ballooning in the capillary it might support what you are saying, but I didn't find that. In these kind of experimental models negative information sometimes is not that meaningful, so I would be careful about that part. I tend to think that the capillary injury is right where that bubble forms. Maybe the bubble embolized there, that is possible too I suppose. But it happened so quickly, when they developed illness

it seems like temporally it preceded what one would expect with arterial gas embolization.

Dr. Goodman: John you have a veritable treasure trove of material in this paraffin embedded material and I wanted to ask you if you had an opportunity or plan to do any of the histochemical studies for APP or apoptosis markers or as far as the capillaries go, do some factor VIII for endothelial cells? Also, did you do any electron microscopy?

Dr. Hardman: I did not, although we obviously could. I have all the material archived so it could be done. My main problem was that when we ran out of funds I didn't have any way of keeping the project going. So that's why we stopped where we are.

Dr. Dietrich: I was very impressed with the axonal pathology. It reminds me of traumatic spinal cord injury. Yes, there's white matter pathology seen in stroke. We are getting more and more impressed by the amount of white matter pathology and maybe that's why some of our drugs haven't worked, because the drugs don't target white matter pathology, just gray matter. But the primary axotomy that you showed appears very reminiscent of trauma induced axonal damage. So I guess in thinking about it, can you tell me if the bubbles burst? I'm just looking for some type of acute mechanism at the local cellular environment that could produce a compression injury that could produce this severe axonal pathology.

Dr. Hardman: I think it's possible in some instances the bubble might actually form right in the axon actually. In terms of the chemistry of the two areas, the density is going to be much greater in the myelin I think. My inclination is that the cause is more likely pressure than anything else, but I don't have any way of proving that. There's definitely injury; definitely necrosis evolves around those bubbles. I don't think there's any doubt about that part. It's the mechanism of how that comes about. Brain tissue and spinal cord tissue do not survive very long if it the blood supply is lost, and in a matter of minutes you would get damage, so it doesn't take very long. I'm always amazed that these patients do as well as they do with the treatment. Theoretically, I would think that hyperbaric treatment wouldn't work at all. However, we know it works so I can't argue that. It's a little bit like immunotherapy for Rh disease, that shouldn't work either but it does. If you analyze it by modern immunology, you would trap yourself on that one. But it definitely works, so I'm not arguing that.

Dr. Moon: I would like to follow up on Claude Piantadosi's question and ask Clay Goodman, Dalton Dietrich and Dave Warner their comments on blood within the substance of the spinal cord. Hemoglobin is a very vasoactive substance at the very least. Could it not be doing something to vascular tone?

Dr. Goodman: I think the blood has multiple potential pathogenic factors, one the iron in it triggering the Fenton reaction. Free radical generation is a serious concern. Of course in subarachnoid hemorrhage there are multiple means by which the blood is inducing vasospasm. The mechanisms are not entirely clear but they may also involve the iron. So the blood itself, even in these small quantities, could be quite a serious nidus of neurochemical damage.

Dr. Hardman: I think in view of the inflammatory response it involves, that you would have to assume that. I think the cells are there so it triggers the inflammatory response in a classic sense.

Dr. Thalmann: Again you get back to the time course because the kind of lesions that you are showing in your dogs would seem to be fairly late lesions which are not going to readily respond to therapy, at least to make them clinically better, and yet in divers, if you get them fast you seem to be able to reverse a lot of the symptoms, certainly over the course of a couple of hours and make a lot of them go away. First of all, do you think these hemorrhage lesions could possibly reverse that fast, in other words, be amenable to recompression? Second, what do you think is going on before that, which is causing a symptom but yet is due to a mechanism that is readily reversible?

Dr. Hardman: I think that you can argue that if a bubble forms, wherever it is, it might cause pressure necrosis before even the capillary is injured. It may be a part of the injury and not be merely a 'carrier' as you were indicating earlier. Once that's happened then there will be release of these other factors, such as cytokines. There is definitely necrosis in the area of these lesions, in both the human cases that I've seen and these experimental models, where we could follow them long enough. The reason we used hemorrhage as a marker is that was the earliest sign we had morphologically to say for sure there was injury,

because generally we say that there is no hemorrhage in interstitial tissue normally.

Dr. Warner: I'm not a pathologist or neurologist but it seems like this is a really critical part of the discussion in terms of selecting adjunctive therapy. I'm getting to understand that this disease is distinctly different from what we classically study as ischemia or a thromboembolic event in laboratory. It seems to be a combination of insults. My sense, though, is that it starts as principally a vascular-endothelial sort of phenomenon, if you are inferring a hemorrhagic response to it that quickly. You showed the cardiac arrest patient who had the same sort of hemorrhagic phenomenon, and that would be in the absence of the microemboli as well. I know that some compounds that are efficacious against ischemic stroke that are not efficacious against collagenase-induced hemorrhagic stroke, for example. It would be important to know what really is the process before you can come up with a meaningful intervention.

Dr. Hardman: Some of the newer imaging techniques where one can actually look at things at the micro level may be useful, although I don't know if they have the necessary resolution. The problem is that these lesions are on the margin where both MRI or CT in the traditional sense can actually detect them. Even if you had swelling in the cord on MRI, I don't know whether that would negate the possibility of underlying small necrotic lesions in the middle of it. These lesions are in the 1-2 mm range, pretty small lesions. I think all the things that have been mentioned are possible: endothelial damage, the blood and the necrosis of tissue itself are all factors. The other thing is, we have seen a lot of bubbles without apparent hemorrhage around them, but they are acute so I don't have any way of knowing whether those would have ended up with necrotic tissue or not. The other thing is, capillaries are everywhere in the body, at least within a millimeter of each other, so it's pretty hard to have any lesion of any size at all that's not going to impact a capillary in some way.

Dr. Dietrich: In terms of the blood question, obviously subarachnoid hemorrhage can produce vasospasm and in a milder sense, maybe the blood can affect vascular reactivity of the vessels, which could predispose the animal to some type of secondary insult that could complicate the pathophysiological picture. In your pig studies, did you measure blood pressure and things of this nature to see if the animals were hypotensive, which could have led to worsening of the primary insult?

Dr. Hardman: We didn't actually measure pressures at all, but initially they seemed to be normal. They went from normal, to symptoms, to death within a minute or so. So there wasn't any long delay as far as blood pressure variation.

Dr. Dietrich: What are the physiological changes in people undergoing recompression therapy?

Dr. Latson: There is a fairly mild increase in blood pressure due to vasoconstriction. In a mild to moderate case of decompression sickness changes in vital signs are not impressive.

Dr. Bove: Given your knowledge of the cord injury, could you hypothesize agents that might be released into the bloodstream that could be used as diagnostic tools, in the same way we use myocardial enzymes for detecting myocardial infarction?

Dr. Hardman: It is possible, but it would depend upon the sensitivity of the test and how little tissue damage there may be in this disease. I would think that the enzyme patterns ought to parallel what you see in other body sites, including myocardial infarct.

Dr. Goodman: I haven't thought of this before, but it might be very interesting, since there are commercially available assays for myelin basic protein for example, to see if there are systemic or CSF elevations.

Dr. Hardman: I would expect there to be but I don't know.

Dr. Vann: What were the exposures that you used: the dives, the depths and the times?

Dr. Hardman: The animals were taken to 200 feet, kept there for 24 hours on air and then brought back to the surface relatively rapidly. They were sick within 10 to 15 minutes after reaching the surface.

Dr. Vann: I wonder if this makes a difference, in other words, perhaps this is not a model that closely reflects what's going on in most clinical decompression sickness. Do you have any sense for the dose/response relationship here in terms of how fast you get very much worse when you go to 100 feet instead of 200 feet?

Dr. Hardman: The only answer I have to that is that in one series we did on dogs we had equilibrated them at different levels of pressure, starting at 2, 2.5, 3 atmospheres, and so on. The bubble load was much less in the lower atmospheric group than it was in the higher group, which would be expected. As far as analyzing the kind of injury patterns and so on, there wasn't any appreciable difference. If they were injured they were similar.

Dr. Vann: In your speed to recompression study (the in-water recompression), how important was the rapidity of recompression?

Dr. Hardman: Well, that was part of the issue, so we had a group that was recompressed at 10 minutes and another group at 30 minutes. They were brought immediately to the surface then put down for 10 minutes. At 10 minutes they were recompressed again and at 30 minutes recompressed. By doing that we did reduce the injury from 90% to about 20 or 30% that had petechial hemorrhages.

Dr. Vann: But you did not go out any farther than 30 minutes?

Dr. Hardman: No we didn't. We didn't know what was happening with rapid recompression. We all knew theoretically it should work, but there hadn't been any studies to show that in fact it made a difference pathologically.

Dr. Butler: You touched on the fact that the lesions that you demonstrated in your animals might or might not be demonstrable using neuro-imaging of the CNS. Just a question for those of you who see routinely see severe spinal cord decompression sickness with refractory symptoms. I'd like to get a feel for what this group feels that the role of neuro-imaging is in trying to sort out hemorrhagic from non-hemorrhagic lesions of the cord.

Dr. Moon: Our attempts to image the spinal cord in decompression illness have been relatively fruitless. We have probably imaged 20-25 cases over the last few years, and in a very small number of them can one see an abnormality, probably on the order of 10-20%. Since we are not sure exactly what the pathology is, I don't think that we can sort out embolic versus hemorrhagic lesions.

Dr. Hardman: Did you do it sequentially so that you have time frames? Even in infarcts, big lesions don't show up very early.

Dr. Moon: Most of the images were a few days after the event; they weren't hyper-acute.

Dr. Hardman: The pia-arachnoid is very tight around the cord, so it doesn't give very much. So, even if there was severe injury it might not change the size of it very much.

Dr. Butler: A question for you, Richard. The 20 patients that you mentioned imaging or trying to image the cord, were those all patients with severe fixed deficits or were those a mixture of people who'd been treated and done well? Where on the chemical spectrum of severity were those patients?

Dr. Moon: Many of them went on to do well, but at the time of the imaging they had relatively severe neurological deficits.

Dr. Goodman: Following up also on the imaging question, were these diffusion-weighted images or were these T1, T2 images?

Dr. Moon: These were a few years ago, they were largely T1 and T2 weighted images.

Dr. Hardman: Actually there are some methods available now that might be more valuable than the primary screening. CT is generally is more sensitive for acute hemorrhage then any of the other modalities, but most of the systems don't resolve things that small, so that's where your problem is.

Dr. Thalmann: It would seem that the imaging was great from an academic standpoint but actually had no impact on treatment. It was nice to see that there was a lesion where you would expect it to be, but it was of no use in determining what the treatment would be.

Dr. Hardman: Well the hemorrhage would be something that would come early and that would be the one thing you might be able to see. But, a hemorrhage resolve if it's small; macrophages can lyse it out pretty quickly. So, sometimes one can be fooled regarding whether there is hemorrhage or not.

Dr. Warner: I'm back to sorting out the cause of the hemorrhage. I realize that we have limited information. But there are two possibilities that come to mind. One is that the tissue becomes ischemic, necrotic and allows hemorrhage to occur. Alternatively, the endothelium itself becomes sick and hemorrhages. If that's the case you would

expect to see hemorrhages out in the fat, and conversely if it's the neurons and glia that are dying and causing necrotic morass, in which the endothelium now bleeds, you would expect only to see it in the highly metabolic tissue like the cord. So did you see hemorrhages in the fat?

Dr. Hardman: Yes, sometimes we did.

Dr. Warner: That sounds like an endothelial sort of phenomenon.

Dr. Hardman: Yes, it could be. I don't know the answer to your question. There are tiny lesions everywhere, when you find them, and there are hemorrhages. But the problem on some of the ones that we did see the hemorrhages on, the ones I saw best, were a couple of days out. By then there's a lot of time for things to change.

Dr. Bove: This is an important critical issue because I could argue that hemorrhages are caused by the mechanical disruption of the bubble forming and just tearing some of the capillaries, or the capillary endothelium being disrupted by intravascular bubbles, or by tissue necrosis and breakdown. The fact is that it would be good to sort these things out because we could begin to hypothesize therapies. A blunt injury to a skeletal muscle causes interstitial hemorrhage which is resorbed in the muscle, and it's not a big consequence. You could imagine interstitial hemorrhage in the cord being caused by mechanical injury, which when absorbed would leave most of the neurons intact later on. That would be one model. So it seems to me that it would be important to sort this out because we could understand prognosis a little better, and would fit this better recovery model some of us think is there It would also give us some ideas about therapy. When we, in cardiology give thrombolytic agents we are not thinking about interstitial hemorrhage, we are thinking about intravascular thrombosis. Interstitial hemorrhages would usually worsen by any of the things that we would normally do to improve intravascular thrombosis.

Dr. Hardman: I don't have any quibble with that, but the problem is, I'm not sure how to design a model to test it. Because bubbles are more likely to be formed in lipid-rich tissue than elsewhere, if I were picking one possibility over the other I would think pressure is more likely, but I don't know of any way to test the hypothesis.

Dr. Massey: I was impressed in your pig model that there was marked sparing of the posterior columns and the ventral and lateral spinothalamic tract areas. Do you agree with that and are they different in the amount of lipid?

Dr. Hardman: As far as I know, maybe the quantities of lipid are different, but in terms of the character, as far as I know it's the same. As far as I know, the chemistry of spinal myelin and central myelin is the same but those lipids are hard to study chemically. It used to be thought that endothelium is the same everywhere, and we now know that that's not true. So I wouldn't be surprised if there are be differences, but I don't know what they are.

Dr. Massey: On your longitudinal sections is that sausage appearance related to the oligodendrocytes?

Dr. Hardman: It's probably related to the orientation of the axons, which are covered with myelin sheaths. It seemed like the blood was dissecting between myelin sheaths.

Dr. Flynn: You mentioned that the pia-arachnoid was fairy tight, particularly in the thoracic region, which would, if I understand it correctly, increase the probability that this would be a compressive injury, because the cord couldn't expand very much. In your sections did you see any normal portions of the cord that looked like the blood had been squeezed out or there was a compensatory response that would support a pressure hypothesis?

Dr. Hardman: Only in the sense that the way the tissue cells layer out would suggest that possibility, but I don't know that you could rely on that. It does layer out in a way that you might think it's pressure but I think we'd have to test it some other way to be sure about that.

Dr. Dietrich: In terms of the hemorrhage again, one of the current hypotheses concerning hemorrhagic transformation after stroke is the activation of a family of enzymes, the matrix metallic proteases (MMPs). So it would be interesting to look at that particular pathway to see if the MMP's are up-regulated. We have inhibitors of the MMP's that could be used as a treatment protocol, in contrast to things like prostaglandin inhibitors and things like that.

Dr. Hardman: That would make sense. I have always thought the model would lend itself to a lot

of these things. I think if we are going to use the model it would need to be adapted to smaller animals. To do the kind of things you are talking about takes a large amount of animals, so mice or other small animals would be better, and I have no idea what kind of problems that might create. I know rats are a little different than other animals but mice seem to be similar. I think that would be a logical step, to do what we have done before on mice.

OUTCOME AFTER RECOMPRESSION THERAPY

Ward Reed, MD MPH

In this section I will:

1) briefly outline the history of recompression therapy, mainly to attempt to explain how the therapies in use were developed,
2) introduce likely mechanisms for recompression therapy,
3) review the published some of the published outcomes of recompression therapy, and
4) present some compiled data from the Divers Alert Network experience from the years 1987-2000.

History

When bridge building technology required large numbers of workers to be exposed to a hyperbaric environment in the nineteenth century, the clinical entity now known as decompression illness began to be recognized. The first recorded suggestion of the use of hyperbaric conditions for the treatment of hyperbaric medicine was first suggested in 1854 by Pol and Wattelle[1]. Return to pressure, probably noted to relieve the pains of decompression illness by caisson workers long before physicians recognized its benefit, was observed in the later 1874, during construction of the Brooklyn Bridge[2] and Mississippi River Bridge at St. Louis[3]. Air recompression was first used as a standard treatment in 1889.

Air recompression was in use for half a century, when the possible benefits of oxygen under pressure for recompression were recognized. Oxygen recompression was initially suggested by Yarborough and Behnke as in 1937. The first oxygen treatment tables were developed in 1944. A significant failure rate was observed with these protocols, as high as 50% in serious neurologic cases, similar to that seen with air recompression.

Deeper oxygen treatment tables were developed in the early 1960s. These protocols involved longer exposures to higher pressures of oxygen. Goodman and Workman developed the basis for the current U.S. Navy treatment tables in 1965.

Current U.S. Navy guidelines recommend treatment of decompression illness (DCI) with an initial recompression to 2.8 ATA on oxygen. Except in rare cases, initial recompression to a deeper depth is not recommended.

Simple Theoretical Basis For Recompression Therapy

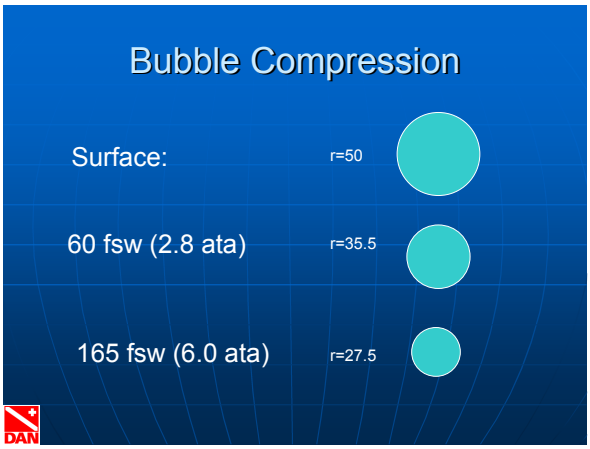
There have been numerous theories set forth for the observed success of recompression with oxygen. Some important current theories include:

- Bubble Compression
- High gradient to eliminate inert gas
- Delivery of oxygen to compromised neural tissues
- Other possible mechanisms such as
    - Restoration / maintenance of blood flow
    - Inhibition of WBC activation

Bubble Compression

Bubble recompression is the simplest of all of the theoretical constructs to understand. It was postulated very early by Paul Bert that bubbles of inert gas caused what was then know as caisson disease. Compression to a higher atmospheric pressure will decrease the size of the bubble according to Boyle's law. A smaller bubble would, therefore be produced with recompression. This smaller bubble would be less likely to obstruct blood flow. An examination of relative sizes of the bubbles shows that with recompression protocols currently in use, the radius of the bubble, and thus the ability of the bubble to obstruct blood flow, is only modestly diminished.

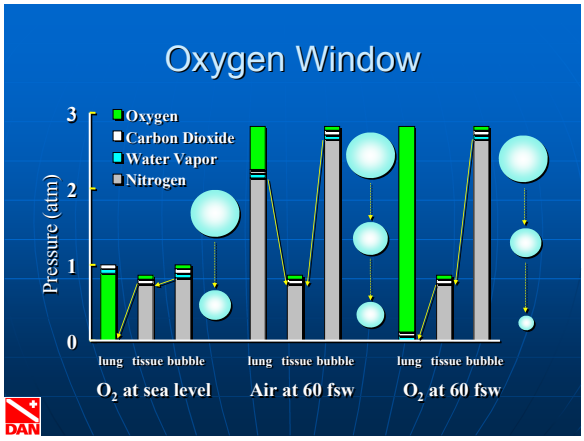
Figure 1



A bubble with an radius of 50 arbitrary units would reduce in size to only 35.5 units at 2.8 ATA (60 fsw or 18.3m). Even with compression to the deepest depth conventionally used, 6.0 ATA or 165 fsw (50.3m) decreases the radius of the bubble to only 27.5 units, a decrease of less than 50%. Given the relative small effect size, and the historically poor results of air recompression it is likely that bubble compression contributes only modestly to the overall effectiveness of recompression therapy.

Oxygen Window

The use of 100% oxygen at pressure leads to a very high gradient for the removal of inert gas, both from saturated tissues, as well as from bubbles of inert gas. As can bee seen in figure 2, the gradient present at atmospheric pressure in the presence of an FiO_2 of 1.0 is approximately .8. When exposed to an ambient pressure of 2.8 ATA. With an FiO_2 of .21 (air) the gradient from the bubble to the tissue is 2.1 ATA (initially), but it should be noted that the gradient from the lung (and thus bloodstream) is negative, that is, nitrogen is being added to the tissues. When the FiO_2 is increased to 1.0 the gradient from the tissue to the blood increases where there is a near 2.8 ATA gradient from the bubble to the bloodstream. This is one of the major (if not the major) mechanisms of action of modern recompression therapy. It is also the mechanism for the use of oxygen under pressure to accelerate decompression.



Increased Oxygen Delivery

It was recognized relatively early in the treatment of decompression illness that they appeared to be benefit from treatments even when there was a very long delay to treatment.

It has been shown that neuronal activity is decreased even after physical bubbles have been resorbed.[4] Despite evidence that physical bubbles had long since been resorbed a demonstrable clinical benefit was observed in some, perhaps many, cases. The primary presumed mechanism for this increased oxygen delivery.

At .21 ATA of oxygen is delivered at a radius of approximately 60µm at the arteriolar end of the capillary and 12 µm on the venous end. This compares with a radius of oxygenation of 300 µm at the arteriolar end and 60 µm at the venous end when oxygen is delivered at 2 ATA. In both the acute and subacute time periods, delivery of oxygen to neurons in an ischemic penumbra may improve outcomes of decompression illness.

Other Mechanisms

While the above mechanisms are thought to be the most important mechanisms for recompression therapy, there have been many other proposed mechanisms. Many of these have been discussed elsewhere in this symposium. These include inhibition of leukocyte adherence to the endothelium[5] and others.

Published Outcomes of Recompression Therapy

There have been a number of published series on the outcomes of recompression therapy. These studies have been summarized in a previous UHMS publication[6]. The publications are reported in table 1.

Table 1

Author	Year	N	Complete Resolution	Pt Type	Substantial Resolution	Comments
Workman[7]	1980	150	85%	Military	95%	2 Treatments
Pearson[8]	1972	28	67%	Military	83%	
Erde & Edmonds[9]	1975	106	81%	Civilian		
Davis[10]	1977	145	98%	Military		Altitude
Bayne[11]	1978	50	98%	Military		
Kizer[12]	1979	157	58%	22% Military, 78% Civilian	83%	Delays
Yap[13]	1980	58	50%	Civilian	84.5%	Mean Delay=48h
Gray[14]	1984	812	81%	Military	94%	
Green[15]	1989	208	96%	Military		
Ball[16]	1993	14	93%	Mostly civilian		Mild
		11	36%			Moderate
		24	8%			Severe
Total		1763	85%			

Examination of the table gives some mixed messages. The overall effectiveness of recompression therapy in the treatment of decompression illness was good, with 85% showing complete resolution of symptoms with one recompression treatment. These results must be tempered, however with the observation that this was not universally the case.

First, there appears to be a difference in outcome between decompression illness cases which arose from in a military setting and those which arose in the civilian, specifically the sport diving, population. When the series of military only cases are evaluated separately there 91.6% of the cases were reported to have complete resolution of their symptoms after one treatment. When the cases of altitude DCI are removed from the analysis (altitude DCI is generally thought to have a better prognosis than hyperbaric induced DCI) recompression therapy is slightly less effective, with 90.8% of the patients reported to have complete resolution.

In the series which were mostly or all civilian there appears to be a substantial drop in the reported effectiveness of recompression therapy. In the civilian series, 65.4% of the patients experienced complete relief of their symptoms after one recompression. In Yap's[13] series from Singapore, with median delays of 48 hours, there was only a 50% complete response to treatment. Ball[16] reviewed cases from the U.S. Navy chamber in Subic Bay, R.P. The most severely injured divers, some of which had significant treatment delays, only had an 8% complete response to one recompression.

A number of theories have been put forward to explain this observed difference. There are a number of demographic differences in the two groups. The military divers are almost exclusively male, may be younger, and have been screened for many co-existing diseases. There are differences in training, dive profiles, equipment, and technique. The most important difference may well be in the time to recompression. Most military dives take place with a recompression at the dive site, divers are trained to report possible symptoms, and supervisors are trained to rapidly evaluate and act on possible cases of DCI. These factors result in a relatively rapid recompression. Sport divers have (comparatively) little access to recompression facilities, and often divers are unclear where to go and what to do when a problem arises. Many of the "good" dive sites are now remote, both from recompression therapy and rapid transportation to medical care. The result of this is too often a long delay to recompression, which may also contribute to poor response to treatment.

Lessons from the DAN Database

The Divers Alert Network Diving Accident Database consists of voluntarily submitted data on diving accidents. The data represents almost exclusively recreational divers, although there are rare commercial and military cases present. Dive guides, and recreational diving instructors are well represented. The database contains over 6300 cases collected between 1987 and 2000. The data were submitted voluntarily by the injured divers and the treating facilities. Most of the data comes from diver recollections, and as such is incomplete in many cases, and may be subject to bias.

The gross outcomes are consistent with the recreational divers reported previously in the literature. While almost of the injured divers reported some improvement with the first recompression, only 43.1% reported complete resolution of all symptoms. However, at the time of discharge 92%, or almost all, reported that they were asymptomatic. There has been a slight improvement in the portion of divers who had complete resolution of symptoms after one treatment (figure 3).

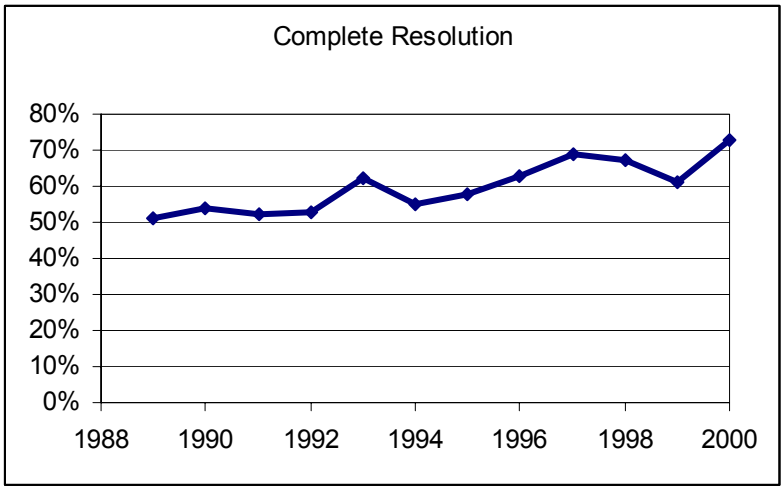


Figure 3

These data indicate that recompression therapy is reasonably effective. However, these data are gross outcomes. They do not take into account any potential confounding factors which may predispose to a better or worse outcome. For example, these figures probably overestimate the effectiveness of recompression therapy for severe spinal cord decompression sickness. They may underestimate the effectiveness in mild decompression illness.

Personal factors may also affect the outcome of recompression therapy. As an example, a simple multiple regression model of the accident database suggests some possible confounding factors.

	Odds Ratio	**95% Confidence Interval**	**p value**
Female Sex	1.15	1.03-1.29	0.017
Age>45	1.16	1.01-1.34	0.027
BMI≥30	0.837	.707-.991	0.039

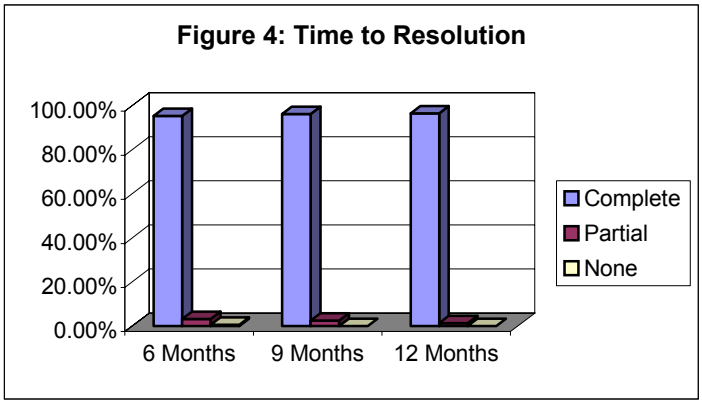
While these data do not prove, by any means, that any of these is any real clinical significance to any of these factors; it is at least suggestive that there are personal factors which effect outcome.

The greatest confounder in measuring the outcome of recompression therapy is the severity of disease. It is nearly axiomatic that more severe presentations of decompression illness are expected to have a worse outcome. Freiberger, et al[17] examined the DAN database. They examined cases from 1987-1996 using a logistic regression model. Of the 4889 cases available for analysis, 22% reported incomplete resolution of their symptoms following recompression therapy. Of the 27 presenting symptoms 13 were shown to be associated with incomplete resolution of symptoms at the time of discharge. The data are shown in table 2.

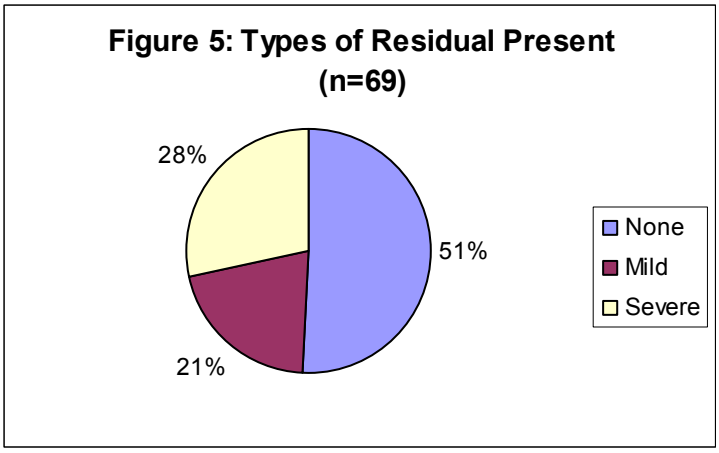
Table 2

Symptom	Odds	95% CI
bladder problems	4.53	2.69-7.63
hearing loss	3.43	1.77-6.65
numbness	3.17	2.68-3.76
paralysis	2.86	2.08-3.95
semi-consciousness	2.14	1.44-3.17
convulsions	2.08	0.90-4.85
bowel problem	2.07	1.19-3.59
decreased skin sensation	1.77	1.39-2.26
personality change	1.61	1.08-2.38
dizziness	1.49	1.25-1.77
difficulty walking	1.51	1.21-1.77
visual disturbance	1.43	1.08-1.88
weakness	1.28	1.08-1.51

The data support the contention that worse disease has a worse outcome. Bladder dysfunction, numbness and paralysis, symptoms which are associated with severe decompression sickness, had a greater likelihood of incomplete resolution. Similarly, symptoms which indicate a significant degree of air embolization, such as hearing loss, semi-consciousness, and convulsions also had a worse outcome.



The most common symptoms present after treatment are usually considered to be pain, sensory deficits, motor deficits, or autonomic dysfunctions (usually urinary retention or incontinence). Clinical experience (again) has shown that most residual symptoms will resolve or improve with time, even in the absence of specific therapy. Limited data taken from the 2000 diving injury database supports this theory.

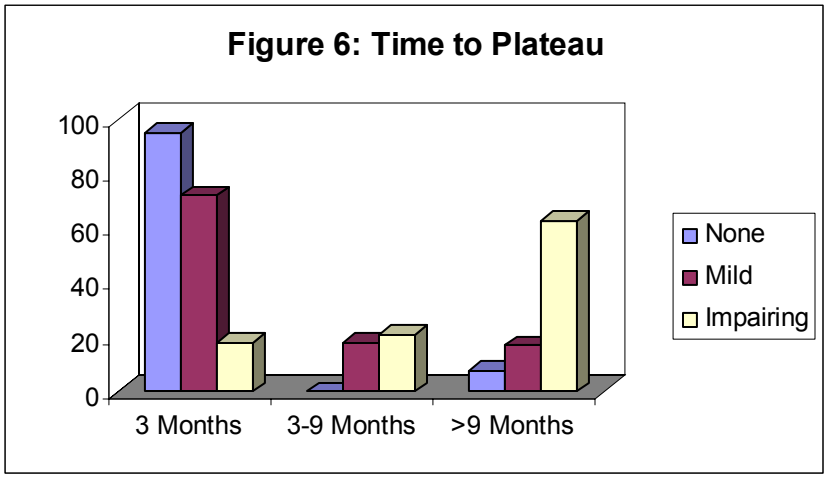


After 6 months greater than 95% of the injured divers reported resolution of all symptoms, with only 4% still reporting a residual problem and less than 1% reported no resolution of symptoms. After one year there were no patients, in this limited dataset, who reported no improvement in their residual

symptom, only 3% who reported any residual present and 97% who reported complete resolution of all symptoms.

These data include all types of presenting symptoms and types of residuals. Another small study examined the natural history of residual symptoms which resulted from very severe initial disease. Dovenbarger et al[18] examined 175 individuals which had paralysis as a presenting symptom. Of these 175, 69 had sufficient data available for review. At the time of review more than half reported complete resolution of all symptoms. Of the remainder, however, more than a quarter still had residual symptoms which were categorized as severe, and the remainder had symptoms which were categorized as mild.

These data also indicate that patients with residual symptoms present upon discharge will continue to improve for a considerable period after the accident. Almost all of those with mild residual symptoms had reached a plateau within three months of discharge. This contrasts starkly with those who were discharged with impairing symptoms. Most of those individuals were still having improvements in functional status more than 9 months after discharge. This also is consistent with numerous previous clinical observations.



Of those who reported residual problems which were considered impairing, ongoing bowel dysfunction, bladder dysfunction, and sexual problems were most frequently cited. Other commonly cited problems are problems with ambulation and writing. The full details are in table 3.

Table 3

Type of Problem	Percent Reporting
Bowel Function	71.4%
Sexual Function	71.4%
Urination	61.9%
Running	80.9%
Walking	52.3%
Lifting	28.5%
Writing	9.5%

Summary

Overall, the historically reported outcomes of recompression therapy are good, but tempered with the caveat that they are not universally good. There seems to be a difference in the outcomes of recompression therapy between military divers and sport divers. There are undoubtedly factors which may predispose to a poorer outcome, and it appears that individuals presenting with more severe symptoms are more likely to have residual symptoms. However, there are many cases where individuals who initially presented with mild to moderate symptoms progressed to severe symptoms which responded poorly to treatment, and those with severe symptoms who also responded poorly to treatment.

These data have implications for possible future adjuvant therapy. Therapeutic modalities which have neuroprotective properties may be useful early or just before recompression to avoid complications which may be caused by reperfusion injury. Since very long treatment delays have historically been associated with a worse outcome in case series, treatment with an adjuvant therapy early when recompression therapy will be delayed due to transport time may be beneficial.

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DISCUSSION 3:

Dr. Piantadosi: The Divers Alert Network database was set up as sort of an ecological study. It's not designed to answer the kind of questions that we're interested in here and so I'd like your thoughts about some of the important missing information or variables, or things that we can do to make this better and to get at the kinds of questions that clinicians ask. In other words can you see a way to stratify the patients on the basis of severity, on the basis of did they receive adjunctive therapy, what was the treatment delay, can initial treatments be standardized, and then what kind of end points should we be using? I think those are the questions that are probably on lots of people's minds right now, so go ahead and take a crack at it.

Dr. Reed: I think that with any database such as that one, which was really developed ad hoc, there are significant problems with it. There are problems with symptom categorization, which varies from person to person. The biggest problem I would say with this and most others is in outcome. What exactly was the outcome of the therapy, and if an individual has what they would consider to be a non-complete resolution of symptoms, which appears to be more common in the disease that we are most concerned about, which is neurologic and relatively serious neurologic illness. What problems are they having, what is the natural history of those problems, and does it improve also in terms of treatment? Even in terms of diagnosis we would like to get a better handle. I think in a significant number of these cases, and we'll never be able to know, because this is all self-reported, or reported by the treating physician. There could well be a mis-categorization in terms of diagnosis and or treatment. There is also a wild variation in initial treatment and treatment protocols.

Dr. Bove: A question along the same lines has to do with how you make the diagnosis of DCI because, I think what I heard you say, although you didn't say it directly, was that any recompression is listed as a DCI case. The question would be, can you go back and come up with some kind of a score that says 'very likely DCI' or 'very unlikely DCI', so that we don't see all these cases as bubble-related diseases even though somebody made a diagnosis and they are following the "if in doubt, treat" approach? This confuses the database, by calling everything DCI.

Dr. Reed: One can do that, and people have looked at it in the past, but you run problems such as this: an individual who was reported to have type 2 decompression sickness, but their list of symptoms doesn't appear to contain any type 2 symptoms. Now, which is wrong, is it the diagnosis or the symptom collection? That gets back to data collection, which I think is the crux of the matter, that the data collection has got to be improved.

Dr. Piantadosi: This is an opportunity. I think we have to try to see if we can get a better handle on data collection, because we're not going to get multicenter trials and no one center has the critical mass necessary to do this kind of work properly. DAN has an advantage because it is a central collection agency. I would like to ask Jake Freiberger if he could make a couple of comments about what we can do to improve our data collection, maybe standardize it a little bit more and see if we can at least get some idea about clinical answers to some of the questions that have been raised.

Dr. Freiberger: DAN is in a unique position to collect this data and is probably the only organization that can do this. We would like to get information from this group as to what you believe to be appropriate outcome measures. As Ward mentioned, that's the most difficult part of the data set, to analyze with the present data we have. We have thought about a couple of options. One is using a different collection method, which combines not only asking the questions about symptoms and treatment, but also incorporating a quality of life measurement. We have here an expert at Duke who has designed a quality of life instrument, which is called the Duke Health Profile, it's very similar to the SF-36 and it has along with it another instrument that measures the severity of illness. So our notion was to use this instrument to measure the divers' outcome at the time of treatment, and then at selected periods after treatment, possibly 3 to 6 months later to get long-term outcome. We also are looking for methods to decrease the errors so we won't have confounding between reported diagnosis and symptom reporting, as Dr. Bove was stating. That's a significant problem when you depend on symptoms to determine diagnosis, it confounds any measurement of severity you are trying to do. So we felt that we might attempt a telephone call-back system, where we would get the reports of DCI

from the chambers and then call them back. What would be very useful for us would be to know what this group felt would be important data points to collect. I'd like to suggest that we specifically focus on what data points would be our outcomes.

Dr. Butler: One of the things that we have done in the last several years in the Navy, working between the SEALs and the Experimental Diving Unit, is fielding a Navy approved decompression computer. We are now having to deal with our first case reports of suspected decompression sickness coming back in from those individuals. In working with Dr. Southerland and the other people on the configuration management board for this tool, we have developed a reporting system that we hope is going to be able to help us sort out a lot of the points that you mentioned. We look carefully at the profiles, we look at the type of symptoms and when they occur. We had a recent case of decompression sickness that caused a lot of concern until we realized that this individual was on a dive where his average depth was 26 feet for four hours and his onset of pain was at 20 feet. Now, there are not a lot of decompression tables out that are going to prevent that. So, this is a start at what you are proposing as a standardized way to look at these accidents and does incorporate at least some standardized approaches to looking at what type of symptoms, what type of adjunctive therapy, what type of recompression therapy, final residual. Combining those with what you are using at DAN, there may be some mutual benefit there.

Dr. Goodman: It occurs to me as the discussion unfolded that there exist multiple disability scales that are used in other neurological diseases that have robustness and credibility. I would counsel adopting those rather than attempting to reinvent. Certainly you have to take into account the unique aspects of decompression. It particularly occurs to me that the disability rating scales used in multiple sclerosis clinical trials might be particularly relevant to this population. The demographics would overlap and also multifocality through the nervous system might make those scales more appropriate than a stroke or trauma scale.

Dr. Bove: One of the things that we are missing, and we can't do in these two days, is to get a group of experts together talk about the proper diagnosis of decompression sickness from the symptom standpoint and from anything else, history and otherwise. Over time, what I've observed is a broadening of the definition, so that some people say anything that occurs after a dive is decompression sickness, yet from my standpoint there ought to be a group of experts that are used to dealing with the problem to define the likely symptoms and the unlikely symptoms so that you at least have some sense of what the proper diagnosis is. We can't be doing the other thing unless we have some agreed upon set of diagnostic criteria. So that to me would be an important thing to do and it could include blood tests or other things that might fit into the diagnostic pool of information that we can obtain.

Dr. Massey: I agree but I do have to keep in mind that we are talking about symptoms and I think that if you are going to deal with symptoms, it's always going to be that you are looking at these large things that are going to show you trends, which is what we are getting from this, we're looking at trends. We are not going to have any hard data without an examination, for example bowel was 71%, sexual 71%, even urination 61%, which are very subjective and I don't know if they are related to this at all. Obviously everybody who has had some injury to the spinal cord may have a lot of bowel problems. Bowel and urinary control can be imprecise, and are not the same as walking and running data, and they are not synonymous. Getting at 'what's what' is essential and important and maybe we can't use all those symptoms that we think we would like to use.

Dr. Piantadosi: In terms of the diagnosis, I think the best I can see we might be able to do here, would be to call decompression illness definite or indefinite or maybe have three scales. Fred, what do you think about that? Also in terms of severity, just a couple of stratifications might be useful so that what we're concerned about is long term disability primarily and not a little bit of joint pain. So could we see a way to factor out the ones that are truly classified type 1 and maybe leave the overlap also as a separate category? What do you think about that Fred?

Dr. Bove: I think that Wayne was beginning to touch on the issues. We are all trained to do histories and physical exams, record symptoms. We all have our anecdotes, and I saw a woman that had typical C8-T1 radiculopathy developing at 45 feet, was treated in a chamber and told that she was going to die if she didn't go through 20 treatments. Nobody took the history of the fact that she developed this three weeks before, while she was weight-lifting. There are all these other issues. We need histories, we need careful examinations, we need good symptom documentation. I would still

look for new ideas about blood studies, whether myelin proteins are going to be helpful or whether creatine phosphokinase level is helpful for pulmonary barotrauma. There are things that we don't do now that we probably should do that would make a better picture. In putting that all together we should be able to say 'indefinite', 'definite' or 'absolutely not'. If we put all that together we should be able to come up with a system that is better than just recording a few symptoms and putting someone in a chamber.

Dr. Massey: Could we do it just on symptoms? Someone is collecting this information at a far distance from all of the treatment centers. Could we reliably divide it into 'probable', 'possible', 'definite', by at a distant center? Is it at all feasible?

Dr. Chimiak: Along with what Claude Piantadosi said, perhaps what we might want to do is focus carefully on one particular clinical scenario, and that is spinal cord DCS. Those are the cases that are the most troubling and have residual symptoms. That would make your database really pure. You could still record the other cases, but I'd focus on the more serious cases.

Dr. Butler: To respond to Dr. Massey's suggestion, that's exactly what we are doing with our project to monitor the success of our decompression computer. When we have questionable symptoms after a dive, we categorize them into 'probable' 'definite', 'severe' and 'probably not'. Now we usually treat all of them, and we are not trying to reduce the initiative of the diving medical officer on the spot to treat any doubtful case. But at the end of the day we try to go back and sort each case out, to figure out whether it was really bends.

Dr. Freiberger: One of the things that we have to do, I feel, is depend on the examining physician at the location where the diver arrives. The quality of life instrument I was mentioning, the Duke Health Profile, has a part which records the severity of illness as described by the healthcare provider. So that document allows a certain calibration of the diver's symptoms. Some people may under-report and some people may over-report the severity of their discomfort or of their impairment. Thus, you need some outside or third party observer, which in this case would be the examining physician, to report in what we hope is an unbiased manner. One of the questions that Ward Reed raised was how dependable is that, and if a diagnosis of a type I or type II decompression event is reported, is that a reliable categorization? Maybe, as Dr. Chimiak suggested, we should focus on a specific subset of decompression illness. There are methodologies to do this. What we need are suggestions on how to proceed and we are very interested in knowing what you people feel.

Dr. Perkins: Just to revisit the issue of diagnosis and outcome that myself, Dr. Reed, Dr. Vann and Dr. Freiberger have been talking about related to this issue: I think someone has already suggested that developing diagnostic criteria would be useful, in a way similar to that by which psychiatric diagnoses are made. A large consensus could be sought to determine the essential components necessary to make a diagnosis, perhaps including major and minor criteria. One of the difficulties with diagnosis of decompression illness is that there is a wide range of inputs that we consider in making a clinical diagnosis, such as signs and symptoms, and a temporal association with diving. When there are so many factors that go into making the diagnosis, it is possible that this disease process may not lend itself very well to traditional methods for teasing out what exactly the confounders are. By that I am referring to statistical methods such as multiple linear regression. It may be that more novel methods may be better, such as neural net software, which unlike linear models really allows a lot more flexibility in figuring out which of these inputs really makes a difference in the outcome. Once we can agree upon the important parts of the diagnosis, we can then apply one of these methods to elucidate which clinical inputs ultimately affect the outcome, and which of them we thought were important but are not.

Dr. Southerland: I'm just a small town doctor. I have been hearing all about how to design a study to determine what symptoms and outcomes to use, but I'm still trying to figure out what's the question which the study is supposed to answer. It seems to be rather nebulous right now.

Dr. Reed: The question that we are trying to answer is 'What is the outcome of decompression illness with recompression therapy?' In the case of DAN data, the question is 'What is the outcome of recreational diving accidents, short term and long term?

Dr. Perkins: One of the reasons that question is important is it will provide the baseline against which we will measure the effect of any adjunctive therapy.

Dr. Chimiak: I submit that the ability to measure the effect of adjunctive therapy using a database of decompression disorders is going to be almost impossible, because of the large number of variables such as time to treatment, severity of symptoms, and the specific mechanism of disease, that is, AGE vs. DCS. While I applaud the effort, I think that the proof or disproof of adjunctive therapy is probably going to have to come from looking mechanisms in animal models.

Dr. Massey: Collecting large databases for trends are valuable. But as Jim said, if we are going to do an outcome study, we have to severely limit the outcome measures. That is done in studies of stroke or multiple sclerosis, for example using the Kurtzke scale for multiple sclerosis. For the first stroke study that I did here as a principal investigator, there were two of us, both senior professors of neurology. My colleague entered the first patient, who I thought was suffering from hysteria. Even after all those years we thought we had it made and I don't think we did. There's no question it's tough, but I think over the long term you could get a large, you could get rid of the ones that aren't really failed.

Dr. Bove: We need to get a consensus of experts to find a way to diagnose the various decompression disorders. The studies done on the most severe cases would be the easiest and most valuable ones, because they're the ones that need immediate diagnosis and treatment. But, there is a large population of people in the sport diving community who have the other end of the spectrum, the less than severe cases. Some of those cases are misdiagnosed, and provided with very inappropriate comments about prognosis. So I think the first piece, what Frank Butler wants to do, is to get the tough ones taken care of, with a standard for diagnosis and adjunctive therapy. That I think is what we should aim for, but I want to reiterate that there is a long tail of the population who are less severely affected. They show up in all our offices asking strange questions about what happened to them, which is difficult to work out because they haven't been well evaluated.

Dr. Freiberger: One last comment on why to do this is that such a study will have a policy outcome. The policies of, for example Divers Alert Network, on who is evacuated and when and at what cost and at what risk, will basically be supported or undermined by the results of the study.

Dr. Flynn: I want to change the discussion here slightly to the last case Dr. Reed presented, and try to tie it into the pathophysiology we're talking about. This was an individual who surfaced with early premonitory symptoms of spinal cord decompression sickness, recompressed more or less immediately, which you would expect to eliminate bubbles, yet deteriorates under pressure and develops a fixed lesion. We have seen a lot of these things over the years and we used to think this was spinal cord hemorrhage, for which there was no effective treatment. But what we heard previously was that maybe hemorrhage is not important. This particular case seems to argue against that.

Dr. Vann: Let me muddy the waters just a little bit, say you had a patent foramen ovale.

Dr. Reed: This individual's spinal cord was imaged, and he did in fact have findings on MR consistent with a midlevel thoracic spinal cord infarct.

Dr. Bove: Just to discuss patent foramen ovale (PFO), remember every 3rd person has a PFO, so I'm not sure that you can argue that the progression of the disease was due to the presence of a PFO. There are a whole bunch of unknowns, which is why we need to have some diagnostic criteria.

Dr. Flynn: Dr. Reed, what do you think was the pathophysiology in this case?

Dr. Reed: I tend to feel that infarct or hemorrhage following infarct seems to explain the course of these cases very well. Another case, with which I was painfully involved in Guam, ended in the individual passing. That individual's post mortem exam showed large amounts of hemorrhage into the substance of both the high thoracic and mid thoracic cord, and even brain stem. This was an individual who probably had combined AGE and DCI.

Dr. Piantadosi: I'll take a stab at it. What I thought at the time was gas in the cord, cord bubbles, decreased arterial perfusion, maybe with arterial gas from PFO. I'm not sure about that. There may have been just a cascade of worsening ischemia that ended up with an infarct on the MRI a few days later.

Dr. Flynn: Why did he deteriorate while he was under pressure?

Dr. Piantadosi: I'm not surprised it's out of phase though because I think the perfusion and the response of the gas of an injured area like that may be different than what we would model from a normal physiological system. So it may be that the cord ischemia is out of phase in some way with what you would expect from inert gas elimination. As we all know the bubble size issue is not the major thing here.

Dr. Butler: I think that case illustrates the potential value of a good understanding of the mechanisms and appropriate adjunctive therapy. You would expect from the fact that this deterioration occurred under pressure, that it was due to one of the possible secondary mechanisms, At this point we're not sure which one, but if we had a feel for which mechanism was involved perhaps the appropriate adjunctive therapy would be much more effective than the recompression or increasing the oxygen dose.

PATHOPHYSIOLOGY OF CNS INJURY: NEW CONCEPTS REGARDING TREATMENT

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Introduction

The pathophysiology of cerebral ischemia and trauma is complex and involves multiple injury cascades that may be sensitive to temperature variations[1,2] . Previous clinical and experimental studies have reported the benefits of moderate and mild hypothermia on ischemic and traumatic outcome[3-7]. In contrast, brief periods of mild hyperthermia, induced during or after the cerebral insult, have been shown to worsen histopathological and functional outcome[8,9]. Thus, temperature is an important variable in experimental models of CNS injury and clearly important in the clinical setting as well.

The underlying mechanisms of these temperature effects on injury outcome have been investigated in many laboratories[10,11]. Multiple pathophysiological mechanisms, including excitotoxicity, oxygen radical production, intracellular signaling cascades, cerebral metabolism, membrane stabilization, activation of protein kinases, cytoskeletal breakdown, and early gene expression have all been shown to be sensitive to mild temperature variations. Because the pathophysiology of ischemia and trauma are complex, the fact that multiple injury mechanisms are sensitive to temperature manipulations may account for the dramatic effects of temperature on ischemic and traumatic outcome. Indeed, several investigators have emphasized that hypothermia may be the most powerful neuroprotective therapy being investigated in the laboratory as well as the clinic.

Although therapeutic hypothermia holds great promise in the treatment of various neurological injuries, this treatment, like others, has limitations. For example, the recently reported failure of hypothermia to improve outcome in traumatic brain injury (TBI) patients from a multicenter clinical trial stresses the fact that additional preclinical studies are necessary to clarify conditions where therapeutic hypothermia is most helpful[12,13]. This presentation will summarize current knowledge concerning the pathophysiology of cerebral ischemia and trauma and discuss the importance of temperature on these processes.

Hypothermic protection in experimental models

The importance of small variations in brain temperature on ischemic outcome was first investigated in models of transient global forebrain ischemia[14,15]. These early investigations showed that even a 2° change in intraischemic and postischemic brain temperature critically determined whether CA1 hippocampal and striatal neurons were vulnerable to the ischemic

insult. While mild reductions in cerebral temperature improved histological outcome, mild elevations increased mortality, aggravated neuropathological damage, and accelerated the maturation of injury. These findings were supported by studies in cardiac arrest models where moderate hypothermia was also shown to improve histological and behavioral outcome[16,17].

In models of transient and permanent middle cerebral artery occlusion (MCAO), the benefits of moderate hypothermia have also been demonstrated[3,18-20]. Selective brain hypothermia during or after transient MCAO significantly reduced infarct volume. In one study, brain temperature reductions of 8°C were reported to provide complete neuroprotection following 80 minutes of transient MCAO[3]. However, under conditions of permanent MCAO, profound degrees of hypothermia (<30°C) and/or extended hypothermic periods appear to be necessary to provide significant neuroprotection[20].

Temperature has also been shown to be important in models of traumatic brain and spinal cord injury (SCI)[4,5,21-27]. In a model of fluid-percussion brain (F-P) injury, post-traumatic hypothermia (30°C/3 hr) significantly reduced contusion volume and the frequency of damaged cortical neurons[4]. After cortical impact injury, mild hypothermia (32-33°) initiated 30 min before TBI and continued for 2 hr also decreased contusion volume[23]. Post-traumatic hypothermia has also been shown to reduce the frequency of damage to axons[28,29]. Most importantly, behavioral outcome, including sensory and cognitive function, has also been shown to be improved with post-traumatic hypothermia[21,22,30].

Recently, the progressive nature of damage after TBI has been emphasized, with animals living out to 1 yr demonstrating significant degrees of gray and white matter atrophy[31,32]. Studies have therefore determined whether a restricted period of post-traumatic hypothermia leads to long-term protection. In one study, post-traumatic hypothermia (30°C/3 hr) significantly attenuated the amount of cortical atrophy and inhibited the subsequent increase in ventricular volume at 2 months after F-P injury compared to normothermic animals[33]. Thus, post-traumatic hypothermia appears to provide early as well as long-term neuroprotection.

Behavioral and histopathological protection with hypothermia has also been reported in SCI models[24-26]. Post-traumatic hypothermia (33°C/4 hr) was reported to decrease contusion volume at the T10 level and to improve motor recovery[24]. In contrast, post-traumatic hyperthermia (39°C) led to increased contusion volume and less functional recovery compared to normothermia[34]. Taken together, these studies using a variety of CNS injury models emphasize the importance of temperature on outcome.

Pathomechanisms

In addition to slowing oxygen consumption[35], hypothermia has been reported to blunt the rise in extracellular levels of excitatory amino acids after cerebral ischemia and trauma[36,37]. In a model of spinal cord ischemia, hypothermia also effectively attenuated extracellular glutamate release[38]. In contrast, hyperthermia (39°C) has been reported to increase levels of extracellular glutamate compared to normothermic ischemic animals after MCAO[39]. The

location of neurochemical sampling and injury severity remain important factors regarding neurochemical results with hypothermia.

Reactive oxygen radicals and lipid peroxidation play important roles in the pathogenesis of brain and SCI[40]. Several studies have reported that hypothermia attenuates lipid peroxidation and free radical production[38,41]. Using 2,3-dihydroxybenzoic acid (2,3 DHBA) as an indicator of free radical production, Globus and colleagues first showed that post-ischemic and traumatic hypothermia (30°C/3 hr) significantly reduced the extracellular levels of these radicals[37,41].

A recent series of studies have identified other pathomechanisms that may also underlie the beneficial effects of therapeutic hypothermia. Apoptotic cell death participates in pathogenesis of neuronal cell death after traumatic and ischemic injury[1]. Pro- and anti-apoptotic mechanisms have recently been clarified[42] and hypothermia may target some of these processes. In this regard, mild hypothermia has recently been reported to increase the anti-apoptotic protein, Bcl-2, following cerebral ischemia, a response that may protect against apoptotic cell death[43].

Inflammatory processes also participate in the pathogenesis of cerebral ischemia and TBI[44]. In this regard, post-injury hypothermia has been reported to reduce the acute accumulation of polymorphonuclear leukocytes (PMNL) and macrophages/microglia after injury[45-48]. In one study following transient MCAO, post-ischemic hypothermia delayed neutrophil accumulation and macrophage activation[45]. Similar results have been reported in trauma models where a reduction in PMNLs is seen with post-traumatic hypothermia[47,48].

The underlying temperature effects on these inflammatory processes are most likely multifactorial. For example, hypothermia has been shown to protect against blood-brain barrier (BBB) permeability in various ischemia and trauma models[49,50]. Also, recent data have shown that post-traumatic hypothermia reduces expression and levels of the pro-inflammatory cytokine, IL-1β after trauma[51]. It also appears that specific intracellular signaling cascades are affected by temperature, with post-traumatic hypothermia inhibiting the activation of the transcriptional factor, NF-κB[52]. Future studies are required to evaluate the effects of hypothermia on other transcriptional factors important in the production of genes that can regulate cell death.

Nitric oxide (NO) is a highly diffusible radical that may be toxic to neurons[1]. Under some pathological conditions, large amounts of NO are produced by the inducible form of NO synthase (iNOS) in various cell types. Importantly, post-traumatic hypothermia reduces the expression and activation of iNOS and NO production[53]. Thus, hypothermia may reduce NO production and secondary damage by targeting iNOS activity and decreasing the generation of cytotoxic agents, including peroxynitrates.

Factors regulating hypothermic protection

Although hypothermia is a powerful experimental tool by which to investigate the pathophysiology of CNS injury, there are limitations to its effectiveness, in terms of neuroprotection. For example, the therapeutic window for hypothermia may be limited to the

first several hours after injury[54]. Thus, early cooling (< 4 hr) appears to be most promising in experimental investigations. How long cooling should be continued and at what level is another complicated issue. Restricted periods of hypothermia (< 4 r) may provide only transient protection[55], with longer cooling periods being necessary for long-term protection[56]. Because extended cooling periods may lead to unwanted complications, including the increased risk of infection, the optimal duration of cooling needs to be clarified.

A recent factor that has emerged as a critical factor in hypothermic treatment is the post-rewarming phase. Several clinical and experimental studies have emphasized that the rate of rewarming after a hypothermic period can be a significant variable in determining whether good or poor outcome is achieved[57-60]. Thus, more controlled methods of rewarming, including the use of endovascular catheters, are being considered for this purpose[61]. In reference to the present discussion, the post-hypothermic rewarming period may be a critical phase of the treatment strategy where pharmacological interventions targeting reactivated pathomechanisms may be beneficial.

Finally, the importance of gender on the consequences of hypothermic protection has only recently been discussed[62]. Experimental data have emphasized, for several years, the importance of gender on the consequences of experimental cerebral ischemia or trauma, with intact females showing less damage compared to males[63-65]. Because most hypothermic studies have been conducted in male animals, an important question is whether hypothermic interventions are protective in female animals. Importantly, recent data indicate no significant effect of post-traumatic hypothermia on contusion volumes in female rats after F-P injury, whereas male rats show significant reductions[62]. These findings emphasize the importance of "the gender factor" in relationship to therapeutic hypothermia.

Conclusion

Although therapeutic hypothermia offers many advantages in terms of neuroprotection, more studies are required to determine the best ways to use and administer this treatment. Questions, including whether systemic or focal cooling should be conducted in specific patient populations is a critical point. Also, novel methods of imaging regional temperature gradients in patients should provide a powerful approach to assessing and treating this patient population. To date, hypothermic therapy has been tested primarily in relatively simple injury models. Thus, future studies are required to assess hypothermic protection in models complicated by secondary insults that commonly occur in patient populations. The combination of mild hypothermia with administration of pharmacological agents is also an exciting research direction. By recognizing the strengths and weaknesses of hypothermic therapy, researchers and clinicians hope to continue to move this powerful research tool into the clinical arena.

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DISCUSSION 4:

Dr. Molé: I'm curious about the cooling catheter that you showed. Do you introduce that through an intracranial bolt, or how is that catheter placed?

Dr. Dietrich: It's placed in the subclavian vein. There are other places you can put it but that's where we are putting it right now.

Dr. Flynn: The uncoupling of the brain temperature from the core body temperature, in which the brain rises and the rest of the body stays the same, implies to me that in order for the brain to heat up it either has to have a higher metabolic rate or a lower circulation. I'm wondering about the old time strategies of barbiturates and other things that reduce central metabolic oxygen consumption as a way of keeping those brain temperatures from rising, or is the problem there that as you lower the metabolic rate the cerebral blood flow is also reduced, with the end result being temperature elevation?

Dr. Dietrich: I think you are right about the barbiturates; they can lower both CBF and metabolism. We've done studies showing some of the beneficial effects of barbiturates are actually temperature dependent. You take away that hypothermic effect of barbiturates then you do not see any effect. So, there are a lot of PET studies going on now, in stroke patients for example, showing there are areas of hypometabolism that are associated with an increase in temperature. But at the same time blood flow is reduced so that heat does not get carried away, and it's staying in a particular area. But you have these islands of hyperthermia for example, adjacent to an area that may be hypothermic. So, that's what I was trying to emphasize, it's a very heterogeneous response in terms of regional profiles of temperature. The reason temperature goes up could also be hypothalamic dysfunction, and other things we don't even think about, such as infection. But the observation in many institutions is that in a large number of patients bladder temperature and rectal temperature do not correlate with brain temperature. A patient in an intensive care unit may have a mild fever, but it could be that patient has a very severe fever in the CNS. Because temperature affects so many of the cascades we talked about, it may override the benefit of normal therapy. The heat exchange catheter may be a way, instead of having two nurses always around with ice bags and things of that nature, of clamping temperature for the first time, or produce mild cooling, and maybe our drugs will work.

Dr. Vann: We've got pretty good evidence from some basic studies now that leukocytes are implicated in cerebral air embolism and probably also in cerebral decompression sickness. Given your knowledge of what's available, what would you recommend that would be worth while looking at to see if we could modify the effects of air embolism by focusing on leukocytes?

Dr. Dietrich: If you are going to target inflammation, we talked about temperature being important, so mild cooling has been shown by various laboratories, following vascular injuries and brain trauma and spinal cord injury, to reduce the acute inflammatory response. So maybe cooling might be one way. There are these potent anti-inflammatory cytokines: IL-10 and IL-6 potentially could actually reduce the detriment effects of acute inflammation. What we are doing in the laboratory now is continuing studies looking at the adhesion molecules that actually are important in the recruitment of the polymorphonuclear leukocytes into the area of injury. It has been tried before in stroke with not good results. But possibly continuing that type of discussion looking at antibodies that target certain sub-populations of adhesion molecules might be a way as well. The take home message is: that acute inflammatory response may be bad, and you may want to limit it, but at some time point those inflammatory cells, maybe not the polys, but the macrophages coming in actually have a reparative role.

Dr. Freiberger: I heard you say that iNOS is elevated post injury and that elevation is suppressed by hypothermia at 6 to 7 days. Did I miss this or is that through a decrease in white cell migration?

Dr. Dietrich: That's a good point. I don't think we actually know. If you do the immunocytochemistry and look at iNOS activity, many times it's in leukocytes and inflammatory cells. So hypothermia may be blunting some of the inflammatory cells within the tissues such as microglia and astrocytes, but also some of the blood-borne inflammatory cells as well. So we really haven't looked at it that closely. In that particular study we just looked at overall iNOS activity within the brain tissue itself.

Dr. Freiberger: A subsequent question to that: when you see the bad NOS injury are you able to quantify that with measurements of nitrotyrosine, DNA adducts, things that would be a result of the nitric oxide forming peroxynitrite.

Dr. Dietrich: In that regard, there are some studies that have looked at nitrotyrosine immunocytochemistry for example, and seen that it double labels with some of the markers of polys. So we've done that in iNOS ourselves so we see that relationship. But we haven't gone further in terms of looking exactly at some of the downstream mechanisms by which iNOS attenuation could actually damage tissue. We have just, based upon what some of the literature tells us, in some very preliminary immunocytochemical studies, targeted peroxynitrites and some of the radicals.

Dr. Freiberger: That's interesting also in terms of possible effect on apoptosis as well.

Dr. Goodman: I might follow up on that. A surrogate marker of nitric oxide activities is simply nitrate and nitrite, which are fairly easy to measure. In clinical studies we have found the good and bad side of nitric oxide that Dalton Dietrich mentioned. Early on, if a patient has low nitrate/nitrite levels following trauma it correlates with poor outcome. But later on, the secondary induced NOS shows up about 4 to 5 days after injury as you would expect, and then, if you survive to that point, iNOS is a bad player. Patients with elevated nitrate/nitrite do less well than the ones with decreased levels. So what we're doing in head trauma now, is trying to administer arginine early to augment endothelial nitric oxide production, then pulling back later on, because we don't want to give these macrophages any additional substrate to make NO. So, it may be, in developing these therapeutic strategies, that timing will be everything.

Dr. Dietrich: Timing is everything. In models of thromboembolic stroke where, just like the bubbles we talked about this morning, we're throwing emboli up to the brain. As an embolus flies by an endothelial cell it 'tickles' that cell. It doesn't produce a lot of damage but something happens between the platelet and endothelial cell and all of a sudden NOS activity goes down, eNOS production goes down. What is the importance of that? If that vasculature is sitting there and a secondary insult comes along, if that vessel should dilate and it doesn't dilate, it produces some very important stresses on the system. So in that case you want something that can actually up regulate eNOS, maybe using the statin drugs, or something of that nature.

Dr. Massey: A clinical question is, do you know what alcohol does to this system? In about 75% of our spinal cord injuries alcohol is involved. Alcohol may not be 'on board' in that many, since it may be another person who is intoxicated. That is much different from 10 years ago. Cocaine is also more commonly involved now than 10 years ago. Do you have any information on that?

Dr. Dietrich: I think several groups are looking at alcohol, cocaine, caffeine and combinations of these. All of these can be neuroprotective in their own right. How they are neuroprotective, in terms of some of the pathophysiology we talked about today, I don't really know. Some of these produce hypothermia for example.

Dr. Massey: I would have thought alcohol would have produced hyperthermia.

Dr. Dietrich: It depends on whether you are currently drinking, or sometime afterward. I don't know.

Dr. Warner: I think I just read about a trial that was just getting off the ground using something called caffeinol, which is a combination of caffeine and alcohol, for treatment of stroke. I think it's a clinical trial.

Dr. Dietrich: I think Jim Grotta (of the University of Texas Medical School at Houston) talked about that a couple of meetings ago. He thought that was the most potent combination of neuroprotective strategies he'd ever seen.

Dr. Massey: It certainly would complicate care.

Dr. Bove: We have done some studies on how alcohol and cocaine affects the vascular system. Both of them are vasoconstrictors as it turns out. If you measure peripheral vascular resistance or if you look at large vessel dimensions and you infuse ethanol you get vasoconstriction. The resistance of the systemic and coronary circulations both of those go up with ethanol infusion. Ethanol causes hypertension, which we have known that for a long time. Cocaine is a very potent vasoconstrictor. That's one of the reasons that it causes myocardial infarctions - it causes significant coronary spasm. There are similar data for cocaine in the cerebral circulation. I'm not aware of the affect of alcohol

on the cerebral circulation. So those are, from my standpoint detrimental agents, at least from the circulatory standpoint. They are both potent vasoconstrictors.

Dr. Massey: In our situation these would all be on board at the time of the injury.

Dr. Warner: In the clinical trial I just mentioned don't think they are using an inebriating dose of alcohol. I think they are talking about very small doses that maybe aren't going to be a clinical care issue.

Dr. Flynn: In spinal cord decompression sickness, the event is pretty much over in about the first hour of the evolution, and all of the things that you showed were measured in hours and actually out into days.

Dr. Dietrich: Just to clarify, why did you make that statement?

Dr. Flynn: Because that's what happens. It's usually a very rapid onset disease.

Dr. Dietrich: It's a rapid onset disease, but not everything may be over that quickly.

Dr. Flynn: The full presentation is pretty much there within an hour of the onset in most cases. The question pertains to this: the only thing I saw there was the early accumulation of the neutrophils, which look like at 3 hours they were the same as they were at 24 hours. I was wondering if you or anybody else had looked at lidocaine inhibiting adhesion and preventing that early leukocyte accumulation, and whether you think that would be a reasonable strategy for spinal cord decompression sickness, because the drug is extremely easy to use.

Dr. Dietrich: I asked around the table at lunch the mechanisms for lidocaine protection and I don't know what they are. So, I think yes, it is possible that it may have an effect on inflammation. I do not know of any studies that have assessed that. I would like to emphasize that the acute injury mechanisms we talked about: excitotoxicity, release of glutamate, free radical mediated damage, release of pro-inflammatory cytokines could happen relatively fast, producing blood brain permeability, hemorrhage and so. So, some of the acute injury in terms of the structural changes can occur relatively quickly, but my point of the talk is that after that occurs not everything is turned off. It continues, and there are other types of injury mechanisms that, although there may not be sensitive way to see this happening in a patient in terms of neurological outcome, the cellular interactions and processes are very robust for maybe weeks or months after injury.

Dr. Flynn: One of the early uses of lidocaine was to elute neutrophils off filters. That's how this anti-adhesion property was determined.

Dr. Dietrich: I was talking to somebody today about hyperbaric oxygen potentially decreasing inflammatory processes, so that might be something interesting to look at as well.

Dr. Chimiak: In trauma, what would you surmise to be the effect of the coagulopathy that you are going to induce with hypothermia in a trauma patient?

Dr. Dietrich: That's a concern with deep hypothermia. I remember the studies in the 1950's and 1960's were looking at profound hypothermia. More recent studies have led to the understanding that just a 1 or 2 degree decrease in temperature was beneficial. So, although you still have to be concerned about some of the effects of temperature on coagulation systems, that really hasn't presented a major problem in clinical studies as of yet. This is because of the mild level of hypothermia we are now producing. It is still something that has to be looked at, so I think most clinicians that are using hypothermia routinely check coagulation function to make sure. But it's not a severe consequence of the mild hypothermia that we're producing in people. We have a paper shortly to be published in Journal of Neurosurgery looking at hemorrhage and coagulation systems for the first time in a reproducible model of traumatic brain injury. We saw very, very mild effects. So I think they're there; it has to be a concern. Hypothermia is not a perfect treatment, so it is one of the limitations we have to look at, but so far it's something that we can deal with.

Dr. Moon: To what extent are the excitotoxic amino acids important in spinal cord injury as opposed to brain injury?

Dr. Dietrich: I think in the last several years it's become clear to people in the field that we've been spending too much time thinking about gray matter and not white matter pathology. I think the more we understand the pathophysiology of white matter damage, we're now understanding what

oligodendrocytes are sensitive to. Oligodendrocytes seem to be sensitive to excitotoxic mechanisms. In terms of spinal cord injury, a lot of studies are coming out now looking at the excitotoxic mechanisms targeting progressive white matter pathology after spinal cord injury. In terms of the brain we used NMDA receptor blockers for many years, and like other people found that in rodent models these produced hypothermia, and were really of very little benefit. I think we have to continue to think about new receptor blockers that may be more selective for white and gray matter. I feel that some of the more robust excitotoxic process that occur after brain and spinal cord injury occur relatively quickly, and come and go before someone can actually administer a drug to block them. So there may be some limitation in terms of therapeutic window.

Dr. Moon: Two other questions. First, what has happened to poly (ADP-ribose) polymerase (PARP) inhibitors? Second, with all of these data suggesting that hypothermia is such a good idea, why are the clinical studies not positive?

Dr. Dietrich: PARP inhibitors are still being looked at, and are believed to be very important in some of the apoptotic mechanisms we talked about. I don't know where they are going clinically. How to deliver these agents and whether they are selective for the important areas of the cascade is still being discussed as drug development continues. Why hypothermia is not a grand slam is complicated. In the trauma studies the patients didn't get hypothermic treatment for eight hours. Personally I have never shown the benefit of hypothermia in the lab after 2½ hours, so the therapeutic window may be important. In terms of the re-warming phase, it's clear that how fast you re-warm a patient or rat after hypothermic therapy is critical. A group in Germany is doing a lot of studies on using ICP as an indicator of how fast you can re-warm. I think in the clinical studies the patients were rewarmed too fast, which might have had a detrimental effect on the benefit of the hypothermia. I understand from a lunch discussion that there are some papers coming out soon showing dramatic effects of hypothermia in cardiac arrest patients[1,2]. I think we are continuing to learn how to use hypothermia. It's not a drug; you just can't inject it and walk away, but it's a strategy for which the gut feeling is that it affects so many pathophysiological processes it's going to be the type of strategy that you are going to need to produce neuroprotection, long term improvement in function. I think we just have to learn how to use it, but maybe it's going to be best to use it in combination with drug therapy. Maybe there are certain very potent pathophysiological mechanisms that need to be targeted by receptor blockers or certain other types of drugs, and then perhaps mild cooling on top of that may be the answer.

Dr. Warner: You mentioned glutamate antagonists, and we all know that they aren't going anywhere in stroke, but the problem with that is that the stroke patient is going to come to the hospital on average 3 to 6 hours after onset of symptoms in this country. In contrast, taking us back to the topic here, I've never seen a person with the bends, but my impression from the discussion is that these people come up and they start getting sick soon. In my laboratory MK801 [dizoclipine] in an animal that has brain temperature clamped in a focal ischemic insult is a miraculous drug. With it we can stop stroke, no question about it. If I had a stroke I would go to my lab, not to the hospital. Perhaps, because of the unique onset of decompression illness, in a setting where there are other people around, it may be possible to administer a glutamate antagonist quickly enough for it to have a therapeutic effect.

Dr. Dietrich: That's possible, and as you know there are now drugs that do not have the side effects of MK801, in terms of the psychotic problems. There are very nice drugs out there that target the NMDA and the AMPA receptors and so this approach may be worth a shot.

Dr. Warner: I share your impression of the field, in that we will probably end up with a combination of therapy. We treat hypertension, we treat cancer, and if you are going to get an anesthetic you are probably going to get 8 or 10 different drugs by the time you are out of the operating room, and we do that because we target different receptors and different mechanisms of action that cumulatively result in an effect that we call our treatment. That seems to be the direction in which the research against acute CNS injury is headed. But, my experience in the laboratory is that it's virtually impossible to have two proprietary substances and get permission to mix them in the same rat. The corporate proprietary right structure is such that it's very difficult to overcome that issue. Then if you go to the human, there is the whole FDA regulatory component of mixing two drugs, particularly if neither has proven efficacy independently. So where's your sense of the future for working through combination therapy as a treatment for these diseases.

Dr. Dietrich: It's going to be difficult; you bring up an important problem. We're dealing with that now with methylprednisolone, where many of us feel there are better drugs currently available than methylprednisolone in terms of treating acute spinal cord injury. Yet when we try to get funds from a pharmaceutical company to actually test the drug they want to do it separately, not a combination with methylprednisolone. However clinically, because of the legal ramifications of the use of methylprednisolone right now I think the drug will have to be given with methylprednisolone. So it's problematic, I think a suggestion would be that we may not mix the drugs, we may give a drug immediately after injury to target a very robust pathophysiological mechanism that lasts for several hours, and then maybe a day later we'll give a second class of drugs that targets an inflammatory or apoptotic mechanism. Currently the groups using TPA are very excited about combining TPA with anti-apoptotic agents for example, because that's the population of stroke patients you are going to get in early, and you're going to be able to treat early. So there's discussion among biotech companies and institutions to actually combine, but I appreciate your point. It's a difficult one.

Dr. Thalmann: What's the status of methylprednisolone. Steroids have had a spotty record in the treatment of spinal cord trauma: you see them come into vogue and go out of vogue. We have a neurologist at NMRI in Washington who theorized that if you were going to use a steroid in diving disease it's methylprednisolone theoretically which would probably the best one, because it does have some anti-free radical action. But then there have been those big spinal cord studies for which there seems to be some doubt about whether the outcomes were really as good as they made them out to be. Can you look up methylprednisolone with a jaundiced eye and tell me exactly what the status of methylprednisolone is in spinal cord injury?

Dr. Dietrich: Well, I think there's a lot of controversy in everything is just touched upon. Many people trying to get hold of the primary data so they can re-evaluate it themselves, because they question some of the conclusions made from those clinical trials. Our own laboratory has used methylprednisolone in mouse and rodent models of spinal cord injury and found no effect whatsoever. So to answer your question directly, I think it's coming out of vogue and there's actually a neurosurgical group in Canada that are getting together to make a statement about not using it, so they can potentially use other drugs. Again, getting to terms with the legal ramifications of not using a drug, and being liable for that particular action, is very important. But I think many people echo what you just said; they question the clinical trials and some of the conclusions made. Maybe there are other drugs out there that we should be trying. That's complicating my life because some of the drugs that I talked about today, when I give them in a combination with methylprednisolone, they do not work. So that's the dilemma we have here right now.

Dr. Thalmann: And of all the drugs you've tried, which one do you think is the closest you would recommend to try to push forward for human trials?

Dr. Dietrich: First would be temperature monitoring and mild cooling; that's the one I would like to push first. But the second is fibroblast growth factor 2 (FGF2). Fibroblast growth factor seems to be very potent in dilating vessels and improving perfusion, which you have to have, and then, more recently, inhibiting apoptotic cell death. The third one is IL-10. I think the anti-inflammatory strategies are going to be important, we just have to figure them out. We have to make sure that anti-inflammatory strategies are targeting the inflammatory cells that make things worse, not the ones that are reparative.

Dr. Thalmann: Getting back to what we talked about earlier, what's your take on the models that you use to create spinal cord trauma as applying to what we think we know about what causes spinal cord decompression sickness. Do you think that they're so different that you have to say these drugs look promising but we're going to have to go back to square one and try them in a decompression model because you're not confident that your trauma model right now would be useful?

Dr. Dietrich: As I mentioned, I think some of the structural and biochemical changes we see in a spinal cord trauma model seem to be similar to that seen in what we heard about today in terms of decompression illness. The embolization, the endothelial damage, the blood brain barrier changes, the edema, the perivascular hemorrhage, are all things that we can mimic with our spinal cord trauma models. So I think there are probably a lot of similarities and therefore things that you may have a gut feeling that worked in this particular

illness, most likely they should be tried in more conventional models of spinal cord trauma.

Dr. Latson: For your mild hypothermia, how do you propose to accomplish it and how do you inhibit the body's natural attempts to raise temperature back up?

Dr. Dietrich: Conventionally we've given things that target infection, antibiotics and things like that. What we've done with clinical studies in hypothermia are cooling blankets above and below the patient. Now we're turning to the use of heat exchange catheters.

Dr. Latson: You don't get shivering in an attempt to overcome the attempt to cool?

Dr. Dietrich: After we first made some of these original observations, when we talked to neurologists and suggested we should be doing this in stroke patients, they said "no way, because the stroke patient has to be awake for my neurological exam". When we apply it to patients with spinal cord injury or traumatic brain injury are sedated, so we do not have those effects of shivering. But in an awake patient, shivering will occur, and therefore you may not be able to get the temperature down too low because of the effects of the response to hypothermia.

Dr. Latson: So that would be pretty difficult to reply in a situation where you had a diver with a paraplegia but was mentally alert.

Dr. Dietrich: Maybe just mild cooling would be enough, and then maybe you'll have a drug on top of that. Maybe the combination of mild cooling and what you are doing currently may have a positive result. Mild cooling may potentially inhibit hyperthermia, which is happening in the CNS, which you probably do not appreciate because you don't measure it.

Dr. Southerland: With regard to ambient temperature, since it often takes several hours to get a patient from an accident scene into the hospital, and in a cold climate mild hypothermia may occur spontaneously, are there any differences in outcome comparing the seasons?

Dr. Dietrich: We are not allowed to participate in Guy Clifton's next round of multicenter trials in TBI because he was requesting patients to come in to the emergency room mildly hypothermic, and none of our patients in Florida come in to the emergency room mildly hypothermic. In other places they do, so yes, ambient temperature is a factor which you have to deal with. It is going to affect CNS temperature to some degree.

Dr. Warner: In the Clifton study[3] I think they did a post hoc analysis. Patients who came to the hospital cold and then were randomized to the cold group, in fact did do better than patients who came to the hospital cold and were randomized to the warm group. Since it was a post hoc analysis, they didn't allow the authors to draw a conclusion based on that. I'm pretty sure that the ambient temperature effect may be critical.

Dr. Massey: In that setting, when they say hot and cold they are not talking about the brain or the CNS, they are talking about the periphery. EMT's are taught to put blankets on patients and keep them warm. Is that representative?

Dr. Warner: The paper didn't give the details about the latitude in which the accidents occurred or the seasons for that matter. Although I've been following the brain temperature literature and I agree with you that the temperature, the esophageal temperature for example, will not tell you what the temperature in the brain is. There will be a difference ranging from about 0.5 to 1.5°C, but I can't think of any study in which the brain temperature was lower than the core temperature; as measured either with a thermistor and a pulmonary artery catheter or esophageal thermistor. In other words, in most cases where the core temperature has been measured it was underestimating the brain temperature. So regarding temperatures reported in clinical studies, probably the brain was warmer.

Dr. Massey: I was assuming your hypothermia treatment was early. What about in 7 days, is there any effect because that's the maximum inflammation time. Would it have an effect on the inflammation?

Dr. Warner: I don't think anyone has done that and looked at inflammatory effects. In our models, polymorphonuclear leukocytes accumulation occurs 1, 2 or 3 days after injury. So that's what we are trying to target. We may find out that to affect inflammation we have to cool early just because of affecting some of the pro-inflammatory cytokines and some of the signaling cascades adhesion molecules that need to be up-regulated first before the polys are called in. So if you don't inhibit those upstream effects you may have a problem affecting

polys. We haven't done that experiment. We wanted to have babies in the intensive care unit to be warm and happy too so we would put blankets on them and warm them up but that's completely been done away with now. We would like to save the CNS.

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ADJUNCTIVE TREATMENT STANDARDS FOR DECOMPRESION SICKNESS AND GAS EMBOLISM: THE SPECIAL OPERATIONS PERSPECTIVE

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Most military diving operations have the advantage of being able to provide rapid recompression for the victims of decompression sickness (DCS) and arterial gas embolism (AGE) that may result from these operations. When stricken divers are treated without delay, the success rate of standard recompression therapy is very good[1, 2].

Special Operations forces, however, may not have the benefit of a chamber nearby. The 1996 Undersea and Hyperbaric Medical Society (UHMS) workshop on the Tactical Management of Diving Casualties in Special Operations[3] emphasized that SEAL, Special Forces, and Pararescue diving operations are often conducted in remote areas or under other conditions that may entail a lengthy delay should a diver require recompression therapy. Delays to treatment significantly increase the probability of severe or refractory disease.

What can be done for these casualties during the interval prior to recompression? There is general agreement about the efficacy of surface oxygen, but little consensus beyond that. Doctor Ed Flynn recommended the use of lidocaine for the treatment of AGE based on efficacy shown in animal models[3,4,5], but diving physicians have been slow to transition lidocaine into clinical use in treating AGE. The U.S. Navy Diving Manual[6] recommends its use as an adjunct to recompression, but only for DCS. The efficacy of lidocaine in treating DCS has not been documented by controlled human or animal trials. In contrast, there is no recommendation to use lidocaine for AGE, an indication supported by both animal and now human[7] data. The use of corticosteroids is controversial, and, although recommended in the Navy Diving Manual, it is not recommended by some leading experts in diving medicine[8]. There is general agreement that fluids should be part of the therapy for dysbaric diseases, but little consensus or data about the optimal type or amount of fluid to use.

Determination of the optimal adjunctive therapy for DCS and AGE has been hampered by at least two factors. The first is a lack of human trials in this area. Prospective human trials on adjunctive therapy for DCS and AGE are difficult to do for several reasons: 1) DCS and AGE are relatively uncommon diseases; 2) when administered promptly, recompression therapy and hyperbaric oxygen generally provide complete relief of symptoms, making the added benefit of adjunctive therapy difficult to determine; and 3) there has been little interest in funding this type of study on the part of the U.S. Navy or civilian diving organizations.

A second major problem is that no specialty medical organization has undertaken to develop and maintain definitive guidelines for treating DCS and AGE. The U.S. Navy Diving Manual provides adjunctive therapy guidelines, but the recommendations are not presented in a referenced medical format nor do they necessarily represent a consensus opinion of diving physicians. The Undersea and Hyperbaric Medical Society is the best-recognized medical specialty organization in diving medicine in the world and is the natural choice to undertake the development of a definitive set of adjunctive therapy guidelines for the treatment of DCS and AGE.

The need for this research effort was established by the Naval Special Warfare Command[9] in 2001. The proposed project consists of three parts:

> 1) the formation of a standing UHMS committee to review the literature on the treatment of decompression sickness and gas embolism and make recommendations for therapy based on the information available.
>
> 2) a special focus on the pre-recompression phase of treatment, which may be prolonged in Special Operations.
>
> 3) recommendations for future research efforts to study the most promising new treatment modalities.

A separate research effort being planned by the U.S. Special Operations Command Biomedical Initiatives Steering Committee for next year will examine the underlying mechanisms of severe refractory neurological DCS and AGE. The proposed study would undertake neuroimaging and serum assays on individuals with severe, refractory neurological deficits following recompression. This study will help us to better understand the nature of the brain and/or spinal cord lesions involved and the underlying mechanisms that caused them.

In both studies, an attempt will be made to distinguish between DCS and AGE. Although they have in common the presence of a gas phase in the body and a generally good response to recompression and hyperbaric oxygen, the underlying pathophysiology may be somewhat different. DCS in air diving produces nitrogen bubbles whereas a SEAL diving a closed-circuit oxygen UBA who suffers an AGE will have bubbles composed of nearly 100% oxygen. DCS always entails a significant tissue inert gas load; AGE does not. Intravascular bubbles in DCS evolve over a period of time, where AGE may result in a single release of bubbles into the pulmonary veins. Marked and consistent elevations of serum creatine kinase have been documented in AGE[10], but not in DCS. The venous infarct mechanism of spinal cord injury reported by Hallenbeck, Bove, and Elliott[11] in DCS has not been reported in AGE. Progressive peripheral nerve palsies have been reported in DCS, but not in AGE[12]. Clearly, the pathophysiology may be somewhat different in DCS and AGE and there is no a priori assurance that optimal adjunctive therapy for DCS will be the optimal adjunctive therapy for AGE. The implication of this fact for the current effort is that in evaluating case reports and case series, an effort should be made to discriminate between DCS and AGE

where possible. Appropriate animal models for each entity should be developed and proposed new therapies should be tested in both models. This approach will allow adjunctive therapy to be optimized for each entity.

Mr. Don Chandler, the Executive Director of the UHMS, and Dr. Richard Moon, Medical Director of the Divers Alert Network and Chairman of the UHMS Adjunctive Therapy Committee, are to be commended for their efforts to date on this project. The internationally respected panel of expert physicians and physiologists that they have assembled is uniquely qualified to address the complex issues involved in determining optimal adjunctive therapy guidelines. The efforts of this committee should be of great benefit to Special Operations divers in the future. They should also be of great benefit to the recreational diving community, whose members are also often injured in remote locations and have long delays to recompression.

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REQUIREMENT FOR ADJUNCTIVE THERAPY IN RECREATIONAL DIVING

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Statistics on recreational diving accidents are collected by the Divers Alert Network (DAN), established in 1980. Accident statistics and reports (Dive Accident Report Form, 'DARF') are collected and stored in a database. Approximately 1000 recreational divers with decompression illness (DCI) are reported each year; on about half of these, reports with sufficient detail to be included in the database (Fig. 1).

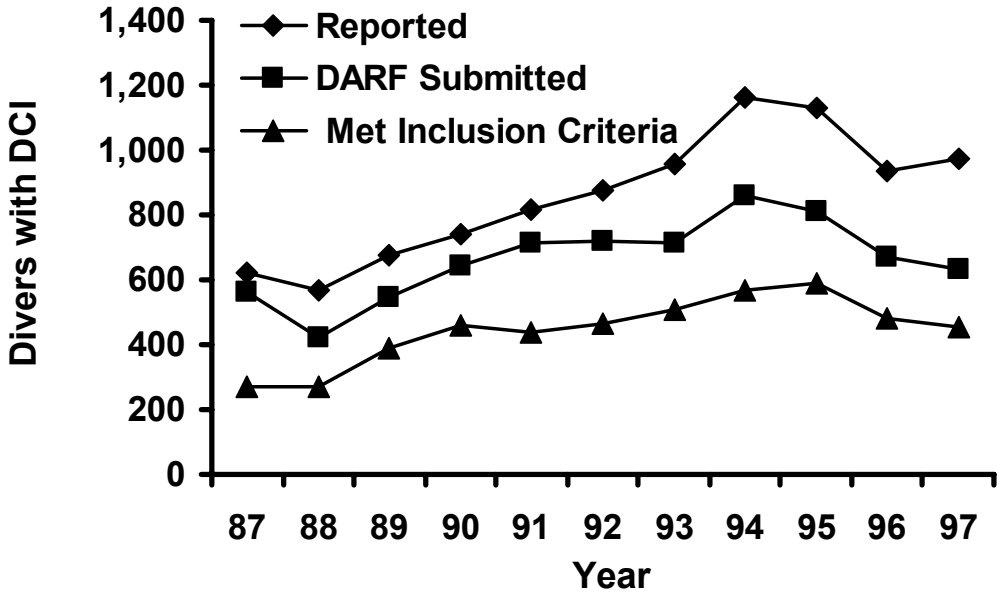

Fig. 1. Cases of DCI in recreational divers reported to the Divers Alert Network, 1987-97.

While many of these divers have relatively minor complaints, from 5-10% have manifestations that impair consciousness, motor strength or urinary sphincter control (Fig. 2).

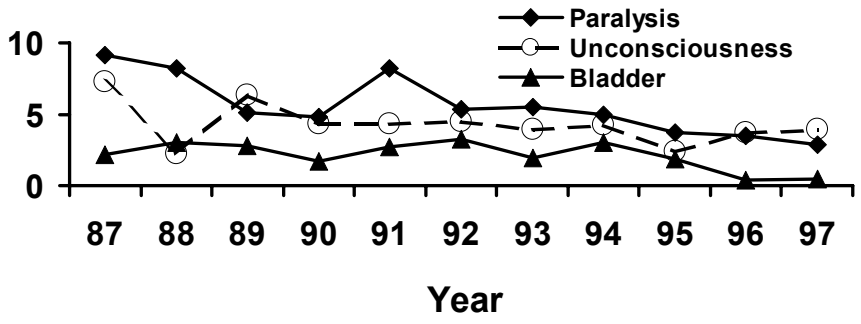

Fig. 2. Serious manifestations in DCI in recreational divers, 1987-97.

In parallel with increasing availability of hyperbaric facilities with physicians skilled in the evaluation and treatment of diving injuries, and 24-hour availability of telephone consultation through DAN, the proportion of patients treated using standard-of-care recompression tables is high (Fig. 3).

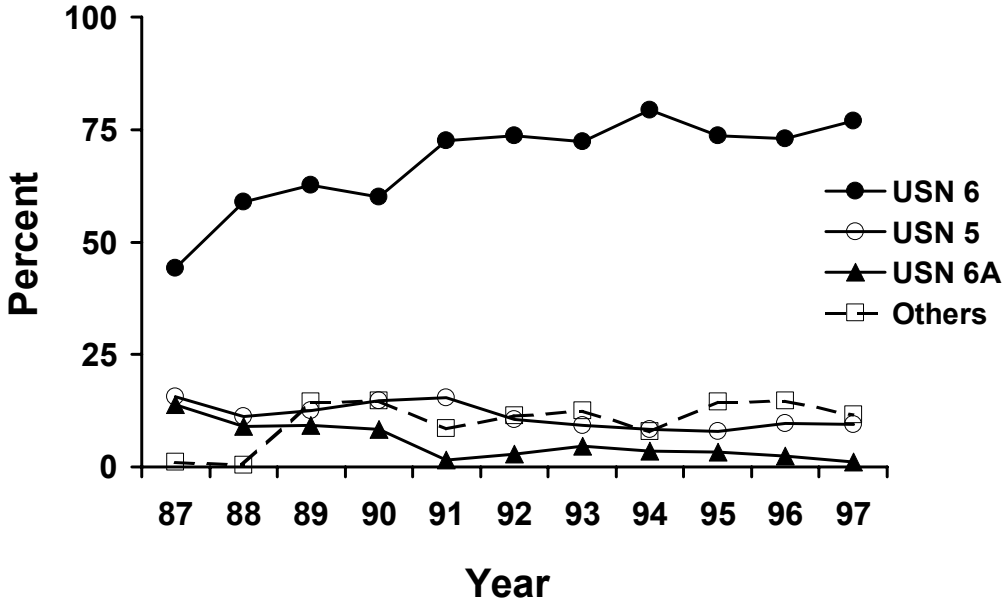

Fig. 3. Treatment tables used for DCI in recreational divers, 1987-97.

Nevertheless, nearly 40% of divers do not experience complete relief after recompression treatment (Fig. 4).

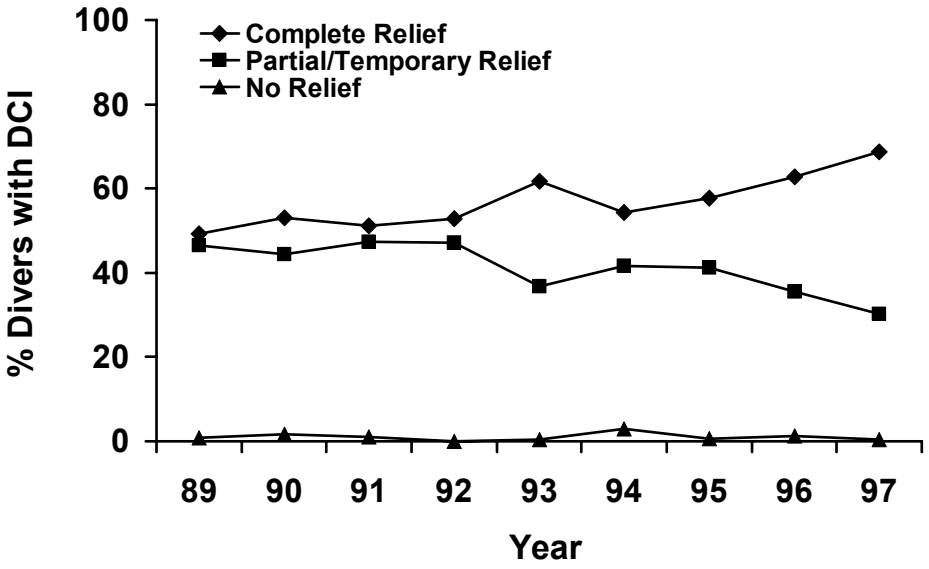

Fig. 4. Outcome of recompression treatment in recreational divers, 1989-97.

The high proportion of divers with incomplete response to recompression is probably in part related to delay to treatment. For the last 10 years, the median time from symptom onset to recompression is close to 24 hours (Fig. 5).

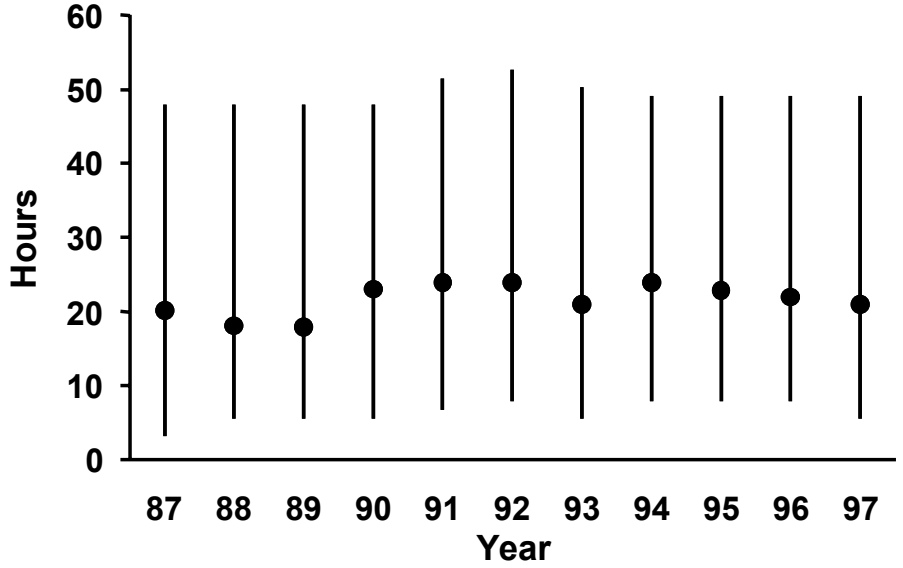

Fig. 5. Time from symptom onset to recompression treatment in recreational divers, 1987-97. Closed circles represent median; lines represent 25th and 75th percentiles.

The delay is caused by limited accessibility to recompression facilities and lack of recognition.

The need for some additional pharmacological treatment is obvious. The onset of severe symptoms is usually shortly after surfacing, and hence almost invariably in the company of a diving buddy. The interval between symptom onset and treatment represents a window of opportunity in which a treatment could be administered. A precedent exists for first aid treatment of medical emergencies. First-aiders have been trained to treat cardiac arrest with defibrillation and artificial respiration, and to administer epinephrine to victims of anaphylaxis. A large cadre of divers has been trained to administer surface oxygen. If a safe pharmacological treatment for DCI can be identified, pharmacological treatment of severe DCI could begin immediately.

SPACEFLIGHT DECOMPRESSION SICKNESS CONTINGENCY PLAN

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Within the past few years, NASA Medical Operations has undertaken an effort to develop an enhanced plan to diagnose, treat, and manage Decompression Sickness (DCS) which may arise on-orbit during Extravehicular Activity (EVA), commonly referred to as Spacewalks.

With the construction of the International Space Station (ISS), a substantial number of EVAs are required to both build and maintain the ISS in the years ahead. This substantial increase in EVA activity has been referred to as the "Wall of EVA". Although neither the U.S. nor Russian space programs have experienced a reported case of DCS to date, it is imperative to formulate appropriate treatment and management strategies. The U.S. spacesuit, know as the Extravehicular Mobility Unit (EMU), normally operates at 4.3 psi (30,000 ft). A variety of oxygen prebreathe strategies are utilized for the EMU to enhance denitrogenation and minimize the potential of DCS. These options include: a 4-hour in-suit oxygen prebreathe, a "staged" decompression of the Space Shuttle to 10.2 psi for a minimum of 12 hours prior to suit donning and a 40-min to 75-min in-suit prebreathe, and for International Space Station Airlock operations, the July 2001of the Exercise Prebreathe Protocol. The key features of this total 2-hr 20-min protocol include a ramped 10-minute cycle ergometry session to 75% VO_2 max on 100% oxygen at 14.7 psi, subsequent suit donning at 10.2 psi, and a final 60-min prebreathe. A coated aspirin (325 mg) is currently taken by EVA crewmembers in all prebreathe protocols prior to suit donning. The Russian Orlan operates at a higher pressure, 5.8 psi, with a 30-minute oxygen prebreathe.

A multidisciplinary team was established at the Johnson Space Center to help formulate the DCS Contingency Plan. The team included representatives from Medical Operations, the Astronaut Office, Flight Directors, the EVA community, and the Mission Operations Directorate. Military, civilian, and commercial-diving experts were consulted throughout the effort. Extensive reviews were completed of the DCS treatment literature and DCS databases.

Key elements of the DCS Contingency Plan include: EVA "Cuff Classification" system development, improved on-orbit DCS treatment, DCS Flight Rules development, and a NASA - JSC DCS Disposition Policy.

The EVA "Cuff Classification" system is an "operational" classification of DCS symptoms. A crewmember experiencing symptoms during an EVA verbalizes to Mission Control a Cuff Class number based on symptoms and level of interference with performance (via checklist

cards located on the EVA suit forearm). A pre-established response plan is then followed which may include termination or abort of an EVA with appropriate "safing" activities of the Shuttle/ISS EVA worksite as required. By establishing predetermined operational responses, this standard system for communication of symptoms to the Mission Control team is designed to maximize the health and safety of crewmembers. The Cuff Classification system also serves as the basis of formulating "simulated DCS scenarios" for the Mission Control flight team and EVA crewmembers to rehearse during pre-mission training.

DCS treatment flows were developed employing the general concepts of diving treatment tables. The principle tenants of treatment include oxygen and pressure over time, with fluids and medications as adjunctive therapy. Database analysis reveals that the return to ambient pressure from the 4.3 psi hypobaric environment of the EMU is anticipated to result in the resolution of nearly all Type I (pain-only) symptoms (96%), with further treatment efficacy achieved with the addition of ground level oxygen. A significant percentage of Type II (serious) symptoms are also anticipated to improve with a return to ambient pressure. A desire existed to not just treat the symptoms, but also treat the gas phase causing such symptoms with higher pressures, and longer times, than simply 2-hours of ground level oxygen. Unless an effected crewmember is severely compromised, they will remain in the suit during the initial phases of treatment with the EMU serving as the treatment vessel. Many technical aspects were taken into consideration when addressing the treatment challenge of a suited crewmember, including communications, EMU and vehicle configuration, suit consumables, and airlock repressurization procedures. Treatment outlines were subsequently converted into Malfunction (MAL) Procedures, which follow the checklist format and decision trees that astronauts are accustomed to using.

Efforts were also successful in modifying procedures for use of the Bends Treatment Apparatus (BTA), designed to increase suit pressure to as much as 8 psi above ambient pressure. Previous installation procedures of this small device on the suit required an approximate 30-min period during which the helmet is removed and lower torso harness lowered. A crewmember would be breathing ambient air during this period since oxygen mask use is prohibited by the EMU neck ring. The BTA can now be attached on the EMU in series with the positive pressure relief valve to allow the EMU pressure to increase without breaking the integrity of the suit. This provides a total treatment pressure of up to 22.7 psi (8 psi suit + 14.7 psi cabin ambient) if symptoms have not resolved during earlier phases of the treatment flow.

Medical kits are flown on both the Space Shuttle and the ISS. Although constrained by available size and weight, they are designed to address a broad range of medical conditions based upon prior spaceflight experience and anticipated illnesses and injuries. Post suit-doffing medical treatment includes oral or IV hydration, as well as additional oxygen by facemask. The Shuttle medical kits currently contain 3.1 liters of normal saline, with 12.1 liters of normal saline aboard the ISS. At the present time, no other adjunctive medications are currently flown for specific support of DCS treatment.

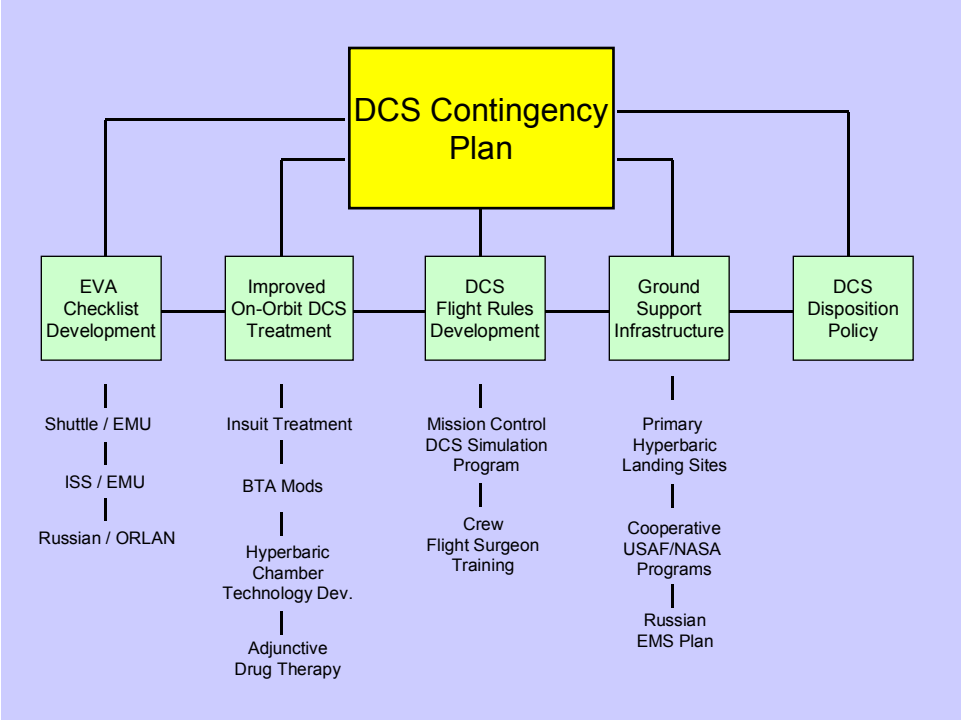
A simple DCS Neurological Exam was developed which can be performed on an EVA crewmember, by a non-physician astronaut, as a tool to assess signs and symptoms over time.

The exam was created to assess motor and neurological functions when evaluating a crewmember either fully suited or with the suit doffed.

Currently no hyperbaric chamber has been identified to fly on the ISS. Continuing analysis will determine the technical feasibility and merit of portable hyperbaric capability. Thus, the availability of adjunctive pharmaceuticals which can be used safely and effectively on-orbit for DCS treatment would be of great potential benefit.

"Flight Rules" are pre-established procedures developed for the Flight Control Team in Mission Control to respond to a variety of potential mechanical and operational scenarios throughout all phases of flight. They seek to avoid miscommunication across disciplines and maximize effective decisions. Flight Rules have been developed for EVA which deal with "oxygen payback" ratios for breaks in prebreathe, specify deorbit requirements to designated worldwide Primary Hyperbaric Care sites, and address both resolved and unresolved Cuff Classes. The NASA - Johnson Space Center DCS Procedures and Guidelines directive was created to define appropriate medical disposition after a DCS event. It includes guidance for return to duty, return to reduced pressure exposure and EVA, and appropriate aeromedical board review. The directive encompasses Spaceflight, EVA immersion training facilities, NASA aircraft operations, and ground chamber activities.

NASA has a strong continuing commitment to assure the health and safety of astronauts and to enhance the performance of EVA activity. Utilizing expertise from both within and external to NASA, a "system" is now in place to more effectively address a potential case of DCS on-orbit. Efforts of the Undersea & Hyperbaric Medical Society (UHMS) Adjunctive Therapy Committee to further elucidate adjunctive pharmacological therapy for DCS would have tremendous applicability to the operational setting in space.



EVA CUFF CLASSIFICATIONS

Cuff Class	Symptoms	Response
1	**Mild pain**, at single or multiple sites and/or single extremity paresthesia. Difficult to distinguish from suit pressure points. ***-Symptoms do not interfere with performance.***	Report in post EVA Private Medical Conference (PMC). No future EVA impact.
2	**Moderate cuff 1 symptoms that interfere with performance.**	Terminate EVA for both crew members, perform worksite clean-up only, minimize activity of affected crew member. Perform repress. *Set up PMC post repress.*

EVA CUFF CLASSIFICATIONS

Cuff Class	Symptoms	Response
3	**Severe cuff 1 symptoms** or migratory, trunkal or multiple site paresthesia, unusual headache.	Terminate EVA. Assisted return of affected crew member to airlock, buddy perform worksite safing, then airlock repress. Set up PMC.
4	Serious symptoms – Central neurological, cardiopulmonary.	Abort EVA. Crew assisted return to airlock. Repress affected crew member. Buddy perform worksite safing, then airlock depress, repress. Set up PMC.

EVA During Hubble Repair Mission

DISCUSSION 5:

Dr. Chimiak: This is probably the most significant part of the program because here you have the opportunity to actually ask the customer here what they want out of the Adjunctive Therapy Committee.

Dr. Bove: I want to ask the diving medical officers: if you have a patient with pain only and you treat him once and the pain doesn't go away, how do you establish a diagnosis? I always worked under the assumption that it wasn't decompression sickness, based on the old ideas that pain only bends very quickly resolves within 10 minutes of oxygen. I'm interested in it because there were a large number of pain only bends, and a large percentage of them didn't resolve. To me that would suggest that they weren't decompression-related disorders. I'm just curious about the other diving medical officers.

Dr. Flynn: I think that's right that most of these do show some indication of resolving so you have some notion that it might be decompression sickness so it wouldn't have to go away in 10 minutes but as long as it was going away progressively you would say okay. Fifty percent or more of unresolved cases: that doesn't sound like decompression sickness.

Dr. Farr: One of the differences with our divers is when they come up they are not finished. We use diving in a lot of cases as a method of infiltration, and so when you come out of the water bent or not, you may have 12 hours with the rucksack to get to that target, to complete your mission, then get back in the water and get back out again. So from a medical standpoint that brings in the issue of the effect of exercise on bubble formation. When an Air Force pilot with DCS comes back to the ground, he's somewhat self-treated and he has completed his mission; with the standard Navy diver, when he comes up bent he's done. With SEALs and Special Forces divers, when they come up bent they're not done.

Dr. Thalmann: To answer Dr. Bove's question, I think if you read the Diving Manual, one of the criteria for calling a case something other than bends is that you have to ascribe it to another cause. In teaching our courses here at Duke with our mock treatments, we do present the fellows with cases that don't necessarily get better, and they have to decide one way or another. But the point is, it's got to be the differential diagnosis. What I tell them is that if it is bends then something's going to change in the first 10 minutes. It may not completely go away but they are going to see some kind of effect, and if you don't then you can ascribe it to another cause. We also recommend that they use at least a USN Table 5, not just a test of pressure, but it gives you a little bit of time to not have too much egg on your face when after the second oxygen period it gets better. The point is that before you treat you have to have it in your differential: DCS or something else. Second of all is that when I was at EDU it was really our job to put recommended medical procedures in the Diving Manual and once we got BUMED to accept it, usually in the guise of a person who was occupying the seat that Capt. Molé has, it pretty much went in there, but in the end it was pretty much up to the medical officer as to whether to use that treatment. That's how things got out into the fleet. Most of those obviously were changes in the recompression therapy recommendations but there wasn't too much politics. So what you are saying is that you would pretty much use the same mechanism and strive to get it into the Diving Manual and once it's in there say here's a treatment you can use and then it would be up to the diving medical officers to have the training and wherewithal to decide when and how they would use it. Is that fair to say?

Dr. Stolp: Regarding pain-only bends, in Richard's data that he just presented, the average delay to treatment is 20 hours. So the requirement for a clinical response to recompression within 10 minutes may not apply to Special Operations or recreational divers who may have waited days before treatment.

Dr. Southerland: Two things. One for Frank: the current mood at NAVSEA is to make the US Navy Diving Manual an operators manual, so you are going to find less and less medical information in the Diving Manual for the medical officer. At least as of last year they would have liked to remove everything so a lot of that is left over and it's gradually being reduced. As they say, medical officer learns it in dive school. They basically want an operators manual for the operator without all the 'big words' in it. A question for you Richard: you showed in recreational divers that the delay from onset of symptoms to recompression is 20 hours or so, and suggested that this might be a window of opportunity for adjunctive therapy. Do you have information on how soon it was before the afflicted

diver decided to get treatment? I have seen divers in whom the symptoms showed up three days before treatment, but it was 2½ days before he showed up.

Dr. Moon: Are you asking about the time between thinking about getting treatment to actually getting treatment?

Dr. Southerland: You can only give an adjunctive treatment if the diver actually reports to a medical facility.

Dr. Moon: Yes, you are right, but what we are concentrating on here are the more severely afflicted divers for whom there is no question that there's something serious wrong. Most cases of severe bends present quickly, within the first three hours and there is never any question that the diver needs treatment.

Dr. Chimiak: If you had a diver that violated decompression, because he had to get out of the water due to operational requirements, would it be useful to discuss an agent that could be administered to an as yet asymptomatic diver? We had talked about using isoproterenol or epinephrine, that sort of thing has been shown to help off-gas in animal studies? Do we want to go ahead and explore those techniques for the average diver?

Dr. Butler: Let me respond to Dave's question first, what if they took all of the medical information out of the diving manual? That might not be such a disaster, if we take the information that comes out in the UHMS report and we used that instead, that may be a better thing. So, we'll work with the people at BUMED and the people at NAVSEA to explore several options. But if they did decide to take all the medical things out of the Diving Manual, that might not be a bad thing. If we have a well-documented report from the UHMS that we can use instead, and we don't have to go through the political process entailed in writing the Diving Manual and getting things in there, if this can be purely a medical document, that might actually be a step forward.

Dr. Bove: The thought that was raised about having these guys come out of the water and get moving is an interesting one because what you'd rather do there is prevent rather than treat. Dr. Dervay just talked about NASA, but NASA just completed a bends medication protocol for the low pressure EVA's, and maybe that's one thought, to have a protocol for these folks to get on an oxygen therapy, either when they are at 10 feet or when they are on the surface. When they are going to start moving you could do something with oxygen, fluids, aspirin or whatever, some medication protocol, so you don't wait for anything to happen. That looks like a pretty successful strategy for NASA for getting the EVA's done.

Dr. Farr: I agree to that. I was going to bring up prevention strategies, because Frank and I both deal with a community who are very mission-focused, and so they'll do whatever necessary to accomplish a mission. If that means violating the dive tables, then they'll do it. We talk a lot about other prevention strategies in our community, including prophylactic antibiotics before you get shot and various other things like that. So, the best of all worlds is to give me something that I can give to the guy before we start out.

Dr. Flynn: Frank, are we talking about non-medical personnel administering these interventions between the time this person is bent and the time they get treated, both in recreational and special forces applications, or are we talking about medical doctors administering these things? How do we deal with the FDA issues, regarding approved use. As physicians we can use any drug on an off-label basis, but if a recommendation for a medication gets specifically published in a manual, we may be at cross purposes with the FDA?

Dr. Farr: The off-label use aspect is something that I have been interested in lately because that has come up in the nuclear, biological and chemical arena. For example, pyridostigmine is on-label for myasthenia gravis and off-label for nerve gas exposure prevention. The military's stance is that is that a physician can prescribe medications for off-label use for up to and including a battalion, about 500 to 600 people. I cannot, in my role as the senior Green Beret doctor in the Army, tell all the doctors downstream from me what to do, but I can tell them that they can use drugs in an off-label manner for their battalions.

Dr. Butler: The answer to the question about whether non-physicians would be performing these interventions is yes, absolutely. You may be familiar with the work that we have done on tactical combat casualty care. We think we have the finest trained combat medical people in the universe, and there's absolutely nothing here that I've seen proposed yet that I wouldn't put in the hands of a SEAL corpsman or an 18 Delta medic

for them to administer. In the tactical combat casualty care paper, we these individuals administering IV antibiotics, IV morphine and doing surgical cricothyroidotomies. These are well-trained people. In our community I don't think there's a problem. In the civilian community you're right, who is going to be the caregiver to these diving accident victims?

Dr. Dervay: In the space program, sometimes we have the luxury of having a physician on board and that person is obviously trained and qualified to do that. We do have certain medications that require a consult with the physician on the deck during one of our medical conferences. Even though NASA wishes to be forward-thinking and innovative, the issue you raise about the FDA is a very pertinent one. Particularly if we are using something that hasn't had a lot of clinical testing, we have to be very cautious in moving ahead.

Dr. Thalmann: First, if all that medical stuff is going to come out of the Diving Manual it has to go someplace. If it didn't go anywhere, relying on what we are teaching at the Dive School would be a disaster, so somebody's got to be thinking really hard about where it is going to go. The institutional wisdom needs a mechanism to get passed on. Maybe a diving officers handbook would be appropriate. Second, with regard to what happens if someone comes up to you two days late, when I get a call from somebody who's been bent for 48 hours I start telling them to bite the bullet. Generally these people are stable, there's nothing going on with them, they may have some joint pain or whatever, which may get better or it may not. If they actually report for evaluation, I am inclined to tell the diver that if their minor symptoms don't get better, he or she will have to live with it, and it's just too late for recompression treatment. The problem we face at DAN is our perceived obligation to medevac these people to a treatment facility if they call up 48 hours after symptom onset. This is a socio-politico-economical problem, not really a medical one. I think we are all smart enough to recognize that once bends is stable and you have 'got what you got', you may be able to salvage what you have got, but you are not faced with somebody who's evolving, for whom you don't know what they're going to do and if you don't treat them they may end up with a serious residual. So the problems are different. I don't think adjunctive therapy would ever be envisioned for stable, minor symptoms. My adjunctive therapy would be symptomatic treatment. But there are doctors who I have talked to who swear that they have treated bends 1-2 weeks after the event and have observed improvement from recompression. I have been trying to figure out the mechanism and I can't. Nevertheless, recompression treatment or not, there is no rush.

Dr. Butler: We all draw from our own experiences. The one that I would draw from was the case of an individual who after a dive had minor symptoms that he chose to ignore, and they turned into quite major symptoms after he waited long enough. So if I was presented with someone I thought had decompression sickness, it wouldn't matter how long after he called, although I suppose there would be a limit of a period of days or weeks, I would tell him to go and at least do a trial of recompression. We had an individual whose decompression insult was over two weeks old. He had a profound ulnar palsy, and we cured him at EDU. It took us three weeks, but by God we cured him. Going back to the off-label drug use, I don't think that's a big problem. In the Diving Manual now, lidocaine and methylprednisolone are mentioned, and I'll bet you neither of those drugs are approved by the FDA for decompression sickness or gas embolism.

Dr. Reed: I just wanted to answer Dr. Bove's question about who would administer the drug in the case of a recreational diving accident. In the case where an individual has been bent and is relatively distant from a chamber but is being treated in, for instance, a community emergency room, that's not really an issue: you can speak to the physician who is caring for the patient. Where I believe where the issue is ill-defined, is, for example, a live-aboard dive boat many hours away from a recompression facility, with a paralyzed diver on board. If there is no trained medical person available, who would be appropriate to administer an intravenous bolus of lidocaine followed by a drip and/or large doses of methylprednisolone, or anything else for that matter?

Dr. Latson: Or, in a couple of years, intravenous perfluorocarbons. If a perfluorocarbon enhances nitrogen elimination and reduces inflammation in the same way that recompression therapy does, why would you not give it just because it was 48 hours later, particularly if it was going to be another 48 hours before you could get the diver to a chamber?

Dr. Thalmann: Nobody can convince me that in 48 hours you have a nitrogen load left at one

atmosphere. So if perfluorocarbons work it's via a mechanism other than reducing nitrogen load. Second of all, in these long-delayed cases we say 'recompression', but I can't be convinced that the effects are due to bubble compression; I think it's hyperoxia. Whether or not a pharmacological agent would actually reverse the lesion is another story. Certainly if you read the literature there are proposals for drug therapies for very old spinal cord lesions in which you provide the basic building blocks for the spinal cord to regenerate itself. So there may be therapies that can be used very late after injuries to help heal. Therefore, we can't write anything off, and I wasn't trying to be too flippant about delayed bends, but certainly for pain-only bends, in which the person is not in danger, I'm not saying that I wouldn't ever use recompression treatment, but such treatment is not as urgent as it would be if the symptoms were evolving. I like to be mechanistic and a strategy that works is trying to figure out why. When 48 hours goes by I have trouble believing that there's a gas phase around.

Dr. Chimiak: Dr. Dietrich, regarding the 'window of opportunity' for the treatment of spinal cord injury, where would you close the door on it, or would you leave it open at this point in this infancy of our understanding?

Dr. Dietrich: I have been listening to the discussion and I don't really know when I would close the door. Today we discussed inflammatory cascades that could be ongoing days after the spinal cord injury, and if you believe that these inflammatory cascades could contribute to secondary injury, that's something that may be targeted days after injury. Apoptotic cell death leading to damage of the oligodendrocytes and demyelination affecting axonal function could happen weeks after spinal cord injury. That's known from human tissues. So I think that if you can propose a pathophysiological mechanism that you think is clinically important, and it's occurring days after the insult, then I would say that it still should be targeted with therapeutic intervention.

Dr. Moon: I would like Dr's Warner, Goodman, and Dietrich to address this question. If you make the assumption that there is some ischemic component to decompression illness, is there any possibility that are there any compounds that could be used prophylactically, that is compounds that are as safe as taking aspirins or vitamin C, that might be useful in the same way as Dr. Farr mentioned taking prophylactic antibiotics before getting shot?

Dr. Warner: One of the problems with many drugs that have come forward as potential therapeutic agents for CNS injury is that, because the drugs are selected to work on neural systems, they will have neurologic or neurotoxic side effects. This has limited the development of many drugs, and giving any sort of drug that would particularly have a sedative effect prior to somebody going deep in the water, I think would not be a good idea as a routine practice. Drugs that come to mind like that would be the ones that may be the best for blocking the initial excitotoxic mechanism, assuming that that's part of this pathology such as glutamate antagonists or benzodiazepines, or GABA agonists or potentiators, which in many studies have been shown to be extraordinarily efficacious if given prophylactically. There are other pathways downstream that you could potentially disrupt with pharmacologic agents, as Dr. Dietrich has been leading to all day long. The value of giving pre-dive a drug that is going to interact with an event hours or days subsequent to the bends that doesn't make a lot of sense on a pharmacologic basis. You'd have to take it and keep taking it to keep enough in your blood to have a pharmacologic effect at the right time. Antioxidants are one class that comes to mind as an option that does not have the CNS depressant or excitatory properties, such as the psychotomimetic side effects of the NMDA antagonists. Probably most antioxidants won't have a CNS depressant or excitatory effect, and there is indeed in evidence we saw this morning with 2,3-dihydroxybenzoic acid (DHBA), there is a very early surge in reactive oxygen species in ischemia and trauma, and probably in decompression illness also. Then there's a second phase that occurs later during inflammation, and a prophylactic antioxidant, of all the things that I can think, would be the one that would make the most sense. There was an interesting article recently[1] on dehydroascorbic acid, the precursor of ascorbic acid. This compound was quite efficacious as a prophylactic agent in an animal model of stroke. That's the kind of drug that one might consider for a prophylactic intervention, but I'm not sure if it has any substantial side effects.

Dr. Bove: I'm trying to figure out what to do with late presenting symptoms. I didn't hear either of you say hyperbaric oxygen in that long list you mentioned. When a diver presents three days after symptom onset, with either pain or some

neurologic symptom, if there is no gas load left you would be treating tissue injury. I think there is still the propensity to treat the patient in the chamber, yet hyperbaric oxygen is not at the top of the list of the things we've heard. Perhaps instead of chamber treatment we ought to be opening the medicine cabinet and treating the tissue injury. Or, if we are going back in the chamber, it ought to be considered hyperbaric oxygen therapy and not recompression for a diving accident.

Dr. Warner: I'm not an authority on hyperbaric oxygen but I have been following it in literature, and there are a couple of interesting things, one of which is potentially at a prophylactic level. There's a phenomenon called ischemic pre-conditioning, in which a stimulus is administered that's not enough to kill tissue. Then, after a period of time, usually 12 to 24 hours, you can hit that tissue with an insult that normally would kill the tissue, but for some reason now it's protected. The brain is very good at this. Hyperbaric oxygen is a very effective stimulant for ischemic pre-conditioning in the brain and potentially spinal cord. Claude Piantadosi and Jake Freiberger have been working on this. That is a prophylactic measure that one could take for an anticipated high-risk dive, but pending some real information this is all theoretical, and I'm not sure it should be advocated without some convincing evidence.

Dr. Chimiak: Dr. Moon, if you were to use medications that have some of these CNS side effects, would that alter the way you treat a patient? The treatment end point may be clouded by altered sensorium. Would you have to rethink your algorithm and administer a certain number of treatments regardless of the patient's clinical picture, due to those side effects?

Dr. Moon: If one were to administer an NMDA blocker that could confound the ability to follow the patient using clinical neurological exam. Another open question is whether any of these drugs might potentiate oxygen toxicity.

Dr. Mitchell: Just a quick comment on the subject that Ed Thalmann and Fred Bove have been discussing, I'm not sure that we should be that quick to embrace the notion that there's definitely no bubble-induced pathology or no residual bubbles 36 or 48 hours after a decompression event. I think there's a lot of evidence that there can be, such as deterioration when people fly after symptoms of decompression have arisen, or even new symptoms of decompression illness in people flying nearly 48 hours after diving. I realize that bubble growth isn't the only explanation for that necessarily but it's certainly one very plausible one. Also the case reports that exist of divers suffering symptoms of decompression on the operating table and given nitrous oxide quite some time after diving[2]. So I don't think the notion that there's no use in recompression more than 48 hours after diving is necessarily valid at all.

Dr. Massey: Frank, what sort of delay might there be for special forces to get treatment?

Dr. Butler: It's a fair question but any answer is just a guess. There's no way to put a specific number on it because it's not just a question of distance, it's a question of tactical circumstances, it's a question of what else is going on with the unit. For example, if you had somebody who was injured and you had a national interest mission and you had a gas embolism, would you stop the mission or would you delay the attempt to get back for treatment until after the mission was over? These are excruciatingly difficult decisions that these young SEALs, lieutenants and army captains have to make. So I'm going to give you Dave Southerland's favorite answer, "it depends".

Dr. Massey: I assume that there is, at least in some settings, a chamber when the divers get back to the ship or base, or at least oxygen somewhere. Also, educating them that a paralyzed leg is a little different than numbness in the ulnar distribution.

Dr. Butler: It's fair to say that at times there may be recompression available quite quickly. The primary example of that would be if you were operating off a submarine, you had a gas embolism event and the submarine was in a tactical environment that allowed surfacing. Theoretically you could get the individual back under pressure pretty quickly. If the submarine left and you were swimming in, the pick-up was in 48 hours and you had a gas embolism when you surfaced, that submarine is probably still coming back in 48 hours.

Dr. Chimiak: This is a question to our customers. It seems that a NASA astronaut during EVA who develops mild "cuff 1" symptoms will continue to work; Dr. Farr has said that special forces divers who develop minor symptoms will push on with the mission as the situation warrants; even some of the more aggressive recreational divers that I have seen will continue diving with minor pain-only bends. What we have gathered from your

presentations is that we are looking at evaluating adjunctive treatments mainly for serious DCS and AGE. Is that a fair assessment?

Dr. Butler: I think it's fair to say that the condition that is most likely to resolve to death or disability for special operations divers is probably gas embolism. I made the statement to our line commanders that decompression considerations should essentially never prevent an operation from being done in the SEAL community. The reason for that is you can typically tailor your depth in the water column to accommodate whatever your decompression situation is, if you're piloting an SEAL delivery vehicle (SDV). So we can usually be clever enough to get around decompression considerations and I don't look at that as our primary problem that's going to require adjunctive therapy. I think it's more likely to be the individual doing a covert insertion using a closed circuit oxygen rig who is in a tactical environment where he is just not able to be removed from that environment for anywhere from hours to days.

Dr. Farr: I agree with Frank with regard to AGE.

Dr. Latson: I will mention one other scenario that has been touched on but not really described, and that's the submarine rescue scenario. If we were to rescue people from a pressurized submarine that had been there for several days we would be dealing with very severe, potentially crippling, decompression sickness. And if we were doing that with the US Navy's present method of rescue, that is the DSRV, attached to a mother submarine where there's no recompression capability, we could be dealing with up to 20 casualties at a time decompressing from 30 to 150 feet of saturation. We would be dealing with them in a submarine with a trunk full of medical supplies and a couple of E cylinders of oxygen. It probably would be from 24 to 36 hours before we could return to port, maybe even more.

Dr. Moon: Dr. Goodman could you comment on that scenario, where there is a high probability if not a 100% certainty of decompression illness. What about giving nitrates or arginine in advance of the decompression?

Dr. Goodman: I have no idea. Getting back to your prophylactic question I think the answers that have already been given were entirely appropriate: anti-oxidants, anything non-sedating, maybe statins to up-regulate the NO, but I have no idea about L-arginine in this situation. Aspirin is good, what every middle aged man should be taking now.

Dr. Moon: Would it be fruitful to investigate such possibilities?

Dr. Goodman: I think L-arginine or other NO donors would be reasonable, safe, FDA approved for human administration and easy to handle. L-arginine is obviously the most physiological. You could even consider adding L-arginine to IV solutions. It is a stable compound. I think it would be worthy of investigation and we plan to investigate it in head trauma.

Dr. Farr: In submarine rescue you're not as concerned as I am with how people function. Functioning during a ride up from a submarine is quite different from actively tracking a target. The range of compounds that could be given in the latter scenario is likely to be more limited.

Dr. Flynn: Just to amplify a little bit on the submarine escape scenario, what we're primarily concerned about there is called cardiopulmonary decompression sickness, caused by massive venous gas embolization of the lung, causing pulmonary edema formation. It's something that we have not discussed here yet, but it's a very relevant situation that we're facing in the Navy. We do have a study ongoing in sheep where we are looking at furosemide and butorphanol in order to treat of the pulmonary edema. It appears to be lifesaving, so in our overall discussions I don't think we should exclude cardiopulmonary decompression sickness, because it's something that we are going to face.

Dr. Bove: It's interesting that we're discussing endothelial protective mechanisms in a prophylactic way because in present medical practice statins are ubiquitous. The fact is that they do have very significant endothelial stabilizing functions. The other drug is sildenafil, which enhances nitric oxide production in the endothelium. Pfizer is looking for new applications for this medication. So it may be that part of the prophylaxis for a dive team should be an endothelial stabilizing agent. You know there's a candy bar containing L-arginine that you can eat like a 'power food'. So that might be another prophylactic approach for the special warfare people.

Dr. Dietrich: If you want to improve perfusion there are a lot of ways that you can target endothelial function. We worked with a series of

drugs, adenosine regulating agents, which at a site specific location when you have an embolus, these particular drugs given prior to injury actually lead to increased release of adenosine, which is a potent vasodilator. We showed in an embolic model of stroke that pre- and post-treatment with this adenosine-regulating agent could actually increase the spontaneous re-canalization of cerebral vessels. So I think therefore there's a variety of adenosine agents, antagonists and agonists, that target the vasculature that can be thought about in pretreatment strategies.

Dr. Vann: One thing just to keep in mind with many prophylactic measures and that is that you don't want to do something that is going to increase your gas load during the dive because that could put you at a greater risk.

Dr. Dietrich: These adenosine regulating agents only kick in when you have a period of local ischemia that leads to depolarization of a neuron and release of adenosine. Therefore the effect is rather site-specific.

Dr. Chimiak: Some of the other agents we may wish to consider may include agents for deep vein thrombosis prophylaxis, which can be a complication of decompression sickness. Also, perhaps we should consider agents that may be useful for diagnosis, such as CO_2, the administration of which could help to differentiate peripheral tingling due to anxiety-related hypocarbia from true decompression sickness.

Dr. Farr: We have talked about prevention strategy, we've talked about adjunct therapy before recompression. What we haven't talked about yet is therapy during recompression. I suppose there would be a place for that if we could come up with a more effective, quicker recompression strategy.

Dr. Chimiak: A recent article has suggested that using USAF Treatment Table 8 (2 hours breathing 100% O_2 at 2 ATA[3]) could be effective for aviation bends. Ground level oxygen can also be used.

Dr. Butler: My first thought is that if an adjunctive therapy could work for a secondary mechanism, then it should work both before, during and after a recompression therapy. However, we need to be tuned in to the excellent observations that have been brought up here before, indicating that the insults and the mechanisms may change over time, so that the optimal therapy before recompression may in fact not be optimal therapy after recompression. In looking at the discussions of the day, I think we have succeeded in rounding up the 'usual suspects'. I think what we have to do now is to go back and figure out where should we start with our studies. Assuming that we are able to get animal studies funded, then I would come up with a lot of possibilities, a lot of potential mechanisms but we need to come to some sort of a consensus on where to begin.

Dr. Thalmann: To me, the drug that's on the table right now is lidocaine; I can't think of another drug that has a track record of being efficacious, at least for AGE. We could argue that studies have yet to be done in DCS. Also the drug has been used in a human trial, although not directly AGE, but in a human trial in which it was used for embolic phenomena. We have a good idea of its safety, how to administer it and its side effects. If the UHMS Adjunctive Therapy Committee can't come to some agreement on lidocaine, it's going to be difficult for us to come to an agreement on anything else. Besides the thrombolytic agents, what's out there right now that works, that people feel comfortable using in real stroke, in real people, on a routine basis, that they think is going to be of a benefit and not a detriment?

Dr. Warner: The answer to that is clearly nothing.

Dr. Latson: I'll second Dr. Thalmann's comment on lidocaine. I think that the evidence in it's accumulated form makes a pretty good case that the risk-benefit definitely favors administration of lidocaine if what else you are doing isn't working. But I will say that I think there is another candidate that is nearly as well documented as lidocaine, and that is perfluorocarbons.

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PRINCIPLES OF PHYSIOLOGIC RESUSCITATION IN CNS INJURY

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Abstract

Meaningful progress is being made with respect to understanding molecular and biochemical processes associated with a variety of insults to the central nervous system (CNS). Although etiologies of brain and spinal cord trauma/ischemia are varied, a similarity in pathologic cascades initiated by these insults has been identified. Consistent with this is the observation that a variety of experimental therapeutics have similar efficacy in treating these varied disorders. It is not yet known to what extent this generalization can be applied to CNS injury associated with decompression illness (DCI) but this should be explored. Regardless, there remains little or no pharmacologic intervention that has proven efficacious in improving outcome from CNS injury in humans. In contrast, a great deal has been learned concerning interactions between physiologic factors and outcome from CNS injury. These factors can be readily managed by clinicians. Again, there has been no specific analysis of the relevance of these factors to humans sustaining CNS manifestations of DCI. However, within the domains of other forms of CNS injury, the data is overwhelming that outcome can be improved by managing temperature, plasma glucose concentrations, and intravascular perfusion pressure. The purpose of this review is to provide discussion of several advances which may have immediate applicability to DCI.

Temperature

There is little doubt that reduction of brain temperature can reduce injury resulting from prolonged intervals of ischemia. Perhaps the most convincing example was provided by Silverberg et al.[1], who reported that adults undergoing cardiopulmonary bypass for cerebral aneurysm clipping were able to sustain up to one hour of circulatory arrest when core temperature was reduced to ≈ 20°C. Despite this, little use of hypothermia was made outside of the cardiac surgical operating room until recently. This most likely was due to belief that the efficacy of hypothermic brain protection is a function of the magnitude of reduction in brain temperature. Small reductions in temperature were not generally believed to be beneficial. More profound reductions in temperature require cardiopulmonary bypass which invokes a host of logistical considerations and substantial concern regarding complications.

The development of rodent models of cerebral injury caused significant change in such attitudes. Dramatic reduction in neural injury was observed when brain temperature was reduced by only 2-3°C in models of focal ischemia, global ischemia, brain trauma, spinal cord ischemia, or status epilepticus[2]. Physicians promptly recognized the logical extension that mild hypothermia might also be beneficial in the care of patients with CNS insults. Mild to moderate hypothermia is feasible to induce in the critically ill patient and presumably the risk associated with this practice is small.

Mechanisms of Action

For several decades it was thought that the predominant mechanism by which hypothermia caused protection was by reduction of cerebral metabolic rate (CMR)[3]. This has been called into question because mild hypothermia offers potent neuroprotection although CMR is only minimally reduced. Other cellular and biochemical effects better explain how hypothermia protects. For example, during an ischemic insult, extracellular concentrations of the excitatory neurotransmitter glutamate become massively increased. Such increases are believed to initiate an excitotoxic cascade ultimately resulting in cell death. Mild hypothermia effectively blocks the increase in glutamate[4] although the importance of this has been questioned[5]. What is clear is that post-synaptic consequences are important. One post-synaptic glutamate receptor type, the NMDA (N-methyl-D-aspartate receptor is coupled with a calcium channel. Because there is an approximate 10,000:1 gradient between extracellular and intracellular calcium, intracellular calcium is tightly regulated. Energy failure is associated with a large influx of calcium. *In vitro* studies have shown that mild hypothermia reduces calcium influx[6]. Presumably, hypothermia causes decreased opportunity for intracellular calcium to accumulate in concentrations sufficient to exert toxic effects.

Undoubtedly there are also generalized effects of hypothermia on intracellular enzymatic activity. Protein synthesis is markedly suppressed during ischemia and early recirculation[7]. Mild hypothermia, while having no effect during this interval[8], hastens recovery of protein synthesis several hours after reperfusion[9]. More specific effects have also been defined. Protein kinase C (PKC), an enzyme involved in regulating neuronal excitability and neurotransmitter release, is activated in response to an increase in cytosolic calcium. Hypothermia diminishes membrane bound PKC activity in selectively vulnerable regions of the post-ischemic brain indicating reduced calcium toxicity[10].

Nitric oxide synthase activity in the ischemic brain is suppressed by hypothermia[11,12]. Nitric oxide, while beneficial in supporting vasodilation during ischemia, also contributes to formation of potent reactive oxygen and nitrogen species that cause tissue degradation. Hypothermia reduces free radical production and consumption of free radical scavengers. Consequently, the accumulation of lipid peroxidation products is reduced in ischemic brain[13,14].

There are also mechanisms by which hypothermia may prevent delayed cell death. Hypothermia inhibits the apoptotic response to ischemia[15]. Neutrophils are recruited to injured brain within the first few days after injury. These cells and activated microglia produce free radicals that contribute to further tissue destruction. Hypothermia reduces the expression of pro-inflammatory cytokines and chemokines with resultant reduction in neutrophil accumulation. This inhibition of inflammatory responses to injury may serve to provide sustained protection against injury in contrast to many pharmacologic therapies that provide only transient cell survival[16,17].

There are also electrophysiologic benefits of hypothermia. In a model of focal cerebral ischemia, tissue in the ischemic penumbra shows recurrent episodes of depolarization which have been associated with transient intervals of tissue hypoxia and depression of electrical activity[18]. Such events constitute secondary insults to the already injured brain.

Hypothermia greatly diminishes the frequency of such depolarizations providing another mechanism for its protective effects[19].

Efficacy

Evidence obtained from laboratory animals is overwhelming that mild hypothermia is efficacious in treating the injured nervous system. Important lessons have been learned that dictate what is required for mild hypothermia to also be beneficial in humans.

No data (from either animal models or humans) exists with respect to efficacy of mild hypothermia in the treatment of DCI. At present, data must be extrapolated from other injury paradigms. Innumerable laboratory studies have shown protection from mild hypothermia when present during an ischemic or traumatic insult. More relevant to DCI are those studies that have instituted hypothermia after the insult has occurred (i.e., post-treatment). While early studies provided evidence that post-ischemic hypothermia is efficacious, it soon became clear that the protection is transient unless certain conditions are met. Specifically, studies that examined short durations of post-ischemic hypothermia (i.e., durations of 3-4 hrs) found no protection when animals were examined several weeks/months after injury despite protection being apparent several days after injury[20]. Careful work in a gerbil model of near-complete forebrain ischemia provided convincing evidence that for post-ischemic hypothermia be beneficial, it must be continued for a minimum of 12 hours [21]. Based on this finding, two recent trials have been conducted in humans sustaining out-of-hospital cardiac arrest[22,23]. Both studies reduced core temperature to 32-34°C for 12-24 hours in patients remaining comatose after restitution of spontaneous circulation. Both studies found improved neurologic outcome attributable to induced hypothermia. Notably, there was not an increase in the fraction of survivors remaining in a persistent vegetative state. These studies are of paramount importance because they provide definitive proof that the injured human CNS responds favorably to post-insult therapeutic moderate hypothermia. The implications of these studies for DCI patients can be debated. It is unlikely that a randomized prospective trial of hypothermia efficacy will be performed in the foreseeable future in patients with DCI. There is animal data that post-ischemic hypothermia is of value in treating spinal cord injury[16,24]. However, to institute sustained hypothermia, endotracheal intubation and sedation are required. As a result, major changes in medical management of DCI would be required to employ hypothermia. In the absence of direct evidence, use of hypothermia in this scenario is therefore speculative with respect to efficacy. However, the two human trials make it reasonable to consider use of sustained moderate hypothermia in severe cases of CNS dysfunction related to DCI.

What might be more important to consider is the diagnosis and treatment of hyperthermia. There is no reason to believe that hyperthermia would be of benefit to the patient with acute CNS injury. To the contrary, numerous animal studies have documented a major adverse effect of hyperthermia on outcome from CNS injury. Cerebral infarct volume resulting from middle cerebral artery occlusion in the rat is more than doubled by increasing brain temperature from a normothermic value of 38.0°C to only 39.2°C[25]. See Figure 1. Global ischemic insults designed to cause mild neurologic deficits in normothermic dogs, result in coma or death if brain temperature is increased by as little as 1°C[26]. Hyperthermia, is a common sequel to a variety of forms of CNS injury[27]. As a result, monitoring of core

temperature is essential and aggressive treatment to reduce temperature to normothermic values is recommended for DCI with CNS manifestations.

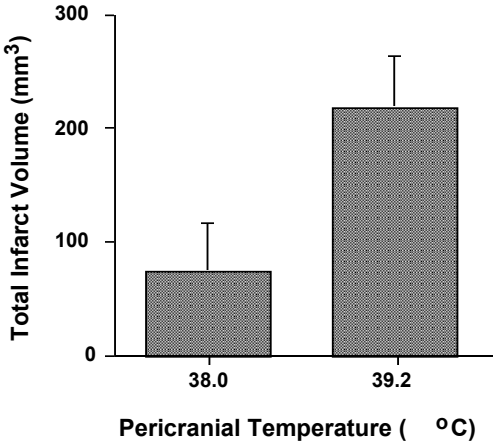

Figure 1: Effect of mild intra-ischemic hyperthermia on cerebral infarct volume resulting from 90 min of middle cerebral artery occlusion and 4 days of recovery in the rat[25].

Aside from clinical considerations, there is another ramification for the effects of temperature. Given that small changes in brain and spinal cord temperature are critical to outcome from an ischemic or traumatic insult, any investigation which purports to seek therapeutic advances in the treatment of such disorders, including DCI, must account for thermal effects of the therapy being examined. Notably, many drugs cause reduction in CNS temperature in a magnitude sufficient to independently cause protection[28]. Studies examining pharmacologic neuroprotective efficacy that fail to monitor and control CNS temperature are of little value.

Implementation

If one accepts that mild hypothermia is indicated then issues arise. The effects of various methods of cooling on brain temperatures in neurointensive care patients have been examined. Intraventricular thermistors were used to compare brain temperature against rectal temperature[29]. During normothermia, rectal temperature was found to underestimate brain temperature by as much as 2-3°C although most often values were within 0.5°C. When attempts were made to specifically reduce brain temperature to 34°C, rectal temperature values (while tracking brain temperature) were often found to be at variance from the brain by 1-2°C. The same study also showed that brain temperature in the comatose patient was surprisingly resistant to efforts of cooling and that only intensive total body surface cooling combined with pharmacologic therapy was effective in achieving that result. During field resuscitation it would seem highly unlikely that brain temperature can be monitored although measurement of tympanic membrane temperature may be practical. Administration of intravenous ice-cold saline has been shown to cause rapid cooling in humans resuscitated from cardiac arrest[30]. Again, it is emphasized that moderate cooling should take secondary importance to simply identifying and treating hyperthermia.

Complications

There are potential complications from induced hypothermia. Most are speculative and only large-scale clinical trials will be able to identify complications which might occur with low

frequency. First, it is well known that significant coagulopathies become manifest at temperatures less than 30°C. However, within the range of mild hypothermia (33-35°C), clinical evidence of coagulopathies in traumatic brain injury patients undergoing cooling has been absent[31]. Second, there is concern that mild hypothermia will suppress the immune system allowing a greater chance of infection. Human trials, however, have not found this to be a clinically important problem. Arrhythmias are not typically observed unless the temperature is less than 30°C. Cardiopulmonary resuscitation may be more difficult during hypothermia. Potencies and durations of action for pharmacologic agents may also be altered.

Normoglycemia Versus Hyperglycemia

While the normal brain and spinal cord are dependent upon continuous delivery of exogenous glucose for maintenance of cellular energy requirements, ischemic or hypoxic neural tissue finds continued glucose availability to be detrimental. Pursuit of an explanation for this has yielded a large body of information, some of which has significance for CNS resuscitation.

The initial observation that pre-ischemic glucose infusion worsens ischemic outcome was serendipitous. Myers and Yamaguchi[32] designed an experiment to assess the effects of a brief episode of cardiac arrest on learned visual tasks in fasted primates. To facilitate resuscitation, an intravenous crystalloid bolus was given prior to cardiac arrest. However, the investigators were inconsistent regarding which type of fluid was given. While most of the animals recovered and went on to have visual cortical function assessed, two monkeys developed seizures and died early after reperfusion. Looking back, the investigators recognized that those two monkeys had received dextrose in their fluid bolus, while those that survived had not. This association between glucose infusion and worsened outcome from global ischemia was soon validated under more controlled conditions in the same laboratory, and has subsequently been repeated with remarkable consistency in numerous models, species, and research centers (Figure 2).

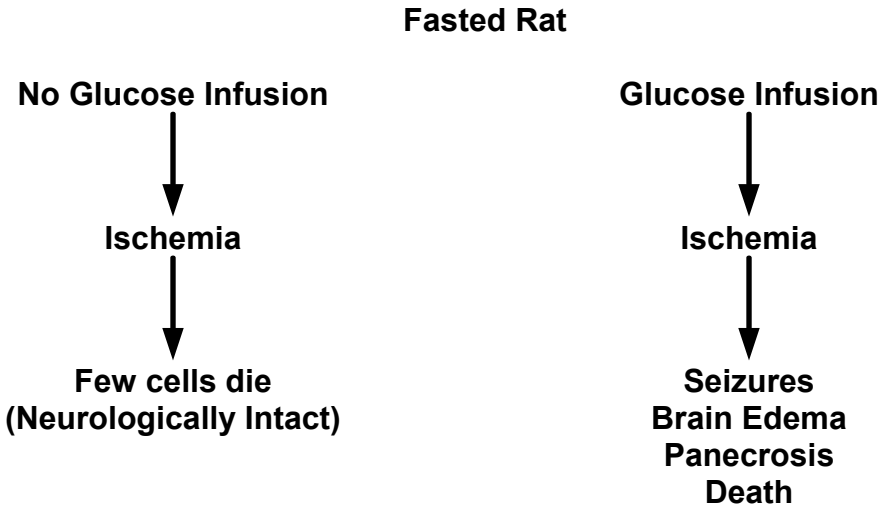

Figure 2: Intravenous glucose (plasma glucose > 180 mg/dl) can have dramatic effects on outcome from standardized transient forebrain ischemia in the rat.

Prior to appreciation that hyperglycemia is adversely related to outcome, other investigators had suggested an unfavorable relationship between cerebral acidosis and ischemic injury[33]. It was not long until that acidosis was linked to glucose administration[34]. In the absence of sufficient oxygen supply, cellular energy requirements may be partially supported by anaerobic glycolysis. A relative hyperglycemia would be expected to allow some ATP production at the cost of an enhanced accumulation of lactate, the end-product of glycolysis. Lactate has a pKa of 3.83 meaning that at physiological pH virtually all of it will be ionized. The predicted and documented effect of pre-ischemic glucose infusion would therefore be an intracellular acidosis. This acidosis is believed to be the cause of worsened outcome[35], although paradoxically, in isolated neuronal cultures, acidosis is protective against a variety of insults intended to mimic ischemia[36].

Although laboratory work has provided a consistent series of results regarding the adverse effect of hyperglycemia on global ischemia outcome, physicians may still be uncertain as to how this information should be employed during attempts at CNS resuscitation. It can be argued that laboratory protocols were designed to produce maximal effects, i.e., animals were rendered severely hyperglycemic. Does this have anything to do with a modest glucose infusion such as would occur with 1 liter of dextrose containing solution administered during resuscitation from a CNS injury? Lanier et al[37] addressed this question by administering D5W (in a volume equivalent to giving 1 liter of the same to a 70 kg human) to monkeys prior to inducing a reversible global ischemic insult. Neurologic outcome in those monkeys was compared to a group which had instead received the same volume of normal saline. A worsened neurologic outcome was observed in the animals receiving dextrose. Thus severe hyperglycemia is not necessary to elicit an adverse effect from glucose loading. Small doses of glucose may predispose individuals to a worsened outcome from acute global brain injury. Subsequent work has identified a plasma glucose concentration threshold of 180 mg/dl which predicts worsened outcome in both humans and animals[38,39].

Although the animal evidence was overwhelming, debate continued as to whether hyperglycemia worsens outcome from CNS injury in humans. This is because all humans studies had been correlative, i.e., plasma glucose was measured at hospital admission and values were then compared to outcome. Although almost all studies found a correlation (e.g., the higher the glucose value, the worse the outcome)[40-43], it could be argued that this simply reflected a reactive hyperglycemia that was proportional to the severity of insult as opposed to being causal. This conjecture has been clearly dispelled. Humans with new onset stroke were serially followed with magnetic resonance imaging. In those patients with an ischemic penumbra (i.e., hypoperfused tissue not yet infarcted) acute plasma glucose concentration independently predicted the fraction of penumbra ultimately transformed into infarct[44].

With respect to spinal cord ischemia, several laboratory studies have evaluated the effects of hyperglycemia on outcome[45-47]. The phenomenon of hyperglycemia-augmented damage was found to persist. For example, rabbits underwent a transient infrarenal balloon occlusion of the aorta[46]. Prior to ischemia, either lactated Ringer's solution or D5W was infused for 90 minutes. A higher plasma glucose concentration was observed in those rabbits receiving dextrose which corresponded to a worsened neurologic outcome.

Should insulin be given to correct hyperglycemia when a neurologic insult is in progress? Further, if insulin is administered, how low should plasma glucose should be reduced? To date there have been no human studies performed to directly answer these questions. However, cumulative laboratory evidence supports the concept that preischemic correction of hyperglycemia with insulin administration improves ischemic outcome[48-51]. The concern with insulin administration is accidental induction of profound hypoglycemia which may in and of itself augment ischemic brain damage. Fortunately, most physicians are comfortable with acute corrections of plasma glucose concentrations allowing this therapy to be a real option. There are no prospective trials in humans that have defined a target for plasma glucose values when patients are treated with insulin. However, as mentioned above, a value of <180 mg/dl has been shown to segregate outcomes in both animals and humans. As result, maintenance of normoglycemia at a value <180 mg/dl is recommended.

Intravenous Fluids and CNS Injury

Because the brain is housed in a rigid cranium, small increases in brain water content may cause increased intracranial pressure (ICP) and decreased cerebral perfusion pressure (CPP). Decreased CPP may result in hypoperfusion which causes additional stress to already damaged tissue. This is most relevant when normal compensatory mechanisms, i.e. reductions in cerebrospinal fluid (CSF) and venous volumes are exhausted. Consequently, it is important to minimize brain edema. A similar concept is applicable to the spinal cord within the vertebrae. Historically, edema was treated by fluid restriction. This practice was based on the observation that large volumes of intravenous crystalloid solutions often cause edema in other organs (e.g., bowel) and thus presumably the brain. Unfortunately, fluid restriction may increase injury. Fluid restriction results in hypovolemia manifested as hypotension and thus decreased CPP. This concern has led to careful analysis of the effects of intravenous fluid administration on brain water content. Information obtained from such investigations has improved our understanding about how various intravenous fluids might influence edema formation (in both the normal and injured CNS).

Three properties of intravenous fluid solutions have been considered important in determining the flux of water between intravascular and extravascular compartments, those being hematocrit, colloid oncotic pressure (defined by the concentration of large molecules only), and osmolality (defined by the concentration of large and small molecules). Laboratory studies, however, have largely failed to find a role for hematocrit or oncotic pressure in promoting edema in either the normal brain or in traumatized or ischemic brain (but see reference #52). In contrast, osmolality plays a major role in determining brain water content, this being due to the blood-brain barrier (BBB) which is relatively impermeable to even ions (Figure 3).

For example, when the rabbit with an uninjured brain undergoes an isovolemic plasma exchange resulting in a 70% reduction in plasma oncotic pressure, brain water content and ICP remain normal. In contrast, a 5% reduction in plasma osmolality under otherwise identical conditions results in brain edema and increased ICP[53]. These same findings have been observed under conditions of severe anemia[54] and also have proven consistent when changes were either acute or chronic[55,56].

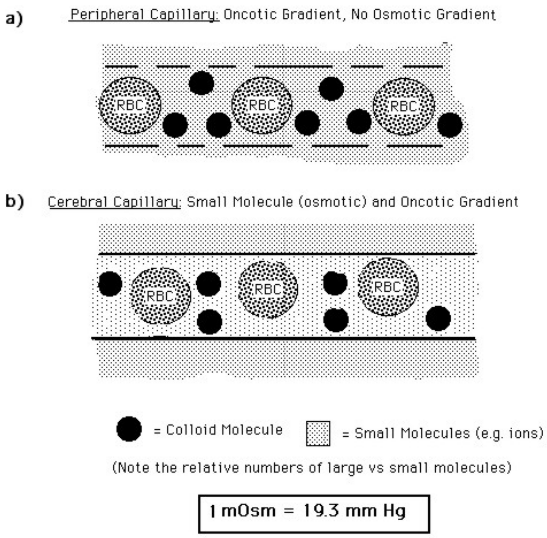

Figure 3: What distinguishes cerebral from peripheral capillaries is the BBB. While the peripheral capillary is impermeable to macromolecules but permeable to most osmotically active constituents (e.g. ions), the brain capillary is functionally permeable to neither. Because a concentration gradient is necessary for water to move between extravascular and intravascular compart-ments, ionic factors are neutral in the periphery, but relevant in the brain. In contrast, oncotic pressure, while theoretically active in both systems, is only relevant in the periphery. That is because 1 mOsm of osmotic pressure equals 19.3 mmHg. Since colloid oncotic pressure is normally 18-20 mm Hg, fluid shifts of only a few mOsms dwarf any potential role for oncotic pressure to cause water movement. For these reasons, colloidal properties of i.v. fluids have little or no influence on brain water content. Instead plasma osmolality is determined and fluids appropriate to holding that value stable are administered.

Similarly, in the case of a lesioned brain induced by cortical freeze injury[53] (the pathophysiology of which resembles trauma or infarct) or global ischemia[57], neither hematocrit nor oncotic pressure affect brain water content (Figure 4). Osmolality remains relevant because of potential integrity of the blood brain barrier in adjacent normal brain.

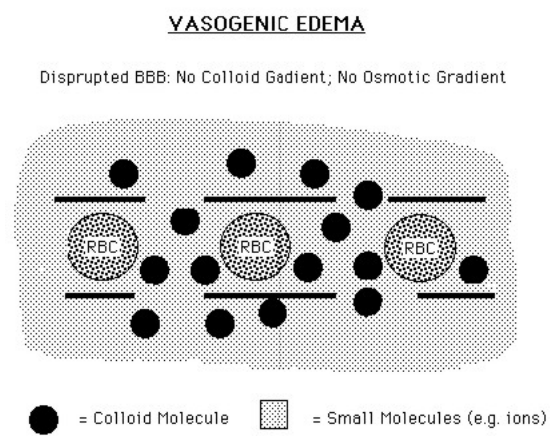

Figure 4: In the case of injured brain, where the BBB becomes dysfunctional, a different scenario applies. Unlike either the peripheral or cerebral capillary, there is now permeability to both oncotic and ionic plasma constituents. Because of this permeability, no gradient between extra- and intravascular compartments can be established. Consequently, manipulations in plasma oncotic and osmotic pressures have little to do with edema formation in injured tissue. It is important to recall, however, that normal tissue in other parts of the brain will continue to respond to changes in osmotic pressure.

Based on these considerations, it is appropriate to utilize crystalloid solutions if deemed necessary to increase intravascular volume. A successful intravascular volume resuscitation might not be reflected by how little fluid was given, but rather by how stable CPP and plasma osmolality are maintained. What fluids are most appropriate to treat hypovolemia and dehydration in patients during the acute stage of a CNS insult? Certainly, severely hypotonic solutions (i.e. D5W, D5.45NS, etc.) should be avoided. In particular, it is prudent to avoid dextrose containing solutions because of their adverse effect on ischemic neural tissue as discussed above, and also because free water is effectively introduced to the system as dextrose is metabolized. This latter case may also be true of lactate which contributes a significant component to the osmolality in lactated Ringer's solution (LR) and would favor restriction of administration of large volumes of LR (i.e. greater than maintenance requirements) particularly in patients who are already hyperosmotic. Normal saline (measured osmolality: 300-305 mOsm/kg) would thus be most appropriate when infusion of larger volumes of crystalloid are indicated. Determination of the patient's plasma osmolality may be very helpful in making these decisions. Because oncotic pressure plays little role in formation of brain edema, the question of whether to use isotonic crystalloid vs. colloid solutions (e.g. hydroxyethyl starch) rests on other considerations such as general cardiopulmonary parameters as well as the potential for a dilutional coagulopathy.

Perfusion Pressure

A commonality to most forms of acute CNS injury is reduction of blood flow and therefore reduction of oxygen/glucose delivery. Whether the cause is cardiogenic, vascular occlusion, or increased tissue pressure (e.g., intracranial hypertension), restoration of circulation is of paramount importance in reducing severity of the primary insult and in preventing superimposition of a secondary ischemic insult on already damaged tissue. Animals subjected to cardiac arrest have improved outcomes if arterial hypertension is induced during early recovery[58]. This correlates with better outcomes in patients who are hypertensive during recovery from cardiac arrest[59]. Mean arterial pressure (MAP) is also important in focal ischemic stroke. In animal models, the amount of tissue at risk for infarction is reduced when blood pressure is pharmacologically increased[60,61]. However, use of induced hypertension must be tempered by the concern for causing intraparenchymal hemorrhage. In the absence of controlled trials designed to define a risk/benefit ratio for induced hypertension in humans, current practice focuses on maintenance of MAP within normal range.

If the lesion is restricted to the spinal cord, there is an alternative method for improving perfusion pressure. Placement of a lumbar intrathecal catheter allows drainage of CSF. Patients undergoing aorta replacement surgery have a substantial risk of spinal cord ischemia. In most cases, neurologic deficit is evident immediately upon awakening from surgery. In a subset of patients, however, neurologic deterioration may be delayed for hours to days presumably due to edema. There are several reports where this delayed deterioration has been reversed by CSF drainage which is presumed to improve perfusion pressure and blood flow within the edematous cord[62,63]. The extent to which this mechanism can be extrapolated to acute spinal cord dysfunction associated with DCI is unknown. However, CSF drainage may be worthy of discussion.

Conclusion

Enormous progress has been made in understanding the pathophysiology of acute insults to the CNS. This work has allowed better definition of the potential to treat such injuries with respect to physiologic intervention. Stabilization of airway, breathing and circulation remain the first line of defense against progression of brain or spinal cord injury. However, additional care should be made to assure that intravenous fluids do not cause changes in plasma osmolality and that hyperglycemia and hyperthermia are absent. Induced hypothermia, induced hypertension, and lumbar CSF drainage remain speculative in the absence of direct study of efficacy in patients with DCI. Specific examination of these interventions is warranted on the basis of known efficacy in other forms of acute CNS injury.

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DISCUSSION 6:

Dr. Dietrich: When I first saw the results of Guy Clifton's multi center trial[1,2] I was annoyed. As we looked at the data more closely we saw that there was a very significant difference in how patients were treated among different centers. Some centers actually had better outcomes with hypothermia than other centers. We are revisiting that idea, and I hope that in the next multi center trial on hypothermia we will have learned from some of our mistakes. Dave made the point that aggressive heating to normalize temperature in patients is probably not appropriate, and we're not going to do that any more. The therapeutic window is just so critical. Many of us feel that there are some very powerful drugs to use, but if they are not administered during the time period when the pathophysiological mechanism is active, and the window is missed, then they're no good. Getting the patient into the intensive care unit or the emergency room in a timely fashion is critical. Regarding divers, when you have someone surfacing from a dive, targeting that person for some type of pharmacological treatment or hypothermia seems to make sense to a lot of us.

Dr. Farr: One of the advantages that we have is we have highly trained medical people deployed forward. One of the things that I saw in our casualties out of Afghanistan was a fair number of head wounds. The men in Afghanistan didn't use Kevlar helmets, because they were trying to look like their local allies. If we have the capability of doing something that's good for head wounding, we should push that forward also.

Dr. Massey: Clinically there's a difference in strokes between patients who have diabetes and who don't have diabetes. Hyperglycemia in a diabetic patient is bad. Hyperglycemia in a non-diabetic patient doesn't seem to do anything clinically, in my opinion. In the study that you showed were these rats diabetic or non-diabetic?

Dr. Warner: In the rat it doesn't matter, because you can induce diabetes with streptozotocin, a drug that induces florid diabetes. In animals it doesn't matter whether you give a bolus of glucose or whether it's an animal that has been rendered diabetic either genetically or pharmacologically. The problem with human data is that it's a chicken or egg question. Most studies have compared admission plasma glucose levels with outcome. Indeed, almost every single study, with one exception, which is Hal Adams work in the early 1980's[3], has shown that the higher the glucose admission the worse the outcome. However, the question is whether the patients with higher glucose had worse strokes, and there were a propensity to reactive hyperglycemia and thus hyperglycemia is perhaps a marker for worse stroke. Or, does the fact that they had hyperglycemia contribute to the worse outcome?

Dr. Massey: Adams study did take into consideration where the stroke was and of course diabetics have different kinds of strokes than other people.

Dr. Molé: We heard yesterday that core temperature is not a good indicator for CNS temperature and heard today that elevated CNS temperature has deleterious effects. Is there any good technology on the horizon that is non-invasive and relatively inexpensive to measure CNS temperature?

Dr. Warner: Most data that we're talking about comparing core versus brain temperature are obtained from either a Swan-Ganz catheter or esophageal thermistor versus a ventriculostomy with a thermistor on the tip, for example the Camino® device, available from Integra NeuroSciences, Plainsboro, NJ. I don't know about your question but I'll tell you one thing we can pretty much count on, in my reading of literature I'm not aware of cases where brain temperature has been measured at less than body temperature. In other words if you are measuring tympanic membrane temperature is that you can pretty well be sure that the brain is going to be warmer than that, how much warmer you don't know. As a clinician if you take a temperature under the tongue and it's 38.5°C you can bet that the brain is hotter than that.

Dr. Goodman: My understanding of anti-pyretics is that they work to bring the temperature back down to a physiological set point. Are there any pharmaceuticals or anti-pyretic like compounds that you are aware of that might permit us to reset the normal temperature another couple of degrees lower without major behavioral or physiological problems? Is this an area worth looking into?

Dr. Warner: It is an area worth looking into and I can tell you that anesthetics are very good at that.

There are a couple of drugs out there that I've heard about that seem to do exactly what you are talking about and are being investigated. That would be the dream: to tell the brain pharmacologically that 35°C was normal, without shivering and everything that goes with that.

Dr. Chimiak: If the studies do come out in favor of hypothermia do you see a change in anesthetic management? If we have to intubate in the chamber, should we be giving ketamine?

Dr. Warner: Regarding the anesthesia, the NIH is sponsoring a study, the international hypothermia aneurysm surgery trial, a $10 million study with one thousand patients requiring intracranial aneurysm surgery and subarachnoid hemorrhage are being randomized to 32.5-33.5°C versus 36.0-37.0°C, with a three month outcome assessment using appropriate measures. That study will probably be finished by the end of next year. I think the result of that will have a lot to do with what we do with the operating room, because that is probably the only appropriately powered non-bypass study that is ever going to get done. If it's a bust then I think that many people will make very, very strong cases to keep patients warm, because even mild hypothermia has been associated with decreased wound healing, increased wound infection, and an increased rate of myocardial ischemic events. Regarding the second question about ketamine, I would not give ketamine alone but if you feel comfortable giving benzodiazepines with low doses of ketamine then it's probably not a bad idea. Actually the GABA receptor is a very good target; there are a tremendous amount of data available suggesting that the volatile anesthetics protect the brain by the GABAergic potentiation. There is overwhelming evidence showing how protective GABA agonists are. However, they put people to sleep, which may not be practical for clinical care. But if you're already at the point where you have to sedate a patient I would not speak against ketamine although I would certainly co-administer a benzodiazepine with it.

Dr. Massey: Dr. Goldstein's stroke data suggest that benzodiazepines are contraindicated or harmful for patients with stroke[4].

Dr. Warner: Indeed it does, but that is not in the acute phase. He has very fine data, and he has clearly shown that persistent sedation in the recovering patient is adverse to outcome. But he is not looking at the first 6-12 hours; he is looking at days or weeks out. That's the difference.

Dr. Massey: The other problem is that with large lesions and sedation it is difficult to evaluate the patient.

Dr. Warner: That's an issue, particularly if they are leading to a state that you could do something about. For example, if they are bleeding one could consider a clot evacuation. Or, if they are sedated to a point in which the brain becomes tight and respiratory compression could compound the situation with hypoxemia or hypercapnia, so sedation is not necessarily a benign event.

Dr. Piantadosi: David, let me make a point and ask you about it. One of the things that you showed repeatedly and hinted at is that the reperfusion period is important. We're stuck with reperfusing. If we are going to make the first step in getting these folks back, what we have to do is restore blood flow. That's true whether the brain is hypothermic or the cord is hypothermic or whether it's ischemic. And that reperfusion period to me is extremely important because that's when a lot of the damage is done by the reintroduction of metabolism. That includes glucose and reactive oxygen species generation by the mitochondrion, which in my experience in the laboratory is a major source of reactive oxygen species production. So that source of damage doesn't occur when the brain is cold, and it doesn't occur when the brain is ischemic and deprived of oxygen and glucose. It occurs during the reperfusion. That's where apoptosis may start as well. There is some reason to link reinstitution of mitochondrial metabolism with apoptosis in some circumstances. So, don't you think that a single therapeutic approach like hypothermia can turn up a lot of negatives because it's not sufficient, because you have to reperfuse? It's the same thing in stroke: when you give the TPA, you have to reperfuse. So we really have to understand this problem: how you turn metabolism back on full blast, turn the furnaces on, without burning up the cell. Would you care to comment?

Dr. Mitchell: Part of the problem is that you don't know when you are going to reperfuse unless you are doing something like CPR. Reperfusion is a double edged sword, for example with hyperbaric oxygen, or even normobaric oxygen, there is evidence to suggest that even administration of 100% oxygen at 1 ATA will increase measurable reactive oxygen species damage. If you take a brain that's reperfusing and you add hyperbaric oxygen you may be adding fuel to the fire. Thus, you may be working against yourself to some extent. I don't know what to say except that I think you are right:

this is the dilemma that we face. We've got to get flow going again but we know that when we get it turned on all these evil humors are coming out. The earlier we can intervene pharmacologically the more likely we are to get a positive result.

Dr. Butler: Have the interventions that you have shown: avoidance of hyperthermia, regulation of blood glucose been shown to be protective in models of decompression sickness or gas embolism, and if not with what confidence can we extrapolate from these other types of insult into the dysbaric injury to the CNS?

Dr. Warner: I don't know of any studies in decompression illness where those have been examined, does anybody?

Dr. Piantadosi: I don't know of any real data on it, but the reason that I brought up the issue of reperfusion injury is because I think we need to think about how much of what we see has to do with reperfusion injury. I mean, does it exist in spinal decompression sickness; does it exist in arterial gas embolism? My bias is that it does, but to my knowledge I don't think there are any real data on it, but I think it's something worth investigating and may be potentially important.

Dr. Dietrich: In some of our reperfusion models hypothermia has blunted the rise in oxygen free radicals and has attenuated apoptotic cell death. Some people are attempting to combine TPA treatment with mild cooling. One of the questions is how cooling will affect thrombolytic agents, for example. In terms of thrombotic models, hypothermia has been shown to be neuroprotective in embolic models of stroke. If some the pathophysiologies involved in embolic stroke similar to some of the things we were talking about in spinal cord pathologies that may be relevant.

Dr. Butler: We have sort of agreed in this forum that we may not be able to get prospective human studies to look at many of these agents very easily, and we may have to fall back on animal studies. The point I'm trying to make is that I would be very hesitant to look at a study of a neuroprotective agent that used a model of traumatic closed injury to show neuroprotection, and then extrapolate that to somebody with gas embolism.

Dr. Mitchell: David, you showed us quite a long list of studies that didn't demonstrate benefits of hypothermia, and cardiopulmonary bypass as part of the case were not considering hypothermia useful in humans at this stage. What do you think of the contention of many that pulmonary bypass or cardiac surgery in general is not a good model for testing hypothermia as a neuroprotective intervention because of the fact that patients are rendered hypothermic? For much of the surgical procedure they may be normothermic, or the brain may even be hyperthermic, as you have pointed out, at both points in the operation where there is maximum risk, that is, going on bypass and separation from bypass, particularly in hard surgeries where there are a lot of emboli around.

Dr. Warner: I agree with you. I'm just trying to examine what evidence do we have that mild or moderate hypothermia works in humans. There is plenty of evidence that profound hypothermia is neuroprotective; there is no debate on that. But as of today, in January of 2002, we don't have evidence that mild to moderate hypothermia works. As doctors we have to take care of patients today, and for somebody it's not a theoretical problem. So, how do we proceed with insufficient evidence? I'm not sure what we should do. Getting back to decompression illness, to take these prototype drugs without knowing the toxicology, dosing or therapeutic window seems ridiculous. I don't think that measuring a patient's temperature and bringing it to normal is a great leap of faith. We have sufficient evidence to indicate that high temperatures injure the central nervous system in a variety of human and animal models. So if you have a central nervous system injury, I think you should measure the patient's temperature and fix it. I think that's an easy conclusion. What about glucose? It's not that hard to measure blood glucose. If a patient's blood glucose is sky high, then fix it. Does that mean that we should aggressively reduce blood glucose below 150 mg/dl or whatever, I don't know? Certainly if I measured a value above 250 mg/dl I would fix it. Now that's what the evidence suggests and that's what I would do if I were taking care of one of these patients. The next step is pursuing some sort of adjunctive pharmacological therapy. My advice is that you should read the literature and continue to have this kind of meeting and talk to people who are focusing on this and other domains, because you probably never will have the appropriate randomized, prospective, controlled studies. At some point you're going to have to take a leap of faith. But if a wonder drug keeps popping up positive in different domains of ischemic or traumatic CNS injury, it's not going to be that great a leap of faith, particularly if it is understood what the drug does and how it should be used. The next

issue is pertinent to drugs that are on every doctor's shelf. These would include steroids, lidocaine, ketamine, benzodiazepines: drugs for which there are some evidence that they work in a variety of models. Almost every doctor knows how to use these drugs, perhaps with the exception of ketamine. These are drugs that you should be debating whether to advocate, since they are relatively safe drugs that most physicians know how to use. That's what you should hope to walk away with on those drugs today, as well as keeping tuned in what's happening with the new stuff.

Dr. Bove: My question has to do with the intrinsic model that we are trying to study. In the case of decompression sickness I sort of envisioned the model as a direct tissue injury model, although there's some evidence that it's a vascular occlusion model. Most of the stroke research has been done on a large vessel vascular occlusion model with reperfusion. Being a cardiologist I'm interested in squirting something that dissolves clots in arteries, but if you have a lot of interstitial injury with capillary breakdown that's not a good therapy, because you will augment hemorrhage in that case. It seems to me that similar research that has to be done is to go back and repeat some of the vascular occlusion studies in a model of more direct tissue injury that would mimic more the spinal cord injury model rather than the vascular occlusion model. If you do vascular occlusion, when does the vascular occlusion model transition into an interstitial injury model? I know in stroke there are about 4 hours before you start to worry about hemorrhage due to the tissue breakdown. They are different models and they require different therapies.

Dr. Warner: I don't know what the answer to that is. What your question sparks is a comment. Although I found the work out of Honolulu that was presented yesterday by Dr. Hardman was extraordinarily fascinating, the date that I saw on that was 1994, and there has been a whole lot going on in the world since then. If that's the best data you have in a model of DCI then you need to do some research, I would suggest. I think that some basic research in this area would not require an enormous amount of money, and you could just bring the models up to current standards and test some fundamental questions, like physiological effects on outcome that you could control on a submarine or on a ship, and get the industry going again so that the new drugs could be plugged in. Then at least you could get an animal study to test drugs that may be beneficial in other clinical settings. So if a drug works in humans, say in head injury, the animal study would then provide some information regarding when to give it to divers.

Dr. Southerland: We have divers that work in water that is relatively warm. If they develop decompression illness they can be pretty warm when they come out of the water, and the chances are that the chamber will also be warm. We've had reports that some of our chambers, upon starting treatment, were 120°F before starting compression. What we normally do is throw in some ice or whatever we can do to try and cool them off. Dr. Rocky Farr mentioned putting ice packs on their necks to try and cool them down, or perhaps at least cool their brains down a little. Based on limited information, would you now recommend now, in the presence of cognitive deficits, rather than simply cooling the chamber, to applying cooling directly to the head?

Dr. Warner: That's a really good question, because it takes us to the next level: how do we do it? In neurosurgical patients this has been studied quite a bit. There is a real problem with surface cooling. However, by placing ice packs on the head, even in a comatose patient, you cannot cool the brain. You need total body cooling, which is difficult to accomplish in someone who has a good musculoskeletal system, and can shiver. So you have the option of anesthetizing the patient so that they can tolerate the cooling or using the central venous heat exchanger that was mentioned yesterday (e.g. Endovascular Temperature Management System manufactured by Radiant Medical, Redwood, CA[5]). I think if you feel that cooling is really important, and you cannot alter the environment of the chamber, then that would be the way to do it.

Dr. Latson: Of course that introduces the risk of an invasive procedure for a benefit that is ill-defined.

Dr. Goodman: I share your concern about extrapolating the trauma and stroke models until there is at least a minimal demonstration of neurochemical congruence of the models, preferable in a small animal model, since that's where most of the trauma and stroke work are done. I say this because to me the pathology looks unique in some respects; I think that at a minimum proof of neurochemical congruence is necessary. Then, whether to take it to proof of therapeutic efficacy would be the decision at that point. I haven't heard a lot of discussion about the small

animal models. I understand that it is hard to "bend" small animals. But that would give you higher throughput and the ability to take advantage of the transgenic animal models. So, I share your concern.

Dr. Flynn: Could you comment a little about the control of hypertension? Dr. Drew Dutka showed a number of years ago in gas embolism that hypertension was extremely deleterious[6]. Hearing about ketamine and particularly intubation with ketamine brought to my mind that we may wish to avoid the associated hypertension. We can also see hypertension in gas embolism if we embolize the posterior circulation while at the same time there is carotid artery embolism, the associated hypertension could be extremely deleterious.

Dr. Warner: I don't know those studies by Dutka. I don't think that the head injury model is a very good one from which to extrapolate, because there is the issue of encasement of the brain in a rigid skull and control of intracranial pressure versus cerebral perfusion pressure. The stroke model is probably more relevant, in which you have obstruction to flow in a vessel and the tissue distal to that obstruction has an ischemic penumbra, the flow to which is dependant upon collateral flow. In animal models the flow to the penumbra and the size of the infarct that results is dependent upon arterial pressure. Low pressure is not good and high pressure seems to help. Now what is high pressure and how does high pressure affect hemorrhage? Should that be an issue, since hemorrhage seems to be a part of your pathology? I guess I would go back to being a doctor on this one and aim to keep the blood pressure in the high normal range. I would not jack the pressure up to supranormal levels.

Dr. Flynn: My question was actually aimed at whether hypertension should be avoided in airway management.

Dr. Warner: An intubation can be done with any drug that is deemed safe for the purpose of getting an endotracheal tube in. To me that's a separate event, and is irrelevant to brain protection. It's what happens when the tube is in and the hours afterwards; if you are going to move towards ketamine then low doses of ketamine are probably what you need. In animal models the NMDA receptor antagonism that is highly efficacious is roughly equivalent to 0.4 or 0.5 MAC of anesthesia, which corresponds approximately to a level of anesthesia which would allow someone to put an endotracheal tube in but not a surgical incision.

Dr. Farr: I'd like to go back to the heat thing. We have a significant problem about warm water diving. Most of the operational areas that we've been in lately have been hot. So, if we have a diving casualty who requires recompression after diving in warm water it is likely that we are going to have a hot patient. I would like to hear your comments on whether I should delay recompression until we have reduced the patient's body temperature.

Dr. Warner: Do you actually have data on what the temperature of these individuals is?

Dr. Latson: We have done some trials with the SEAL delivery vehicles a couple of years ago in Bahrain, and divers were coming out of the water at 39°C or higher. The chamber temperatures, even before compression to treatment depth, were often 110 to 120°F.

Dr. Dietrich: Let's emphasize that under normal conditions the CNS can deal with this. In fact, hyperthermia has been shown to be a stimulus for ischemic pre-conditioning. It's when the CNS is injured that it becomes extremely sensitive to mild elevations in temperature. So I think that if you have data that shows these divers are mildly hyperthermic and they are undergoing some type of neurological insult, then I think you have to think seriously about ways you can bring that down maybe ½ or 1°C. Because, certainly based on all of our data, periods of hyperthermia are not only going to speed up the cascade of cell death but in many cases make it much worse. This also applies to inflammatory cascades that are triggered by cell injury.

To summarize this session: we need to continue to think about hypothermia; try to blunt hyperthermia, and let's talk about developing rodent models, because it's clear that the pathology of decompression illness may be different from other CNS insults.

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PROTECTIVE ROLE OF PROPOFOL IN CEREBRAL ISCHEMIC INJURY

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Introduction

Ischemic stroke reduces or blocks blood flow in neural structures. Following ischemia, severely depleted phosphocreatine, ATP, glucose, and an increased lactate level induce an injury cascade and subsequently lead to irreversible cerebral injury. The phenomenon of reperfusion, by itself, may cause further damage, in part by mechanisms that involve free oxygen radicals damage. Ischemia-reperfusion injury consists of a central area of dense infarct, surrounded by a penumbra of potentially viable tissue, which may be salvaged to varying degrees by prompt reperfusion or pharmacological interventions. Many general anesthetics are believed to possess neuroprotective effect.

In general, the pharmacological mechanisms through which anesthetics produce neuroprotection as well as anesthesia are not fully understood and might conceivably be explained by suppression of cerebral metabolism, oxygen consumption, blood flow, and/or intracranial pressure while simultaneously raising cerebral vascular resistance[1,2,3]. The barbiturates were introduced in the late 1930s for general anesthesia in the neurosurgical operating room due to their favorable cerebral hemodynamic profile. In the 1960s, general anesthesia for neurosurgery was recognized to play a role in protecting brain against intraoperative ischemic events. Currently, possible neuroprotective effect of various pharmacological agents is under investigations. Available data from recent studies suggest that propofol, an intravenous anesthetic may possess neuroprotective property.

Propofol is a substituted isopropylphenol that is administered intravenously as a 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide. The emulsion formulation of propofol appears to be devoid of allergic potential. Changes in plasma histamine concentration do not follow the IV administration of propofol. Clearance of propofol from the plasma exceeds hepatic blood flow, emphasizing that tissue up-take as well as metabolism is important in removal of propofol from the plasma. There is no evidence of impaired elimination in patients with cirrhosis. Renal dysfunction does not influence the clearance of propofol. Propofol can be administered as a continuous intravenous infusion without a cumulative effect.

Effect of Propofol on Cerebral Metabolism

The balance between demand and supply of oxygen and nutrients is essential in maintaining normal neuronal function. While ischemia takes place, the supply of oxygen and nutrients no longer meet the demand, an ischemic cascade initiates and cerebral injury may occur if ischemia persists. It is believed that the neurons would increase tolerance against ischemia if

cerebral metabolism decreases. This is one of the basic mechanisms how the pharmacological intervention achieves. Influence of propofol on cerebral metabolism has been well investigated. Dam et al[4] examined local cerebral glucose utilization (LCGU) during propofol anesthesia and recovery in 52 regions of the **rat** brain. The general pattern of the cerebral metabolic response to propofol anesthesia was a dose-related, widespread depression of LCGU. Cavazzuti et al[2] investigated the effects of propofol on the metabolic activity pattern of 35 regions of the **rat** brain and cervical spinal cord. Functional activity values were reduced in 31 gray matter and two white matter structures in a propofol group relative to controls. Propofol-induced depression of metabolic activity was present in central nervous system regions belonging to sensory (auditory, visual and somatosensory), motor and limbic systems, including spinal cord gray matter. Their studies clearly indicate that propofol reduces central nervous system metabolic activity.

Prevention of high intracranial pressure (ICP) and maintenance of cerebral blood flow (CBF) autoregulation are important to reduce cerebral ischemia injury. Effect of propofol on ICP and CBF autoregulation has also been investigated. Using a **rabbit** model of intracranial hypertension, Watts et al found that propofol had a greater effect in preventing high ICP than hyperventilation when used as the initial treatment and that the two treatments were additive[5]. Decrease in global CBF and spinal cord blood flow has been observed in the **rat**[6] and in the **baboon**[7] and in the **pig**[8] and in the **gerbils**[1] in a dose-dependent manner when propofol was administered systematically. The physiologic responsiveness of the cerebral circulation to alterations in arterial pressure was observed to be well preserved[7]. Propofol induced dose-dependent depression of spontaneous brain electrical activity was in accordance with decreased cerebral metabolism[9]. The property of propofol to decrease cerebral metabolism suggests propofol may have neuroprotective effect.

Neuroprotective effect of propofol

Neuroprotection of propofol has been investigated in both in vitro and in vivo studies. Acute brain ischemia causes neurotoxic cascades including N-methyl-D-aspartate (**NMDA**) receptors and nitric oxide (NO). Shibuta et al established a model of primary brain cultures to examine the influence of propofol on NMDA/NO neurotoxicity. Cortical neurons were exposed to various concentrations of propofol with NMDA or NO-donor. They found that propofol has some degree of neuroprotective effect similar to thiopental against NMDA/NO-induced cytotoxicity[10]. The effect of propofol on the toxicity induced by glutamate (**GLU**) or NMDA on cultured fetal rat hippocampal neurons has also been studied[11]. The study showed that the toxicity induced by brief exposure to GLU or to NMDA was significantly reduced by propofol. These studies suggest that propofol significantly attenuate NMDA receptor-mediated glutamate neurotoxicity in vitro.

In vivo study enables investigators to evaluate neuroprotective effect of propofol by measuring infarct area and assessing behavior changes mimic to clinic situations. The earlier studies suggested that propofol may have the same neuroprotective effect like barbiturates[12] and the better effect than isoflurane[13]. Lee and his colleagues[14] pretreated with propofol in an incomplete forebrain ischemia-reperfusion injury rat model and observed the significantly reduced infarcted area. They concluded that propofol might have a protective effect on incomplete forebrain ischemia-reperfusion injury. Yano et al administered propofol

intracerebroventricularly and found propofol-exhibiting neuroprotection against transient global forebrain ischemia; however, the extracellular glutamate level during ischemia is not a major determinant of this neuroprotection[15]. Increased production of free oxygen radicals plays an important role in ischemia injury. Yamaguchi et al found that propofol attenuated delayed neuronal death probably by preventing lipid peroxidation induced by transient forebrain ischemia[16,6]. Propofol has also been observed to inhibit neuronal apoptosis after brain ischemia and consequently reduced the delayed neuronal death in the CA-1 pyramidal cell layer of the hippocampus[17].

Neurologic complications occur following cardiopulmonary bypass surgery, LeBlanc et al conducted a randomized, controlled, single blind study to determine the effect of propofol on neurologic complications in 24 children scheduled for elective cardiopulmonary bypass surgery. They found that there were no gross neurologic complications in propofol treated patients. Their study suggests that propofol appears to stabilize the energy supply/demand equilibrium of the brain during cardiopulmonary bypass surgery and thus theoretically could reduce the incidence or severity of neurologic complications[18].

Ito et al evaluated the relation between dose and response for the neuroprotective effect of propofol in a rat model with incomplete cerebral ischemia. They found that a high dose of propofol may be needed to provide neuroprotection. The protective effect cannot be completely explained by the attenuating effect on circulating catecholamines[19]. The activation of GABAA receptors, which include the specific binding subunits for propofol, plays a role in the inhibition of neuronal death induced by brain ischemia[20].

Using a **cat** model, Cervantes et al observed the significantly lower neurological deficit scores in propofol treated than in untreated cats the days after cardiorespiratory arrest. The data suggested that propofol is capable of reducing both brain electrical activity alterations in specific brain structures, and neurological deficit elicited by complete global cerebral ischemia in cats[21].

Recent Studies

The effect of propofol on dopaminergic neurotransmitter appear interesting: an ongoing study by our group[22] used in vivo microdialysis techniques to examine the effect of propofol on infarct size and the striatal DA release in a rat model of temporary middle cerebral artery occlusion (MCAO). Sixteen rat had the right striatal microdialysis probe placed. Ischemia was induced by inserting a 4-0 monofilament nylon suture into the MCA. Propofol was intravenously infused in 8 rats during ischemia (60 min) and reperfusion (120 min) period at an average dose of 36 mg/kg/hr. Control rats (n=8) received vehicle infusion. The samples of microdialysis were continuously collected and measured immediately during the entire experiment. The infarct size was determined by using TTC technique at the end of the experiment. Propofol significantly reduced infarct size, the median (inter-quartile range) value in propofol group was 6.84 (7.68)%, which was significantly lower than the vehicle infused rats, which was 28.04 (32.28)% ($p<0.01$). MCAO induced a significantly increased DA level in the striatum of the vehicle infused rats. Propofol infusion significantly reduced MCAO-induced higher DA level. The data demonstrate that propofol, when administered during ischemia and reperfusion provides notable neuroprotection in our experimental

transient focal cerebral ischemia rat model. The data also suggest that reduced extracellular DA level may be one of the factors contributing to the neuroprotective property of propofol.

Doses and administration

The only dose with demonstrated effectiveness in rat so far is relatively large: namely, 600 μg/kg/min, or approx 3-4 times the dose which was proved anesthetic in man. However, this dose does not appear particularly large for our anesthetized rat. In fact the rats continue to breathe spontaneously, have stable, mid-level hemodynamics and show some movement during the reperfusion period. It is our hypothesis that this I/R model represents an extreme of ischemia for one hr. A more suitable "bubble injection" model might show more patchy perfusion, and variable reperfusion after embolization. Presently we are experimenting with microsphere injection models of 50 microns diameter. Finally, in vitro studies have unequivocally shown that much diluted propofol solutions are neuroprotective in defined models. We expect to show effectiveness of neural structure's protection at much lower doses of propofol in the future. This would support the use of diluted propofol solutions in the field, during transport to a recompression facility for definitive treatment, with relative safety of administration by paramedical personnel.

Conclusions

Propofol has been widely utilized in the operating room and in the intensive care units. Its neuroprotective effect has been observed. The enhanced GABAergic inhibitory activity, the reduction of metabolic rate and oxygen consumption induced by propofol on the neuronal components of brain structures, and its antioxidant potential have supported the possible beneficial effects of this drug against brain damage elicited by cerebral ischemia.

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DISCUSSION 7:

Dr. Dietrich: How would you ever hypothesize a drug that reduces blood flow and given before a ischemic insult to be neuroprotective? That's one of the characteristics of propofol, that it decreases cerebral blood flow and you gave it before the occlusion.

Dr. Camporesi: Those are general properties of its pharmacology as an anesthetic. Propofol has been shown to decrease oxygen consumption and to reduce cerebral blood flow.

Dr. Dietrich: Do you think it reduced cerebral blood flow in your animal model?

Dr. Camporesi: I have no idea, I didn't measure it.

Dr. Dietrich: It would be important to look at. The other thing has to do with pharmacological treatment, especially when you give it prior to ischemic insult, you have to be very sensitive to physiological variables that the drug may be producing. I will ask you, did it have any effect on blood pressure, or more importantly, brain temperature?

Dr. Camporesi: Arterial blood pressure and heart rate were well maintained. These were not 'shocky' animals. Temperature we did not measure.

Dr. Bove: The dopamine increase in the brain is interesting, in that we're still looking for diagnostic tools to identify brain injury or cerebral air embolism, and I was wondering if you did any systemic blood dopamine levels to see if they were reflecting the elevated levels in the brain.

Dr. Camporesi: I didn't measure blood dopamine levels.

Dr. Bove: Has anyone in the rest of the group done any blood dopamine levels in stroke or in air embolism? I'm looking for diagnostic tools.

Dr. Camporesi: Dopamine is relatively easy to measure, by HPLC. But if there is a 3% infarct in the brain, how much dopamine could be released into the blood? I don't think it's going to be that much.

Dr. Thalmann: Did you look at arterial PO_2?

Dr. Camporesi: These are air-breathing animals, with PO_2 in the 80-90 mmHg range.

Dr. Thalmann: Did you try 100% oxygen at 1 atmosphere to see if it was effective?

Dr. Camporesi: No.

Dr. Thalmann: Did you try 100% oxygen at any pressures other than what you presented here? Were you able to observe what the dose-response was as a function of PO_2 without the propofol?

Dr. Camporesi: No.

Dr. Chimiak: It has been reported in an animal model that for local anesthetic toxicity lipid administration can produce spectacular results. One of the suspected mechanisms is sequestration of local anesthetic. This may be a factor as far as using these two agents together.

Dr. Camporesi: I did try lidocaine in this model. Lidocaine seems to protect. But my studies with lidocaine were complicated by the fact that a lot of animals died with lidocaine infusion. I am not sure why, so I'm a little reluctant to talk about it because I don't know if there's something fundamentally wrong with the technique.

Dr. Goodman: We've done cerebral microdialysis on about 140 head injured patients have measured amino acids, lactate and glycerol, and the alterations in the extracellular composition of the brain are not reflected in systemic alterations. So I think it would be very, very surprising if you could be able to detect a dopamine change systemically.

Dr. Bove: Enrico, the reason that I mentioned the protocol is because I think you need to remember that lidocaine is a class I antiarrhythmic agent and can prolong the QT interval. Brain injury also prolongs the QT interval, so you could be getting a Torsade type of ventricular fibrillation from it.

Dr. Camporesi: In this rat model I'm having difficulty right now and I'm losing a lot of animals with lidocaine. On the other hand, with propofol these animals are very stable: they have good pressure, they have great perfusion, and I do know that in intensive care we give tons of propofol to patients. I do think that it would be useful to investigate particularly two things: a gas model of

injury, which we have just started doing, and a prolonged propofol protection to a point that we could move the animals to be treated in the chamber. And then, long-term, measure the cognitive results.

Dr. Flynn: Enrico, would you speculate on barbiturate coma versus propofol. I know you didn't study it, but barbiturate coma I believe was eventually shown not to be very useful.

Dr. Camporesi: Barbiturate coma has some side effects from a cardiovascular standpoint, it requires cardiovascular support, maybe including dopamine infusion. It could be that propofol is not as much of a cardiac depressant at these doses. I don't know if there is a study comparing barbiturates and propofol for neuroprotection.

Dr. Mitchell: Enrico, what was your target plasma lidocaine concentration in the rats in which you were using lidocaine?

Dr. Camporesi: I administered the drug as a constant infusion at the same rate per kg as for human use. I did not measure the plasma levels.

Dr. Massey: Enrico, the striatum in rats I assume is similar to human as far as the globus pallidus and putamen, primarily. The stroke that you showed was not limited to the striatum. In diving I don't know that I've ever seen an embolus that I thought was at least limited to the striatum. .

Dr. Camporesi: The striatum in the rate does not have an equivalent structure in the human. In this model there is some involvement of the cortex. However, it is not possible in the rat to occlude the middle cerebral artery and produce only a focal cortical lesion. In addition, I do not believe that preservation of the gray matter only should be our only goal; we should be concerned also about subcortical structures.

Dr. Thalmann: In researching some papers on lidocaine, in the original lidocaine studies, they gave lidocaine sufficient to flatten the EEG, just to see if it was neuroprotective and I don't recall that the animals died. I also recall that it didn't work. And it wasn't until they backed off the dose that they saw the protective effect. Initially the theory was that if the EEG was flat, neuronal metabolism would be shut down, neuroprotection would then ensue, but it didn't.

Dr. Camporesi: I think there are probably similar agents with less toxicity.

FLUID RESUSCITATION, PLASMA GLUCOSE AND BODY TEMPERATURE CONTROL

Richard E. Moon, MD

Blood glucose control

There is evidence that central nervous system injury in both brain[1] and spinal cord[2] can be worsened by hyperglycemia. The mechanism of this enhancement of injury is believed to be due to increased lactate production and the resulting intracellular acidosis. Evidence from series of human head injury patients[3], rats undergoing global ischemia[4] and patients with strokes[5] suggests that the effect becomes significant above a threshold plasma glucose of around 200 mg/dl (11 mM). One study reported no threshold, but rather a monotonic decrease from a plasma glucose of 50 mg/dl[6]. Administration of even small amounts of glucose, for example one liter of intravenous 5% dextrose solution, may worsen neurological outcome, even in the absence of significant hyperglycemia[7]. Of several studies investigating this relationship, only one appears to contradict the effect[8]. Therefore, unless treating hypoglycemia, it is advisable to avoid the administration of intravenous solutions which contain glucose. In the presence of central nervous system (brain or spinal cord) injury, whenever possible plasma glucose should be measured and high levels reduced.

Fluid Resuscitation

Divers with DCI are often dehydrated due to perspiration before entering the water, immersion diuresis and bubble-induced capillary leak[9-11]. Fluid administration to replenish intravascular volume, reverse hemoconcentration and support blood pressure constitute basic principles of resuscitation. Interventions that increase central blood volume and cardiac preload such as supine position[12], head down tilt[13] and head out immersion[12,13] significantly increase the rate of inert gas washout. Therefore aggressive hydration, even in divers who are not dehydrated, may be advantageous.

Rapid intravenous administration of hypo-osmolar fluids can cause central nervous system edema[14]. Reduction in oncotic pressure with unchanged osmotic pressure has no effect, however, and there appears to be no particular advantage of colloid vs. crystalloid solutions[15,16]. Therefore either isotonic fluids without glucose, such as normal saline, lactated Ringer's solution or Normosol-R™ (Abbott Laboratories, North Chicago, IL), or colloids such as plasma protein fraction or hetastarch are recommended. For patients with traumatic brain injury and intracranial hypertension, hypertonic saline may offer improved control of intracranial pressure[17], although it has not been specifically tested in decompression illness.

Whereas for critically ill patients intravenous administration is preferable, oral fluids may suffice for mild disease. Oral fluids have been used for rehydration of patients with acute gastrointestinal illness, including cholera.

Maximum water absorption occurs at a sodium concentration of 60 mM and glucose concentration in the range of 80-120 mM. An ideal solution for rehydration in diarrhea has been suggested as containing approximately 30-60 mM sodium, 70-150 mM glucose and

osmolality of around 240 mOsm/kg[18,19]. Although almost all commercially available beverages are low in sodium and high in carbohydrate, certain beverages, for example Gatorade™ (Gatorade Co., Chicago, IL), contains sodium and glucose concentrations that are close to ideal. WHO oral rehydration salts are widely available; reconstitution of these salts with the appropriate amount of water produces a solution containing 90 mM sodium and 111 mM glucose.

Provided the patient is not vomiting, an oral intake of 1,000-2,000 ml of fluid per hour is safe and tolerable. The gastric distention that occurs after oral fluid intake stimulates gastric emptying. However, if there is protein or high glucose concentrations (over 5% or osmolality >252 mOsm/kg) in the fluid, gastric emptying can be slowed. Ingestion of plain water is preferable to none at all, although the inhibition of vasopressin secretion caused by hypo-osmolality can produce a falsely reassuring increase in urine output[20,21]. Fluid should not be withheld just because an ideal liquid is not available.

End points for fluid therapy include normal blood pressure, heart rate, hematocrit and a urine output of at least 1 ml/kg per hour.

Body temperature

Numerous animal models of CNS injury have shown that outcome is significantly worsened by hyperthermia[22]. Two studies of patients after out-of-hospital cardiac arrest reported improved outcome with mild hypothermia (32-34°C) maintained for 12-24 hours[23,24]. There is sufficient evidence to indicate that high temperatures injure the central nervous system in a variety of human and animal models. Thus, although a recommendation to induce hypothermia for the treatment of decompression illness is premature, it is recommended that simple measures be in place to prevent a diver from raising his core temperature, by avoiding a hot environment and treating a fever. If body temperature of a patient with DCI is elevated, aggressive attempts to lower it should be instituted.

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DISCUSSION 8:

Dr. Bove: I would be interested in separating joint pain from paresthesias, because I would classify paresthesias as neurological. In addition, I think it would be useful to differentiate pure air embolism from severe DCS, which would include a vascular permeability problem. Fluid recommendations for these two entities should probably be different.

Dr. Thalmann: In the data you presented from the old literature, is there anything in there that would distinguish between dehydration being a cause or effect?

Dr. Moon: No.

Dr. Thalmann: It's usually my habit that when someone comes in with decompression sickness that has a neurological component, no matter what severity, I always recommend that we give fluids until we verify they have a normal urine output, and that the patient can in fact evacuate their bladder. I'm surprised why in your 3rd and 4th category in there, you didn't mention anything about looking at the urine output and giving fluids, and that's a little bit surprising. Why didn't you just always give fluids until there is a reasonable urine output, provided the individual can urinate? Obviously if you are very sick you can't do that, but I'm talking about the other two.

Dr. Moon: Yes, I take your point. Really it's very difficult to measure urine output over a short period of time in somebody who doesn't have a Foley catheter. So what I wrote there was a guideline that can be used in the field. However, we could make it more stringent.

Dr. Thalmann: Certainly if we give the individual a reasonable amount of fluid, within an hour or 90 minutes he's going to have to urinate. So if you're treating him anyway, he's going to be in the chamber long enough that you could verify at least that he can evacuate his bladder and that he is putting out a reasonable amount of urine.

Dr. Bove: John Hallenbeck, Dave Elliott and I did some studies showing changes in vascular permeability and that there is a capillary leak in response to bubble load. I think we are pretty comfortable with that from multiple studies suggesting a cause and effect relationship between capillary leak, that is loss of plasma volume, and the presence of gas bubble load[1]. We also published some work on visible endothelial injury in the decompression process from cell adhesion and white cell damage to endothelium[2]. So, I don't have a problem with the notion of a cause and effect relationship between gas bubble disease and blood vessels and a capillary leak or permeability leak. If in dealing with patients one measures only blood pressure, sometimes there can be a normal blood pressure in the presence of a very high systemic vascular resistance, which would inhibit renal blood flow, causing a low urine output even though the blood pressure looks normal. So I think that the presence of a good urine output suggests that the patient is not vasoconstricted and not intravascularly depleted, short of inserting a pulmonary artery catheter to directly measure systemic vascular resistance.

Dr. Thalmann: In normal people who are conscious the real reason we give fluids is to verify normal bladder function. We have seen patients in whom abnormal bladder function may be present in the absence of other really obvious neurological abnormalities. Obviously the side effect is that you are verifying urine output and you can look at the specific gravity. We always want to make sure that bladder function is normal.

Dr. Bove: I think Richard wanted us to try to look at evidence for using recommendations for fluid replacement. I mentioned a couple of studies that I think I'm comfortable with indicating the relationship between capillary leak and gas bubble disease, not pure cerebral gas embolism but mostly the other gas bubble disease. Is everybody comfortable with that relationship?

Dr. Butler: Looking at the data that you have presented, it's of interest but could be in the category of 'true, true and unrelated'. My question for you and for the group is, do we have any direct animal or human data that shows that administration of either crystalloids or colloids improves outcomes in either decompression sickness or gas embolism?

Dr. Moon: John Hallenbeck once related to me that the only intervention other than recompression in conscious animals with decompression sickness that would make them better was fluid administration. A few months ago I asked him if he had any video documentation or other observations

to shed more light on this, but he said unfortunately not. So, nothing is published as far as I know.

Dr. Butler: The reason that I mentioned it is that when we are talking leaking capillaries and CND edema, it is certainly potentially a two-edged sword. You don't treat closed head trauma with fluid loading, and I'm not sure if you would want to treat CNS edema caused by decompression sickness or gas embolism with fluid loading either. I noticed that your draft guidelines include both crystalloid or colloid. A second issue that I would really like to see worked out a little bit is, that those two types of fluid wind up in very different spaces after an hour, with 80% of the infused crystalloid being in the extravascular space, and only 20% in the intravascular compartment, as opposed to a colloid, in which it seems that 100% of the fluid remain intravascular. I can't imagine that doesn't make a difference.

Dr. Moon: That's certainly the case, if the capillary is intact, but if there are leaky capillaries, it gets out. I'm going to ask Dave Warner to comment on both of those issues that you raised.

Dr. Latson: There is some limited evidence that you can tease out of some other studies, suggesting that fluid administration has a benefit. Lynch's study done at Temple University in hamsters with decompression sickness showed a benefit of saline and surface oxygen compared with no treatment[3]. On the flip side of that there's a cautionary note, that if you have a severe case of AGE or DCS, particularly with chokes, animal models have shown that fluids are actually damaging, and increase mortality and that furosemide is therapeutic. So just like in a case of congestive heart failure or cardiogenic shock, you have to guide your fluid therapy based on what you think the volume status is. It's not a clear cut, 'always give fluid' kind of situation.

Dr. Warner: Mike Todd, who is an anesthesiologist, spent about 10 years asking the question about appropriate fluid resuscitation, but it was in the context of trauma or ischemia, not DCS[4-8]. This has been a controversy in neurosurgery for decades. We know that during surgery when we load the patient with crystalloid, we can watch the bowel and the liver expand; we know that the patient is 'third spacing' and that most of that fluid is going into the extravascular, extracellular compartment. But the brain is different; the brain has a blood brain barrier, as does the spinal cord. As a result, the flux of water across the blood brain barrier is predominately mediated by ionic gradients, and not by colloid oncotic pressure. In numerous models Todd has shown that the water content in the injured brain is not altered by plasma colloid oncotic pressure, and laid to rest the controversy of crystalloid versus colloid in terms of formation of brain edema. In contrast, very small changes in plasma osmolality will yield very large changes in brain water content, and correspondingly, in intracranial pressure. The key is therefore to control plasma osmolality. I don't think the crystalloid versus colloid question is relevant unless considering renal or cardiovascular issues, which of course may be important in this disease. I agree with the comments suggesting that it is necessary to look at the overall patient to decide about volume resuscitation. What I would like to do is ask Dr. Dietrich about the albumin story. Myron Ginsberg and his colleagues have demonstrated fabulous results in animal models by resuscitating animals with stroke using intravenous albumin[9-11]. It doesn't seem to be related to intravascular volume; the albumin itself seems to be pharmacologically active.

Dr. Dietrich: Myron Ginsberg has been looking at albumin administration for many types of CNS injury models, including global ischemia, focal ischemia, both permanent and transient, and traumatic brain injury. As far as I know those investigators do not understand exactly how albumin protects the nervous system after injury. The literature states that albumin could affect free-radical formation and many other types of pathophysiological mechanisms, so I don't think they really understand exactly how albumin works. Yes, NIH is funding a stroke trial to use albumin, but it's very controversial. When people ask me about it, they ask what the rationale for using this is, but I'm really not involved with the studies.

Dr. Bove: We've done some studies in animal models with albumin, looking at it's effects on endothelium. It actually does reduce adherence of blood elements onto endothelium, so it may have some intravascular contributions at that level as well.

Dr. Moon: Dave could you address the issue of which colloid From a military point of view, since a 500 mL bag of starch solution, such as Hextend™, is half the weight of a bag of lactated Ringer's solution, that may be important. We now have at least three colloid solutions available in the United States: Hextend™, Hespan™ (hetastarch)

and physiological albumin in a variety of forms. I have two questions. First, since there are questions pertaining to the effects of the starch solutions on coagulation function, is there a preferred solution for situations in which there may be brain hemorrhage? Second, what about the glucose in Hextend™? Do you think that could be detrimental?

Dr. Warner: I am going to inject one piece of data. In one animal model of spinal cord injury, making the animals hyperglycemic after injury did not adversely affect outcome[12]. In hyperglycemia, it is possible that there has to be an element present during the acute pathophysiologic cascades that are occurring during the injury. If there is an acute discreet event and then you give glucose afterwards, it may not worsen (although even then there is a study reporting worse outcome), but if you give glucose before the event, it does worsen[13]. DCS I presume is an ongoing event as opposed to an acute event such as a weight dropping on the cord. Thus, in the midst of that process, if you inject a glucose load, plasma glucose level in the patient might adversely affect the outcome. Regarding Hextend™ versus Hespan™, I'm not an expert on that. My understanding is that Hextend™ does not have the coagulopathy problems that hetastarch has; bleeding may limit how much Hespan™ you can give. Regarding Hextend™ or hetastarch versus plasma protein fraction, I don't see a difference personally, outside this theoretical issue that Dr. Ginsberg has raised as a possibility, that albumin may be a pharmacological agent as opposed to being merely a volume expander. So from my observations of patients for 20 years using hetastarch or Hextend™, as far as I can tell they are doing just fine. I don't see why using hetastarch versus plasma protein fraction would cost the brain anything. I don't know of any evidence that hetastarch is adverse to the brain or spinal cord as volume expanders. My vote here would be to avoid the glucose containing solution.

Dr. Bove: Is there a consensus from the stroke or brain injury literature that using glucose in a pure brain injury model is bad? That would be a Class "3" type of indication. Do we know that there's literature saying that if you give glucose in a brain injury model it wouldn't be good? I think there is but I'd just like to say yes or no. Do we have enough evidence that it is a Class "3" indication?

Dr. Warner: At a human level I don't think that we do, but from the animal data the dextrose in water (D5W) issue should come off as quick as you can get it off. There are two really strong reasons for that: there is a glucose load, and as that dextrose is consumed, you're dumping in free water to create a hypotonic plasma state and it's going to exacerbate any edema. Even a normal brain would expand under those conditions.

Dr. Bove: If the D5W drove up the blood sugar we could definitely say that was a bad thing to do, right? We have evidence that elevated glucose levels are detrimental in stroke for example.

Dr. Warner: I think that's generally accepted.

Dr. Bove: So we can put a Class "3" indication for D5W in pure arterial gas embolism. Then we go to crystalloids. I guess not everyone feels that flooding the circulation with crystalloids is a good thing to do. We just know that there's very little evidence that there is crossover into the brain. That's an issue that we need to decide upon. But in arterial gas embolism with pure brain injury, in most cases the circulation is intact. In most cases the blood pressure is okay, and what you are doing there is trying to deal with brain-related problems and not necessarily circulatory-related problems. Would anybody comment on the use of lactated Ringer's solution in a pure cerebral model?

Dr. Moon: Before you say anything, is there any reason to push fluids, to fluid load somebody with an isolated cortical lesion: a stroke or a gas embolism?

Dr. Bove: Fluids not including D5W?

Dr. Moon: Right.

Dr. Warner: Not that I am aware of, other than to promote maintenance of blood pressure. If you have a hypotensive patient, I think that most people would accept that you need to treat it, if it's due to hypovolemia, then volume is the treatment. I don't know of a theoretical reason why you would want to make an individual hypervolemic in response to the sorts of disease that we are talking about here. Sometimes it's used for vasospasm after subarachnoid hemorrhage, but that's a completely different matter, unless you postulate that there is vasospasm occurring around those microhemorrhages, but we don't have any evidence for that.

Dr. Bove: Any other comments regarding that?

Dr. Warner: One thing about lactated Ringer's (LR) solution is that it has been calculated that a liter of LR given to a 70 kg patient who has a plasma osmolality of 280 mOsm/kg is equivalent to giving about 110 ml of free water. This is relatively small and would not be expected to alter plasma osmolality or exacerbate brain/spinal cord edema. Thus balanced salt solutions, such as LR, despite being slightly hypotonic would be reasonable if given in modest quantities. In contrast, large volumes (e.g., many liters) could plausibly worsen edema.

Dr. Bove: There's at least a level "2" for the other two fluids. I think your recommendation for maintenance fluids only and not consider fluids a resuscitative tool in pure brain injury is probably reasonable at this point.

Dr. Mitchell: One of the reasons that has often been stated in support of giving fluids to pure arterial gas embolism patients is they do have a vasculopathy, and that divers are often dehydrated. Some of the dehydration that is seen in divers with increased hematocrit and divers with decompression illness may just be because they are dehydrated from their dive rather than from decompression illness. Giving fluid then alters the rheology of blood favorably. I don't know how valid that argument is, and I suspect it's not based on any data but it's a theoretical reason that has often been quoted. If we're just going to abandon that here, then that's okay if that is what everybody thinks, but we should at least think about that issue.

Dr. Bove: I don't think we are abandoning it. What we're saying is that you're not going to use lactated Ringer's for brain resuscitation. Obviously you're going to use it for maintenance of vascular volume or maintenance of hematocrit, but if you look at these Level "2" indications, you can find reasons to use Level "2" but they're not as strong. So the issue here would be if you're going to use crystalloid, you're using it not with the idea of brain resuscitation involved but rather, you are going to use it for circulatory reasons, that is keeping the blood pressure or hematocrit normal.

Dr. Moon: Where it says "and normal blood pressure", how about adding "normal hydration"?

Dr. Bove: Okay. After all, we are clinicians, and if divers with decompression illness have other issues we have to deal with them. This always comes up in the presence of lung leak, for example, if the patient is hypotensive.

Dr. Molé: Are we using 'LR' as synonymous with 'crystalloid'. From an emergency medicine perspective usually we use normal saline for volume replenishment.

Dr. Moon: I don't know of any evidence that there's any difference between the two except that when you give large volumes of normal saline you can make patients hypernatremic and hyperchloremic, whereas with lactated Ringer's solution you can give as much as you want and most electrolytes stay within normal limits.

Dr. Bove: Does anybody have any concerns about distinguishing between the two? No, then we'll leave it as crystalloid/lactated Ringer's. I know most of the military medical crystalloids are lactated Ringer's. We had a tractor trailer of lactated Ringer's sitting outside our fleet hospital in the Gulf in 1991.

Dr. Massey: The hypovolemic difficulties, the cardiovascular difficulties, in these situations, are they the same for AGE and DCS? AGE seems possibly related to stroke, but DCS does not.

Dr. Moon: Yes, that's exactly right. For a normovolemic, normotensive patient with AGE, I don't think anything more than maintenance fluid is required.

Dr. Bove: Does anybody have any encouraging statements about colloid in a pure brain injury AGE? I think we heard that there wasn't any difference. I'll throw one piece in is that it's much easier to put somebody into heart failure with colloid than it is with crystalloid, and so you've got to be a little more careful with how much volume load you're giving to even a normal person with colloid. So if you don't need to use colloid I would suggest that you don't use it or try not to use it in this kind of a situation. I would be interested in putting a "3" down, but maybe we could put a 2B. Does anybody have any issues about putting a "3" for colloid in pure brain injury?

Dr. Warner: If you put a "2" for crystalloid, you should also put a "2" for colloid.

Dr. Bove: Okay. We can give a 2B to the crystalloid, so we'll give a 2B to the colloid as well. Okay, we're dealing now with decompression sickness. I think we all agree that pure arterial gas embolism to the brain is a fairly localized injury; decompression sickness with gas bubbles in the venous system probably in the arterial system, but

in the tissues is a more disperse disease and does in fact have more consequences for the vascular system. So in that case we have a little different need for fluids. I'll ask is there any evidence against or for using D5W in that model, in the decompression sickness model, where there is probably more vascular permeability than there would be in pure brain injury?

Dr. Moon: I think it's going to be the same, Class "3".

Dr. Bove: Okay so I think we can comfortably put a "3" here for D5W? The next one is the crystalloid issue, again with the military always having access to crystalloids in the field, either normal saline or lactated ringers. Indications that it is efficacious to use crystalloids in decompression sickness, let's say spinal cord decompression sickness as an example. The indications would be maintaining normal blood pressure, maintaining hematocrit, maintaining urine output, is that reasonable? Okay. Let me ask a question, if everything is normal, hematocrit 42%, blood pressure 120/80, and urine output was 2 ml per kg per hour, and the patient had neurologic decompression sickness in the spinal cord, would you still start loading fluids? No. So I think all of these things are going to be contingent on the patient's clinical status as well as the diagnosis. I think that's probably an important piece of information. So indications would be a "1" for crystalloid or lactated Ringer's. I didn't talk about level of evidence, that's another story, but is there any particular value in distinguishing crystalloid from colloid in the decompression sickness model? Does anybody have any particularly burning issues? Are we comfortable in using the same ideas for the cord in terms of the blood brain barrier?

Dr. Warner: Dalton, you have a better idea on that one. This is a debate that has been going on for years: can the brain be a surrogate for the spinal cord? We know that the spinal cord autoregulates, we know it has CO_2 reactivity, we know there is blood metabolism coupling, and that there is a blood-spinal cord barrier. So at the macroscopic level, physiologically it's very similar to the brain. So, to my mind it is rational to extrapolate physiologic events between the two. When we get down to the molecular and cellular level, of course the white matter-gray matter ratios are different and the axons are longer. It's probably a different biology, but largely I think you can extrapolate, at least in the absence of better evidence. Do you agree with that?

Dr. Dietrich: I agree with that. I would add that in my experiments in terms of comparing traumatic brain injury and traumatic spinal cord injury, it appears that the microvasculature is actually more sensitive to trauma in the spinal cord versus the brain. We see more hemorrhage and permeability changes and we see greater inflammatory response. That would be the only major difference that I see. But in terms of water regulation and some of the endothelial functions, in the spinal cord these are very similar to the brain.

Dr. Moon: Regarding cardiorespiratory symptoms, chokes or pulmonary edema, there is animal evidence that diuretic therapy for this disease may reduce mortality, but I don't think that's really relevant to human disease. General supportive measures such as CPAP are not usually administered to goats or sheep with decompression sickness, nor are they are intubated or mechanically ventilated. If somebody has chokes, they have enough venous gas embolism to injure the lung, and it is very likely that they have generalized capillary leak, and probably hypotension. So my opinion is that they should be given fluid until blood pressure is normal and urine output is appropriate, with management of the oxygenation by whatever means is necessary.

Dr. Butler: As a follow up on that, going back to the crystalloid and colloid part of that plan, I mentioned that there's concern about endothelial dysfunction and that perhaps in the setting of intravascular bubbles, crystalloids and colloids both exit the intravascular space very quickly. Do we have any evidence for that, that the distribution of colloids and crystalloids is the same in decompression sickness and blood gas embolism?

Dr. Bove: All I can say is that the labeled albumin studies showing albumin leaking out of a capillary circulation, so the large molecules leak when you have endothelial damage, but whether they leak at the same rate as the crystalloids I'm not sure.

Dr. Moon: In other clinical situations in which there is capillary leak, such as sepsis, the use of colloid versus crystalloid has been aggressively looked at for years with, in the end, very little outcome difference. So to the extent that ARDS due to other causes is a surrogate for endothelial leak due to decompression sickness, I think colloids and crystalloids are likely to be the same.

Dr. Butler: Considering that colloids cost 50 times as much, if in fact we think that the effect is the

same we ought to discuss that and say in this setting maybe we should use crystalloid, because in the setting of endothelial dysfunction the colloid does not remain intravascular, and would not be expected to contribute to your intravascular maintenance any more than colloid.

Dr. Latson: I contend that 50 times greater cost is not an issue considering the small volumes of fluid that would be required: you're talking about a few dollars in a resuscitative effort that may cost thousands, so I don't think that the difference in cost between crystalloid and colloid is worth considering. Now if you're planning to deploy thousands of units for a multi-contingency trauma situation I would agree, but in an individual case of decompression sickness, where you're going to give one or two units of fluid, I don't think it's a big issue.

Dr. Butler: I disagree with that because you are not talking about a few cases you're talking about stocking every chamber in the Navy with Hespan or lactated Ringer's solution. The second thing is, if truly the endothelial dysfunction causes a significant alteration in the crystalloid versus colloid metabolism, then it may be that having these colloid molecules leak into the interstitial space is actually detrimental. In the setting of endothelial leaks, perhaps it is not a good thing to have the colloids being distributed in the interstitial space. I don't know if we can say that's physiologically equivalent unless we have evidence to prove it.

Dr. Bove: Could we hear a word about the possible use of fluorocarbon, which don't leak; they are red cell-sized particles and they absorb gases as well.

Dr. Latson: If we stay on the time schedule, we'll have about an hour to talk about that.

Dr. Flynn: I think in the chokes situation we have to clearly distinguish between two different situations. One is the operational situation in which mechanical ventilation and intubation are going to be nearly impossible, if not impossible. The other is a chamber ICU situation attended by physicians in which all these things may be done. In the latter situation maybe fluid replacement would be okay there, but in the operational setting for somebody with severe chokes, it's been shown, at least in animals, that diuretics and morphine analogs have been lifesaving.

Dr. Bove: I put this extra note on here, ARDS, because there's lots of literature on ARDS, that is non-cardiogenic pulmonary edema, and to get this done, let me ask if anybody is aware of literature showing that D5W is detrimental or useful in a non-cardiogenic pulmonary edema situation?

Dr. Moon: Fred, we're not actually treating the pulmonary edema with fluid, we're maintaining blood volume.

Dr. Bove: I understand, but I guess what I'm asking is, has anybody seen any literature that says that giving D5W in a patient with ARDS due to some other cause, will cause more trouble, will cause more pulmonary edema for example? I'm not aware of any evidence. So seems to me that we could probably come up with some equivocation like a 2A or B here and I can tell you that in the intensive care setting if there's ARDS we don't worry about using a glucose solution, because we're treating the pulmonary edema with other modalities actually, usually PEEP. Is anybody aware of any evidence that crystalloid has value or is detrimental in this case?

Dr. Latson: I think there are some as yet unpublished data in Dromsky's pig study[14] that showed that crystalloid infusion in the animal model of saturation decompression insult increased morbidity, which was attributed to the increasing pulmonary edema. I think that you have to be extremely careful about giving fluids to a patient with chokes. One more clinical caveat about mechanical ventilation in chokes: it is possible for AGE with severe respiratory distress to resemble chokes. In the presence of pulmonary barotrauma, if you institute positive pressure ventilation, additional air could enter the circulation, worsening AGE. I suggest that if you need airway control, tracheal intubation is appropriate, but as long as oxygenation is adequate spontaneous respiration is preferred.

Dr. Bove: Okay, I'm going to arbitrarily put 2B's for these last two, just for the sake of getting on. I think the issue here is we're not using fluid for resuscitation to treat the pulmonary edema of chokes, we may be stuck with needing to use fluid resuscitation for other reasons, and I guess my question is, is there any really severe negative reason to avoid one of them? I'm guessing that there probably isn't. We'd like not to use them but we probably have to use them in some cases.

Dr. Warner: I just have to stand up for the brain here on this one because if this goes in a book someplace and someone stumbles on a page and sees D5W for chokes on a guy who's got a reasonable chance of having spinal cord or a brain injury, that is the worst solution I know to give.

References (Discussion 8)

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USE OF 100% SURFACE OXYGEN IN TREATMENT OF DCI

E.D. Thalmann, M.D.

A preliminary analysis of cases of DCI from the DAN database shows that 100% oxygen breathing at 1 ATA prior to treatment does not necessarily influence the ultimate treatment outcome but does reduce the number of treatments needed to achieve that outcome.

Our experience with 100% O_2 breathing at 1 ATA is somewhat limited and mainly anecdotal. However, there are instances where symptoms have completely resolved breathing surface O_2 raising the question of whether or not it can be considered definitive treatment in some cases. This would become especially important if long and/or expensive medical evacuation is necessary in order to administer recompression therapy.

In dealing with 100% O_2 breathing at 1 ATA the following must be addressed:

- How should O_2 be administered?
- How long can it be breathed?
- Under what conditions can it be considered definitive treatment?
- How will it influence subsequent recompression?

The goal of O_2 breathing at the surface is to achieve as close to a 100% inspired level as possible. The best way to achieve this is with a demand system, but lacking that a non-rebreather mask will achieve levels close to 100% if fitted properly. Free flow masks or nasal cannulas should not be used unless there is no other alternative, and in these cases the flows should be kept as high as possible.

There is very little data specifically addressing the maximum breathing times for 100% O_2 at the surface. A USN TT6 is 285 min long of which 240 min is spent breathing O_2 at 2.8 or 1.9 ATA. TT6 is routinely administered without concern for oxygen toxicity so it would seem that 4 hrs of surface O_2 breathing should have a low risk of symptoms. If TT6 is fully extended with two additional 20 min periods at 60 fsw and two additional 60 min periods at 30 fsw, there is and additional 160 min of O_2 breathing, resulting in a total of 400 min. Fully extended TT6's are administered without too much concern for O_2 toxicity and given that much of this breathing is at pressures greater than 1 ATA, it would seem that breathing 100% O_2 at 1 ATA for 400 min should be acceptable. In deriving their UPDT estimates, Clark and Lambertsen looked at rates of vital capacity decreases in subjects breathing 100% O_2 at pressures of 2.0, 1.0, and 0.83 ATA (Clark JM & CJ Lambertsen. Pulmonary oxygen tolerance in man and derivation of pulmonary oxygen tolerance curves. Institute for Environmental Medicine Report 1-70. Philadelphia; University of Pennsylvania. 1970 as cited by Clark JM. Oxygen toxicity in: Bennett PB and Elliott DH The Physiology and Medicine of Diving, fourth edition. WB Saunders, Philadelphia. 1993). Using their data, they estimate a minimal effect of O_2 on vital capacity reduction even after 12 hrs. Thus it would seem reasonable that durations out to 12 hrs are possible breathing 100% O_2 at 1

ATA. Air breaks are probably not necessary but can be taken as needed to administer medication, for intake of food, or to talk to the diver.

There are anecdotal cases where breathing 100% O_2 at the surface has resulted in symptom reduction or resolution. In cases of symptom reduction, cessation of O_2 breathing has sometimes resulted in return of symptoms that are difficult to treat. So, as long as symptoms are present, even if improvement is noted, transport to a recompression facility should be pursued. If oxygen breathing has ceased because the supply has become exhausted and **complete** resolution has occurred it seems reasonable to consider the treatment definitive so long as symptoms do not return. The problem arises when complete resolution is obtained but sufficient O_2 is available to continue breathing for some time. In these cases a firm recommendation is hard to make. One approach that seems reasonable is to continue O_2 breathing for 2 hrs after complete resolution then discontinue breathing and observe. If there is no symptom recurrence and the physical examination is normal, then definitive treatment can be assumed. If there is any hint of recurrence then O_2 breathing should be restarted and transport to a recompression facility undertaken without further interruption in O_2 breathing.

The final consideration is how does 100% O_2 breathing at the surface influence subsequent hyperbaric oxygen therapy. This is unknown. However, it does not seem reasonable to limit surface O_2 breathing in anticipation of future hyperbaric treatments. In the author's experience, conscious divers will refuse to continue O_2 breathing because of oxygen toxicity due to breathing discomfort long before any irreversible pathology results. This means that pulmonary O_2 toxicity will be self-limiting. At this point all that can be recommended is that so long as symptoms are present, surface O_2 breathing should be administered until recompression therapy can be started.

DISCUSSION 9:

Dr. Latson: Surface oxygen should be beneficial via two mechanisms, one being increased delivery of oxygen to ischemic cells due to a slight increase in the blood oxygen content albeit a very small increase, and breathing oxygen enhances elimination of nitrogen and hence more rapid absorption of nitrogen bubbles. Does anybody argue with that?

Dr. Thalmann: A comment to clarify an earlier point. The diffusion radius is partial pressure-dependent, not content-dependent. When you administer 100% O_2, the oxygen content of blood doesn't increase very much but the partial pressure goes up a lot. This causes the capillary oxygen partial pressure to increase and causes the partial pressure all along the tissue partial pressure gradient to increase. So while the oxygen content increase may be only minimal, the oxygen partial pressure at a given distance from the capillary may increase significantly. This means that a given capillary can oxygenate tissue at a further distance, compensating for neighboring capillaries whose blood flow may have been compromised.

Dr. Vann: We have been working with some of the live-aboard dive boats in collecting Project Dive Exploration data. A number of them keep logs of how often they give their divers oxygen. This is of great interest, we want to follow up on this but have not yet done so. This is something we do have in mind to do at a suitable time and if this group can encourage us to do it maybe we'd be able to do it sooner rather than later.

Dr. Piantadosi: I just want to make a comment about this disconnect between what we think physiologically and what we see clinically with surface oxygen. If you give symptomatic patients just a little bit of oxygen, 2-3 liters per minute even, a lot of them have substantial symptom relief, and I don't know why that happens. A counterargument is there are some reasons why it might be bad, in terms of vasoconstriction and so forth, but the bottom line is that it's good first aid for decompression sickness. I don't think that there's enough evidence to say that it's more than that right now. I think we should have it available and give it; it relieves symptoms, and may decrease the number of treatments. However, we don't know what the recurrence rate is if you treat with surface oxygen alone, so I suspect that we'll have to come up with the opinion that let's use oxygen for now as first aid, and recompression therapy is the definitive treatment and we recommend it.

Dr. Thalmann: In the dog studies done at NMRI, one of the things they found was that giving oxygen during recompression caused the dogs to have a less tendency to relapse[1-3]. Giving 100% oxygen administration prior to recompression tends to reduce the probability of recurrence. However we currently have no evidence to say that surface oxygen should be anything other than first aid.

Dr. Bove: Can you talk about the administration of oxygen and concentrations that you'd like to achieve? Are we talking about nasal prongs at 2 liters a minute; can we be specific?

Dr. Thalmann: Our recommendation is if someone is going to have an oxygen set on to use a non-rebreather type of mask. We haven't been able to stratify any of the data by delivery method, so the answer to that question is that we don't have the foggiest idea. We do know that you get the highest concentrations from a non-rebreathing mask, and that's what we recommend, but whether lower oxygen concentrations may be just as useful, we can't tell.

Dr. Reed: Actually in the last year's of DAN data there was a noticeable effect in terms of residuals in people who received surface O_2 versus people who didn't. But it was only seen in people who got what we would call 'higher flow'. Those who received oxygen by nasal cannulae actually looked very similar to those who received no oxygen at all.

Dr. Bove: Those were outcomes after treatment?

Dr. Reed: Yes.

Dr. Bove: We don't know the long-term outcomes.

Dr. Reed: No.

Dr. Flynn: Of those roughly 6,000 cases that DAN had, that were shown yesterday, about how many of those had surface oxygen?

Dr. Vann: About 40%.

Dr. Thalmann: It's getting to be an industry standard, to have oxygen on board a dive boat.

Dr. Flynn: Is there enough evidence that this should be a standard, that for any first aid situation oxygen should be available as part of a standard routine or is it still iffy enough that if you have it give it, and if you don't have it, so what?

Dr. Thalmann: I think that the evidence in general shows that oxygen is beneficial. I don't think there is any question of that, and it's certainly not expensive. It is rapidly becoming an industry standard that there should be O_2 on the boats. More and more frequently now when we get an emergency call about an accident, the diver is already on oxygen.

Dr. Flynn: So you think there's enough evidence that it would be required to have oxygen in a first aid situation? This is a defensible position?

Dr. Thalmann: Right, there's no question about oxygen administration for first aid, from the time the diver has developed decompression sickness symptoms until he reaches the treatment chamber.

Dr. Vann: Do you want to address the question of what you do after you give the oxygen if the symptoms go away?

Dr. Thalmann: I would feel obligated to recompress and treat as soon as they showed up, based on their original symptoms. We have no guidelines to do otherwise. There are cases where we don't have a choice, because of unavoidable delay in transportation. If after 12 or 14 hours the diver is still asymptomatic I think it may be safe to say that perhaps he doesn't need recompression treatment, but for the case that is only 3 or 4 hours from symptom resolution, I would say treat him, even if the symptoms have gone away.

Dr. Bove: Is the DAN data granular enough to be able to sort out isolated brain gas embolism from cord injury?

Unknown speaker: No.

Dr. Bove: So the DAN data is collectively a whole spectrum of different kinds of responses. Perhaps the question regarding the response to oxygen therapy of, for example, pain only bends versus other types of symptoms, could be done in the future. Does anybody have any class "3" concerns for using oxygen, that is detrimental effects of oxygen? No, then I think we can say that there's not any particular reason not to use oxygen. I suppose there may be a concern in somebody with severe end-stage emphysema who is a CO_2 retainer and who has been diving, but I don't think we're going to see too many of those. So we're probably okay with no class 3's, and so we can't sort out the separate categories for use of oxygen in terms of a class "1" indication.

Dr. Chimiak: Oxygen is considered definitive treatment for some types of altitude-induced bends.

Dr. Latson: A class "1" simply says that if therapeutic oxygen is usually indicated, always acceptable and considered useful and effective. I vote that it is a class "1" indication.

Dr Bove: I'm comfortable with putting "1" for all three of these. If we discuss different levels of evidence, which we don't have time to do right now, I don't think we're going to have the best levels of evidence at this point. We don't have randomized clinical trials but I'll just stop there with the oxygen. Any other comments about that?

Dr. Southerland: If we're talking about DCS we definitely have to be sure to specify DCS related to diving as opposed to DCS due to altitude exposure, because in altitude DCS oxygen is not just first aid, it can be therapy. With altitude bends you only go to a chamber after you've failed surface oxygen therapy. I have a question regarding the DAN data. If surface oxygen blunts symptoms, it might affect the speed with which a patient is transported to a chamber. Did you adjust for delay to treatment?

Dr. Vann: No, it's still a work in progress.

References (Discussion 9)

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ANTICOAGULANTS IN DECOMPRESSION ILLNESS (DCI)

Richard E. Moon, MD

Secondary effects of intravascular bubbles induce platelet accumulation, adherence and thrombus formation[1-5]. Thus, prevention of this effect with an anticoagulant could conceivably limit ischemia and increase the effectiveness of recompression therapy.

Isolated case reports are consistent with a beneficial effect of heparin[6,7]. In a canine model of arterial gas embolism, therapeutic anticoagulation promoted a return in a short-term outcome: evoked potential amplitude, but only when heparin was combined with PGI2 and indomethacin, agents that inhibit platelet function. Recovery after treatment with heparin alone was no greater than in control animals[8]. In other experiments, heparin given either prophylactically or therapeutically to dogs with DCI was not beneficial[9,10]. Moreover, histological evidence of hemorrhage in decompression illness has been observed in spinal cord[11-14], brain[15-18] and inner ear[19,20]. Thus, since there is no consistent evidence that anticoagulation is effective in the setting of acute DCI, and that there is the potential for worsened hemorrhage into the CNS or inner ear, the Committee does not recommend routine treatment with intravenous heparin.

However, patients with leg immobility due to spinal cord injury are at increased risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PE). In a study of 1,419 patients with acute spinal cord injury, the incidence of clinically recognized DVT and pulmonary thromboembolism was 14.5% and 4.6%, respectively[21]. A review by of 9 series of patients with acute spinal cord injury indicated that 40% of 419 patients experienced deep vein thrombosis confirmed by venography[22]. In a prospective study of major trauma, of 26 patients with spinal cord injury 21 (81%) had DVT confirmed by venography, 5 (19%) had proximal DVT and 2 (8%) died of pulmonary embolism[23]. A review of 6 reported series of patients with acute spinal cord injury noted DVT diagnosed using either fibrinogen leg scan or venography in 62% of 160 patients[24]. The greatest risk of thromboembolic disease is in the acute phase after the injury, although it can also occur during rehabilitation[24].

Prophylactic methods have included oral anticoagulation, graded compression elastic stockings (ES), intermittent pneumatic compression (IPC), fixed low dose unfractionated heparin (LDUH), adjusted-dose heparin (typically to achieve an APTT in the range 41-50 seconds[25]), low molecular weight heparin (LMWH) and combination regimens. There are no large, controlled studies of DVT prophylaxis in patients with spinal cord injury. However, analysis of published data suggests that neither fixed dose unfractionated heparin nor IPC are adequately effective[24]. ES have not been studied in this setting, but appear unlikely to be effective in view of the apparent inadequacy of IPC. Oral anticoagulation instituted after hospital admission appears to be protective[24]. The usefulness of LMWH prophylaxis in patients with spinal cord injury is supported by two controlled studies, in addition to an uncontrolled study of 60 patients, in whom there was no detectable DVT[24]. However, the authors pointed out that further trials are needed, but made the following recommendations for patients with acute spinal cord injury with leg immobility:

1. LMWH is recommended.
2. LDUH, ES and IPC appear to be relatively ineffective when used alone, and are not recommended.
3. ES and IPC might have benefit if used in combination with LMWH or LDUH or if anticoagulants are contraindicated early after injury.
4. During the rehabilitation phase, patients should receive either LMWH therapy or full oral anticoagulation (INR target 2.5, range 2.0-3.0).

For patients with motor-incomplete traumatic spinal cord injury and evidence of perispinal hematoma, it is recommended that initiation of LMWH therapy be delayed until 24-72 hours after injury[24]. For patients with hemorrhagic stroke undergoing active treatment, ES or IPC are recommended[24].

There also appears to be a high risk of DVT and pulmonary thromboembolism in patients with leg immobility due to DCI, in whom fatalities due to thromboembolism have been reported[26,27]. Spadaro reviewed 28 patients who were unable to walk for at least 24 hours after decompression illness. Two of the 28 developed life-threatening pulmonary thromboembolism and one died. Subcutaneous unfractionated heparin had been started 36 and 72 hours after the accident, respectively[26]. Experience in patients with spinal cord injury suggests that LMWH is an effective prophylactic against DVT/PE. Presumably it is also effective in leg immobility due to spinal cord DCI, although it is not possible to base any recommendation upon outcome studies in this disease, since at present there are none. It is conceivable that the combination of bubble-induced endothelial injury and hemoconcentration that often accompany serious DCI may render LMHW less effective than in other types of spinal cord injury.

Currently there are two LMW heparins available in the US (dalteparin, enoxaparin, tinzaparin), one heparinoid (danaparoid) and a new inhibitor of activated factor X (fondaparinux). Of the drugs approved for use, only enoxaparin has been studied in spinal cord injury, at a dose of 30 mg subcutaneously every 12 hours. There have been no studies of any regimen in the setting of decompression illness.

Whether anticoagulants used in dosages appropriate for prophylaxis of DVT have any adverse effect on neurological DCI is unknown.

Another possible option is to screen patients with DCI for DVT, reserving full anticoagulation for patients with demonstrated clots. Physical examination is neither sensitive nor specific, and is not adequate as the only screening modality. In a series of 201 patients with DVT confirmed by venography after major trauma, only 3 had physical signs suggestive of the diagnosis[23]. The gold standard for the diagnosis of DVT is venography, but because it is invasive it is not useful as a screening tool. 125I-fibrinogen uptake is no longer used because of the risk of infection transmission. The other available tools are: impedance plethysmography (IPG), ultrasound imaging and MR venography. In patients with suspected DVT, withholding anticoagulation is justifiable in the setting of repeated negative studies using either IPG or ultrasound imaging[28]. However, this management algorithm has not been

demonstrated safe for asymptomatic patients[29]. MR venography, although it is capable of detecting pelvic vein thrombosis, is unlikely to become routine because of its high cost and limited availability[29].

Recommendations:

1. Routine therapeutic anticoagulation of patients with neurological DCI is NOT recommended.
2. LMWH is recommended for all patients with inability to walk due to leg weakness caused by neurological DCI. Enoxaparin 30 mg, or its equivalent, subcutaneously every 12 hours, should be started as soon as possible after injury. Clinical experience with early administration of LDUH or LMHW does not suggest a major tendency for deterioration in neurological function due to intramedullary hemorrhage.
3. If LMWH is contraindicated, ES or IPC are recommended, although their effectiveness at preventing DVT is probably less than LMWH.
4. Repetitive screening for DVT while withholding anticoagulants until clot is identifiable is a strategy likely to be less efficacious than routine LMWH administration. However, given the uncertain efficacy of LMWH in DCI, when facilities exist, performance of a screening test a few days after injury is recommended.
5. These recommendations are based upon observations in patients with traumatic spinal cord injury. Neither the efficacy nor the safety of these recommendations in neurological DCI has been confirmed. Anticoagulants may be withheld when a physician judges that they may put the patient at greater risk due to bleeding (e.g. because of associated combat injuries).

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DISCUSSION 10:

Dr. Bove: I agree that probably the most important indication for anticoagulants is to prevent deep vein thrombosis. We showed 30 years or so ago that there is venous endothelial injury in decompression sickness. This is a systemic disease; white cells are activated; there is a propensity for venous thrombosis in this disease. When there is immobility from paralysis as well these patients do have a high risk for DVT. So, treating DVT has got to part of the algorithm. What is your opinion as to when to start anticoagulation?

Dr. Moon: I think it should be started on Day 1.

Dr. Bove: Okay, but I thought you said that, with the bleeding into the cord, that might be detrimental.

Dr. Moon: Yes, I think it possible that it could be detrimental. What I actually said was that the triple combination (PGI_2, heparin and indomethacin) used in experimental animals by Hallenbeck[1] would possibly be detrimental. I wouldn't be too worried about hemorrhage in patients given low dose subcutaneous heparin. In fact, in patients with serious traumatic injury of the cord, where it could be argued that the risk of bleeding is much higher, it seems that low dose heparin is relatively well tolerated.

Dr. Bove: You didn't mention Coumadin™ (warfarin). In using Coumadin you could separate the INR levels into below 3 and above 3. An INR less is 3 is probably safer. It works in this kind of case and is less likely to cause bleeding. You can provide pretty good anticoagulation and prophylaxis with Coumadin after the initial heparin or Lovenox™ (enoxaparin). Does anybody have any problem with treating DVT in somebody who has spinal cord injury?

Dr. Latson: How many hours of immobility does it take before the risk of DVT becomes significant?

Dr. Moon: I don't know the answer to that in this setting, but in the series that I showed you from Duke, everybody in that group of 28 patients had paralysis for 24 hours or longer.

Dr. Latson: I submit that since hemorrhage is a risk, and that risk is present a little higher in the early stages before coagulation and fibrosis has had a chance to take hold, that it might be good to recommend that anticoagulation, even in a low dose, be delayed for a few hours. In that way the acute hemorrhage due to the disease process might have ended. This is similar to using anticoagulants around total hip replacement surgery for instance you don't give heparin during surgery, you start it about an hour or two after surgery. That might be a safer recommendation, just so that you are not aggravating that initial hemorrhage, but you would still get the benefit in terms of prophylaxis for the prolonged immobility.

Dr. Moon: Heparin can be given subcutaneously before surgery with very little, if any, increase in surgical bleeding.

Dr. Latson: We're talking microscopic structures here.

Dr. Massey: We also worry about anticoagulant administration for 72 hours after intracranial hemorrhage, and then after that we sometimes have to do it. It always scares us. In 30 years of experience treating spinal cord disease, including traumatic spinal cord injury, I don't remember ever seeing a bleed into the spinal cord after administering mini-dose heparin. We didn't usually use high dose IV heparin so I can't comment on that. I do think that using Lovenox versus using low dose heparin, the data show rather small differences, although there is a great difference in cost. I think you have to remember that there's a big difference in DVT's in the pelvis versus the calf. Most people believe that the calf DVT's don't ever grow, whereas those in the pelvis always have to be considered.

Dr. Piantadosi: I think most of us in pulmonary medicine feel that prophylactic heparin in patients who are immobile is worth any theoretical risk of bleeding. In clinical practice there is no evidence that spinal cord bleeding is a problem. So, for prophylaxis I think the earlier you start subcutaneous heparin, the better chance we have of preventing proximal DVT, which is what we are worried about, because that's what breaks off and kills people. In terms of full dose heparin, I think there's very little rationale for using it until you have a DVT that is in a proximal vessel, pelvis or thigh. So, my feeling about this is that it's safe and efficacious in immobile patients, and that we ought to be using it as early as possible.

Dr. Flynn: It seems to me that in DCS, where you know you have endothelial damage and stripping in the veins, with all these bubbles flowing from peripherally to centrally, that it's not only the immobility it's also the pro-coagulant surfaces being produced, so it seems to me that we should argue for starting earlier rather than later.

Dr. Bove: I'm quite comfortable with putting a "1" and an A here. Taking DVT out of the diving environment, there are plenty of good clinical trials that give you a level of evidence of A for using anticoagulation for preventing DVT. So, that part of the process is quite reasonable and it seems to me that that would be a standard of care after the injury. So let's go to the top and talk about, now we're on the anti-coagulants, I've got separated out the NSAIDs. So let's just talk about anti-coagulants, thrombolytics and 2B/3A agents, all things that have to do with preventing blood clotting. Is there anybody that feels that there's a class "1" indication to use these agents in arterial bubble disease to the brain, that is, arterial gas embolism?

Dr. Warner: I don't have any evidence that it would benefit the brain per se, but it would depend upon the magnitude of the neurologic deficit. If there is a neurologic deficit and the patient is unable to ambulate then I would expect that he probably might benefit from some anticoagulation.

Dr. Bove: Dr. Massey again could you comment on what you do with thrombotic or embolic disease to the brain in terms of anticoagulation. I think you mentioned 72 hours for patients with hemorrhage. What if you know that the deficit is due to an embolus after the initial CT scan or MRI?

Dr. Massey: In that setting anticoagulation is used very frequently, although there are studies both in favor and against. If it were to be suggested that AGE is similar to stroke due to thromboembolic disease, it probably is reasonable to administer anticoagulants. What bothers me, unfortunately, is the only studies we have which clearly demonstrate that anticoagulation helps with cerebral emboli are those with atrial fibrillation. Still, we do use it in suggestive situations such as low ejection fraction, cardiomegaly, carotid ulceration and the like.

Dr. Moon: Apart from the issue of deep vein thrombosis prophylaxis, would you advocate therapeutic anti-coagulation for gas embolism?

Dr. Massey: I think it is reasonable to do some form of anti-coagulation. Aspirin or something equivalent to that is reasonable. Clinically, one always weighs the risks vs. benefits, of course: in this case, bleeding vs. stroke.

Dr. Moon: Reasonable being a Class "2"-ish indication?

Dr. Goodman: Don't we anticoagulate in stroke simply to prevent additional embolization, and is that really relevant to arterial gas embolism?

Dr. Massey: I agree, which I guess is a little different than with air.

Dr. Bove: Do you want to comment on extrapolating thrombolytic therapy in stroke to arterial gas embolism?

Dr. Massey: Thrombolytic therapy is a little different, in that it attempts to remove the clot that appeared many hours ago.

Dr. Bove: Yes, thrombolytic therapy is trying to lyse the thrombus that has occurred.

Dr. Latson: 'Embolytic', in other words trying to resolve the embolus, is what we try to do with acute recompression. I would like to allude to the ability of fluorocarbons to resolve that bubble faster.

Dr. Bove: Okay what should I put up here, should I put a "3" or should I leave it open to something than "3"?

Dr. Thalmann: Some studies have shown that gas phase is washed through the cerebral circulation in 20 minutes or so what you're faced with is no longer blockage but endothelial damage from the bubble passing through, so that's really what you're faced with treating. As I pointed out in my talk yesterday, one of the differences between stroke and AGE is that AGE the thrombus resolves fairly rapidly compared to thrombotic stroke and certainly even more than that if you recompress.

Dr. Butler: For either AGE or DCS it seems that the indication for anticoagulation should be based on the patient's ability to ambulate, because that seems to predict the risk of DVT.

Dr. Flynn: I guess I'm getting a little confused here. I thought John Hallenbeck had pretty clearly shown that at least triple therapy was very

beneficial in cerebral air embolism, and that there was no hemorrhage associated with that. And I believe he also showed that heparin alone showed similar if not all of the effects, and it was actually beneficial. So the speculation about hemorrhage is just that, a speculation. What that study clearly showed was that administering these anti-coagulant type drugs was beneficial.

Dr. Moon: In that study[1] he used the somatosensory evoked response 15, 60 and 120 minutes after embolization, using PGI_2, heparin and indomethacin singly and in various combinations. At those times there was no benefit for either single drug treatment or any of the binary combinations. The animals that received the triple combination (PGI_2, heparin and indomethacin) had a greater recovery of SSEP. Heparin by itself didn't do anything, at least in that study.

Dr. Bove: John actually got permission to do a clinical trial but when they started it they were having so much trouble with hypotension from the PGI_2 that they stopped the trial. So, using something like prostacyclin would be very difficult because of its problem with hypotension.

Dr. Flynn: There was also an idiosyncratic reaction to indomethacin, which I think is the thing that really stopped the trial.

Dr. Bove: Okay, so I'm going to have to put some numbers in here, I'm going to put a "3" for using anti-coagulation in mild DCI/DCS. Does anybody have any problem with that? If you have joint pain only, I don't see any reason to start anti-coagulating somebody, does anybody argue with that?

Dr. Moon: By anti-coagulation you mean what?

Dr. Bove: This would be heparin or thrombolytics. I have the NSAIDs on a separate sheet.

Dr. Moon: Are you separating low dose from therapeutic heparin or is this any kind of heparin?

Dr. Bove: Any kind of heparin, that's just a joint injury. Neurologic, arterial gas embolism seems to be if you ended up with somewhere in the 2's here, is that what we agreed? I'm going to put a B.

Dr. Warner: I don't want to complicate things but how can you intelligently compare low dose heparin or enoxaparin to Coumadin? I don't use Coumadin every day like you probably do, but I suspect that while there is not a lot of risk with low dose heparin, say 5,000 units subcutaneously three times per day is relatively safe, using Coumadin to attain a therapeutic INR I think is associated with much more risk. When you are talking about thrombolytics or real anti-coagulation versus this a low prophylactic dose of heparin, I think there should be separate discussions for the two.

Dr. Massey: I think that low dose Coumadin that is controlled is not a big risk, but it's still a risk if you don't watch things closely. Maybe the issue should be divided, maybe that would be wiser.

Dr. Bove: The issue is that heparin or Lovenox is a transient in the care of DVT. The long-term care involves Coumadin; you can't keep someone on injectable anticoagulant long term, so it's a routine process to go from heparin or Lovenox and immediately start transferring to Coumadin. There are adequate clinical trials; there is class A evidence for that. Using Coumadin is something that everybody does all the time now. You start with heparin because you want to get an immediate effect, but in many cases when starting heparin, you start Coumadin at the same time to try to get the INR adjusted. The efficacy is there for long-term prevention of DVT with Coumadin.

Dr. Piantadosi: I think really the idea that we need to be very careful to separate prophylactic heparin and Lovenox in patients at risk for DVT in patients from patients who have had DVT who have an indication for full anticoagulation then 3 to 6 months of Coumadin therapy. I don't think most of us use any anticoagulation in pain-only DCS, neurological DCS or even gas embolism unless the patient is at risk for DVT due to immobilization.

Dr. Bove: What I'm saying here is that we're not treating DCS; we're treating DVT or preventing DVT. So, I don't have any problem with that as a separate entity. Does anybody have any particular scoring or reason to talk about using anticoagulation in neurologic decompression sickness, that is particular spinal cord injury? Is there a "3" here? We know there is intra-cord hemorrhage, I mean should we put a "3" here or a "2" something here?

Dr. Moon: Again I think for low dose heparin, I think the risk is very low.

Dr. Bove: We're talking about DVT now, if that's what you're talking about.

Dr. Moon: Yes, I am talking about DVT prophylaxis.

Dr. Bove: That's okay, we already agreed that that's all right. What I'm talking about is specifically to treat the neurologic decompression sickness.

Dr. Massey: I don't think we can say it's useful, but nor can we say that it's harmful.

Dr. Bove: Okay, that's what I'm asking the question for. We could put a "2" here if we want to equivocate. Although published animal studies have not consistently supported the use of heparin, there is anecdotal evidence suggesting that anticoagulation as a therapy in the treatment of decompression sickness may have some value[2], but I don't think there have been any studies done since then. So, my question is: would it be a 3, because we are worried about causing cord hemorrhage and worsening the disease, or a 2B, meaning indeterminate, indicating that we don't know that it's clearly detrimental?

Dr. Thalmann: We have to have some data, either experimental evidence or clinical experience.

Dr. Bove: It's a 2B; it's indeterminate, but we don't know that it's clearly detrimental. Actually there is an indeterminate class, so we could put indeterminate there. Do we want to put indeterminate there? It's the same for chokes? Richard, this is not talking about DVT. For DVT we've got clear indications to use it. Let's do NSAIDs and aspirin. Let me just say a quick word about the pain issue. In the state of Pennsylvania by law we are required to treat pain and we have to document in the chart that we're treating it. The idea of not giving a pain medication because you want to use the pain for something, is illegal in Pennsylvania actually.

Dr. Moon: Although you could argue that your recompression treatment is in fact treatment of the pain.

Dr. Bove: What I'm saying is that if somebody has pain we're obligated now by law to treat the pain. In the long view, allowing the patient to be in pain because you want some diagnostic information, may not always be a legitimate argument. I'm just throwing that out there because there are people who don't think it's a legitimate argument.

Dr. Butler: Maybe we need to do the same kind of discussion for the control of blood glucose and prevention of hyperthermia, for two reasons. One is that so far we have heard absolutely no evidence in dysbaric models. Second is that's going to impose a significant economic burden on both the diving industry and the military services. So before we give it a class one I think we need to talk about it a little bit.

Dr. Bove: What I'd like to do is finish this first, eat lunch and then we can deal with that. I raised the issue of using NSAIDs for pain or NSAIDs with aspirin for pain. How do you want to put that down? Do you want to put a "2" down, a "3"? Your suggestion would make it a "3".

Dr. Mitchell: This may be something that the committee has to deal with. I can tell you that the Australian randomized double-blind trial of tenoxicam and decompression illness is now complete. I think it's probably the only one that's ever been done in any decompression illness. Mike Bennett was the principal investigator, and he will be presenting the results at the UHMS meeting. What they showed when they assessed these patients for outcome at discharge and a month after discharge that there was no difference between the groups, but the median number of treatments required to achieve that outcome was one less in the tenoxicam group. This was actually was a highly statistically significant funding. The number needed to treat was 5: out of every 5 patients you treat you'll save one hyperbaric treatment by giving tenoxicam. I guess it's an economic issue rather than a clinical one.

Dr. Bove: I think there's piece of information that suggests that it might be useful to give this for pain-only bends. As I said, there are some ethical issues being raised around the world regarding avoiding treatment of pain for diagnostic purposes. I would put at least a "2" in here rather than a "3".

Dr. Thalmann: In myocardial infarction, aspirin is recommended in the acute phase. Is that for a platelet effect or an endothelial effect?

Dr. Bove: It's for a platelet effect.

Dr. Thalmann: NSAIDs don't have that effect right?

Dr. Bove: They do, but they're not as effective as aspirin.

Dr. Thalmann: So lumping them all together seems to be unfair. If these drugs work for coronary artery disease, why wouldn't they work in DCS, where we think platelet sludging may be a factor, not necessarily for its pain effect but for its anti-platelet effect?

Dr. Bove: Back in the 1970's when the platelet information came out from Dick Philp and others[3-6] a whole bunch of the diving community started taking aspirin. The commercial divers were all taking aspirin, but nobody ever did a trial to see if it had any long-term benefit. The question here is should we prophylax the military divers with aspirin before they go, which isn't a big deal, and should we use it for treatment after an event occurs? Any comments on that?

Unknown speaker: What if someone gets shot?

Dr. Bove: I see your point. The surgeons don't like aspirin when they're doing surgery; the dentists don't like aspirin when they're doing dental work. That's a good point.

Dr. Southerland: Navy divers already prophylax themselves with Motrin™ (ibuprofen).

Dr. Butler: Not any more, at least not the Special Warfare divers. That is a specific point that I would like to make, because any time someone is diving for a combat purpose they may get bent but they are just as likely to get shot, maybe more likely.

Dr. Bove: So you've got particular operational reasons not to use an NSAID or aspirin, so I guess we can put a "3" down here for operational. I guess the other issue if you're not worried about trauma, is aspirin still indicated to give somebody that's developed neurologic injury? I think most everybody recommends it at this point.

Dr. Dervay: One thing that might not have come up yesterday when I was discussing the EVA's: we have historically given aspirin to our astronauts who are not allergic to aspirin the morning of their prep and also the morning after.

Dr. Moon: I don't think most people recommend aspirin for acute treatment of neurological bends.

Dr. Bove: Okay because I've seen it written down somewhere in the past. Other comments, How many people would give a diver with evidence of spinal cord injury two aspirins on their way to the chamber? Is there anybody that does that or would not do it? No one does it. So a "3" for gunshot wounds, is this a "3" for other aspects or do we put a "2" equivocal, maybe yes, no?

Dr. Moon: It should be indeterminate; there's no evidence one way or the other.

Dr. Butler: I was just going to toss out the idea of giving the "3" for pain as well. There are other analgesics available that don't increase the possibility of spinal cord hemorrhage. Why not use those?

Dr. Bove: We heard that we're going to hear that there's a good clinical trial of NSAIDs actually improving the outcome of type 1 or pain-only bends, and they also help reduce the pain. So, I think using an NSAID might be the right indication, and not using an aspirin might be the right indication in a pain-only bend, which I think is what you said isn't it?

Dr. Butler: I don't think that's what I said. I think that when dealing with pain only-bends and you are treating pain, there are other options besides aspirin or NSAIDs. On the other hand, if you think that you are going to prophylax against the development of subsequent spinal cord injury with aspirin, that's a whole different topic, and that would require different studies.

Dr. Mitchell: Most of them were actually milder cases of decompression sickness. The vast majority had typical pain with a bit of tingling.

Dr. Chimiak: The treatment of pain entails assessing the pain, treating it and then reassessing. The recompression treatment would count as a pain treatment modality; it's written right in the protocols. If it doesn't work, nothing tells you to go ahead and give multiple pain therapies at the same time, because you won't know where you are. After you've done the treatment, and the patient still has that same shoulder pain after completing a Table 6, then you might conclude that the pain is probably not due to bends, and then you go on to use NSAIDs or some other analgesic. So, you don't have to do it currently with recompression, and you will not be in violation of the new JCAHO (Joint Commission on Accreditation of Healthcare Organizations) standards.

Dr. Bove: So put a "2" for that, or a "3"? We don't have a lot of data, but I think the aspirin information has been at least equivocal and, in the case of traumatic injury we don't want to use it. In

arterial gas embolism with pure brain manifestations, does anybody want to use something that blocks platelets in that entity?

Dr. Moon: I think maybe we are in the indeterminate range everywhere, except for patients who might fall into the category of Mike Bennett's study.

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INTRAVENOUS PERFLUOROCARBON EMULSIONS IN THE TREATMENT OF DECOMPRESSION SICKNESS AND ARTERIAL GAS EMBOLISM – A REVIEW OF EVIDENCE OF THERAPEUTIC BENEFIT

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Introduction

Decompression Sickness (DCS) and Arterial Gas Embolism (AGE) are two potentially life-threatening conditions encountered as a complication of diving or exposure to changes in barometric pressure. They share a common pathophysiologic process involving bubbles of inert gas in the blood or body tissues, and are both most effectively treated by compression in a hyperbaric chamber and administration of high concentrations of inspired oxygen (Hyperbaric Oxygen Therapy or HBO). When treated soon after injury, HBO is very effective, yielding complete resolution in the vast majority of mild to moderate cases, and significant benefit in serious cases, but many cases of DCS and AGE occur in situations where there is no immediate access to HBO therapy. In the absence of HBO, current therapy is limited to administration of oxygen and intravenous fluids, and supportive care. The natural history of DCS/AGE not treated with HBO includes a chance of spontaneous recovery, but also a significant risk of permanent neurologic damage, bone necrosis, and even death. Therapy with corticosteroids, lidocaine, or other medications has not been shown to have significant therapeutic benefit without HBO. Thus, there is a pressing need for an effective therapy for DCS/AGE when HBO is not available.

Intravenous perfluorocarbon emulsions (IVPFC) show great promise to fill this need. IVPFCs are chemical preparations of synthetic oils with the ability to dissolve and transport oxygen and many inert gases. They are being investigated and developed for a variety of medical applications, including use as oxygen-carrying plasma substitutes to reduce the need for blood transfusion. The ability of these substances to dissolve and transport both oxygen and inert gases may enable them to significantly alter the pathophysiologic process caused by inert gas bubbles. One product, Oxygent™ (perflubron emulsion, Alliance Pharmaceutical Corporation, San Diego, CA) is currently in the final stages of evaluation by the FDA for use as an oxygen-carrying plasma substitute during surgery, and may be available in the U.S.A. within two years. There is considerable evidence that this product is safe to administer and has a significant chance of benefit when administered in conjunction with oxygen for serious DCS/AGE. The purpose of this report is to summarize the currently available evidence for critical review and debate so that physicians faced with a serious case of DCS/AGE without access to HBO therapy can make educated decisions regarding the use of Oxygent™ or other IVPFCs if they become available.

Chemistry and History of IVPFC

Perfluorocarbons (PFCs) are a diverse family of chemically inert, water insoluble, synthetic aromatic or aliphatic compounds with fluorine (F) substituted for all hydrogen (H) atoms. They were originally developed for the Manhattan Project as solvents for radioactive compounds, but have found their way into use in many common products including Teflon™

and Scotchguard™. The electron-dense F atoms limit intramolecular interaction and give the compounds low surface tension, making them excellent solvents for gases[1]. Some PFCs can dissolve up to 100 times more oxygen per unit volume than plasma[2], but, unlike hemoglobin, the oxygen carrying capacity is linearly related to the partial pressure of oxygen. This remarkable property has interested scientists for decades; in 1966, Clark and Gollan demonstrated that mice could be fully submerged in an oxygenated PFC solution and kept alive for hours while "breathing liquid"[3].

Because of the insolubility of PFC in water, it is necessary to develop emulsions to allow their use in blood. The use of PFC as an intravascular oxygen carrying substance began in Japan in 1979[4] and led to the FDA approval of Fluosol DA™ (FC-43, Green Cross Corporation, Osaka, Japan) in 1989 for use during coronary angioplasty to provide oxygen to cardiac tissues distal to partial obstructions. The small size of emulsion particles allows the IVPFC to carry oxygen to ischemic microcirculatory beds that RBCs cannot reach[5]. Fluosol DA™ contained only 20% w/v of two PFC compounds (perfluorodecalin and perfluorotripropylamine) in a synthetic polaxomer emulsification (Pluronic F-68). This "first generation" preparation had a very short shelf life, and had to be stored frozen in components and reconstituted and used within hours of thawing. Additionally, the synthetic emulsifier (Pluronic F-68) may have been responsible for some complement-mediated side effects[4]. Fluosol DA™ was withdrawn from the market in 1994 due to poor sales for the approved indication[2].

Although it was never approved for use as a blood substitute, Fluosol DA™ was used experimentally to provide temporary oxygenation during surgery on Jehovah's Witness patients and others when compatible blood was not available[4]. Although this 20% PFC emulsion could provide only limited and temporary clinical benefits in this group of patients who would not accept eventual transfusion, it was shown to provide significant increases in oxygen consumption, mixed venous oxygen tension and mixed venous oxygen saturation[4]. FC-43 was also used to investigate the potential of IVPFC in multiple other conditions including DCS and AGE.

A "second generation" formulation (Oxygent™) has an improved emulsion and a much higher concentration (60% w/v) of a different, but similar PFC (perfluorooctyl bromide, C8F17Br, or Perflubron) and thus a greater oxygen carrying capacity. It is emulsified in egg yolk phospholipid, similar to current preparations of intravenous nutritional supplements and the commonly used anesthetic propofol. Thus, problems attributed to the synthetic emulsification agent in the Fluosol DA™ preparation have been resolved. Another IVPFC preparation is under development (Oxyfluor™, 40% perfluorodichlorooctane emulsified in egg yolk lecithin and safflower oil, HemaGen Inc, St. Louis, MO)[6], but is not as far as Oxygent™ in the FDA review process. Other perfluorocarbon preparations have been developed for use as contrast agents for ultrasonography, prevention of adhesions, and for delivery of inhaled medications[7]. At least one preparation is comprised of perfluorocarbons in stabilized microbubbles. Future applications could include enhancement of drug delivery or elimination, treatment of stroke, ischemic heart disease, organ preservation for transplantation, and treatment of sickle cell disease.

Oxygent™ development and testing is in the final stages of the FDA review process for the following indication[7]:

> "Transfusion Avoidance: Oxygent used in conjunction with an elevated FiO_2 and acute normovolemic hemodilution or intraoperative autologous donation is indicated as a method to reduce and/or avoid the need for allogenic blood transfusion in moderate to high blood loss surgical procedures"

There have been several successful phase II and phase III studies involving administration of Oxygent to over 600 patients. There was a delay in 2001 due to a question of complications in one phase III study involving hemodilution during cardiopulmonary bypass that necessitated suspension of the study. Subsequent review (by the FDA and others) indicated that Oxygent™ was not responsible for the complications, and the study has been resumed with some modifications[7]. It is anticipated that Oxygent™ will be approved by the FDA, and manufacturing and marketing arrangements are at an advanced stage (for current information, refer to the Alliance Pharmaceutical Corp. website, www.allp.com).

Therapeutic Effects of IVPFC of Importance in DCS/AGE

The physiologic effects of IVPFC which could be beneficial and relevant to DCS/AGE are: (1) oxygen delivery to tissues with impaired circulation, especially the central nervous system (CNS), (2) enhanced solubility, transport and elimination of inert gases, (3) effects on intravascular volume and blood rheology, and (4) effects on white blood cell aggregation. These effects have been documented by the studies cited below.

Oxygen Delivery to Ischemic Tissues

One of the eventual pathophysiologic events in severe DCS/AGE is disruption of oxygen delivery to tissues, either by vascular blockage by bubbles, hemorrhage, or inflammatory response. Any intervention that results in improved oxygen delivery to tissues should thus be beneficial. This is believed to be one of the primary benefits of HBO. IVPFCs have a high affinity for oxygen and other inert gases, and they are dissolved in PFC in direct proportion to their partial pressure in the surrounding environment. Unlike hemoglobin, the process is not a chemical binding process, and gases are exchanged by simple diffusion at a rate approximately two times faster than the uptake and release of oxygen by hemoglobin. For maximum benefit, high inspired oxygen concentrations are needed and it should be noted that 100% inspired oxygen is a critical part of any proposed therapeutic regimen using IVPFC for DCS/AGE. Oxygen extraction at the tissue level is very efficient, with as much as 90% of dissolved oxygen available to tissues. A comprehensive review of the IVPFC oxygen transport and delivery was written by N.S. Faithful in 1994[2].

The ability of IVPFCs to deliver oxygen to tissue beds with compromised circulation has been extensively studied and led to FDA approval of Fluosol DA™ for use in coronary angioplasty. Emulsion particles of IVPFC (~.2 micron), which are much smaller than red blood cells (7 micron), can carry oxygen through partially obstructed microvascular beds and supply ischemic tissues. Because the oxygen carried by PFC is in the dissolved state, the increased partial pressure of oxygen in the plasma results in a higher concentration gradient

that favors diffusion of oxygen to the tissues[2]. This effect is somewhat analogous to the increased oxygen delivery by oxygen dissolved in plasma under hyperbaric conditions.

Of particular relevance to DCS/AGE are the following studies that demonstrate the potential of IVPFC to improve oxygenation in models of CNS ischemia:

> Sutherland et al[8] in 1985 showed that Fluosol-DA, when combined with 100% inspired oxygen, improved oxygen delivery and oxygen availability in cats during middle cerebral artery occlusion.
>
> Padnick et al[9] in 1999 measured tissue PO_2 in the primary visual cortex of cats given stratified doses of a Perflubron emulsion (similar to Oxygent™), and showed substantial increases in tissue PO_2 when combined with 100% oxygen.

The most recent study to demonstrate effects of Oxygent™ on tissue oxygenation was reported in October 2001. Bennett-Guerrero et al[10], using gastric tonometry, showed that patients receiving Oxygent™ during cardiopulmonary bypass had improved oxygenation of the GI tract and had more rapid resumption of post-operative GI function.

In summary, there is ample evidence to support the assumption that oxygen delivery to tissues is significantly enhanced with administration of IVPFC in conjunction with oxygen. This effect has been documented in both normal tissues and conditions where circulation is disrupted. Since improved tissue oxygenation is the postulated mechanism for much of the benefit of HBO therapy in DCS/AGE, it can be logically inferred that IVPFC should have a similar beneficial effect.

Enhanced Solubility, Transport, and Elimination of Inert Gases from Body Tissues

Depending upon the specific perfluorocarbon, an IVPFC emulsion can carry from 25 to 30 times more nitrogen than saline solution or plasma. Oxygent™ is estimated to carry 27 times more nitrogen than normal saline[11]. The net increase in nitrogen elimination from body tissues is dependant on many factors, including the final concentration of IVPFC in the blood, cardiac output, ventilation, and perfusion of individual tissues, and is thus quite complex to determine, but several studies have documented significant effects. As early as 1974, Cassuto[12] showed that nitrogen absorption from subcutaneous air pockets was increased by up to 175% in animals infused with a primitive IVPFC emulsion. In 1993, in a more sophisticated study, Novotney[13] demonstrated that animals infused with a perfluorocarbon emulsion (perfluorodecalin in glycerol) eliminated Xenon from a canine muscle preparation more than twice as quickly. Based on an even greater solubility for nitrogen in IVPFC, they estimated that nitrogen would be eliminated approximately four times as quickly with IVPFC. In 1998, Dexter and Hindman[14] used computer simulation to estimate the effect of several factors on the absorption of cerebral air emboli, and estimated that absorption time for large emboli could be reduced by up to 23%. It is notable that he apparently modeled the effect of IVPFC while breathing air, not 100% oxygen as is recommended, which would greatly enhance the effect of increased solubility.

Further evidence of the enhancement of bubble absorption comes from direct observation. Several in-vivo preparations have demonstrated reduction in visible gas bubbles in animals treated with IVPFC and then exposed to either a decompression insult[15,21] or gas emboli[16].

Effects on Intravascular Volume and Blood Rheology

Because DCS/AGE is often associated with hemoconcentration, administration of intravenous fluids has long been recommended in treatment of severe cases, even though direct evidence in support benefit is sparse. Synthetic colloid solutions such as Dextran™ were once advocated on the basis of anti-aggregation effects on platelets and reduced clumping of RBCs, but several studies showed no benefit of these solutions compared to normal saline. Nonetheless, IVPFCs do show some similar rheologic benefits that could be beneficial, and as a colloid volume expander, they help maintain intravascular volume, and should be considered to be at least as beneficial in this regard as other volume expanders. One recent study, showed impressive benefit with Oxygent™ in ameliorating vaso-occlusion and red cell aggregation in a rat model of sickle cell disease[17]. This could have direct relevance to DCS induced spinal cord injury which has been hypothesized to be due in part to vascular congestion of the epidural venous plexus.

Effects on White Blood Cell Aggregation

Reduced accumulation of WBCs has been proposed as a therapeutic benefit of both HBO and lidocaine. At least two studies have documented reduced neutrophil activation and lowered chemotactic response with perflubron, the active ingredient of Oxygent™ [18,19]. Another study demonstrated similar effects with a different PFC[20]. It is not yet clear whether this would play a significant therapeutic role in human DCS/AGE.

Controlled Animal Studies Showing Benefit in DCS/AGE

Ultimately, to demonstrate benefit of the basic physiologic effects cited above, studies in intact animals with the pathologic insult of interest must be conducted. Because of the well documented potential benefits of IVPFC in DCS/AGE, sporadic research efforts specifically directed toward the treatment of DCS/AGE have taken place since at least 1974, when Cassuto et al[12] investigated the ability of IVPFC to enhance washout of inert gases from subcutaneous air pockets.

To date, at least three studies have specifically sought to demonstrate therapeutic effects in decompression sickness:

> Spiess et al[21] in 1988 exposed two groups of 12 rats to 6.8 ATA for 30 minutes followed by decompression to 1ATA at a rate of 2ATA/minute. One group was treated with 6% hetastarch and 100% oxygen breathing, and 11 of 12 animals died within two hours. The second group was treated with an equal volume of IVPFC (Fluosol 43) and 100% oxygen, and 8 of twelve survived to 24 hours with no gross neurologic deficit. Rapid resolution of bubbles visible in extremities was noted.
>
> Lynch et al[15] in 1989 exposed three groups of 16 anesthetized hamsters to 7 ATA for 30 minutes followed by direct decompression to 1ATA at 60fsw/min. Untreated

control animals had only 6% survival at 30 minutes. Animals given i.v. saline and ventilated with 100% oxygen had greatly improved 62% survival, and animals given IVPFC (Fluosol-43) and 100% oxygen had an impressive 94% survival. Additionally, IVPFC treated animals were observed to have fewer bubbles, more rapid bubble disappearance, and fewer cardiac dysrhythmias.

Dromsky et al[11] in 1999 exposed 57 swine to 4.9 ATA for 22 hours then decompressed them to 1 ATA at .9 ATA/minute. 25 of 27 (93%) untreated control animals suffered DCS, and 14 of 27 (52%) died. 14 of 15 (93%) animals given 100% oxygen suffered DCS, and 6 of 14 (43%) died. Only 8 of 15 (53%) of animals treated with IVPFC (Oxygent™) suffered DCS, and only 4 of 15 (27%) died.

Additionally, the following studies have been directed at arterial gas embolism (AGE). Most studies have been directed at AGE as it would be expected to occur in clinical settings, but they still have relevance to diving induced AGE due to common pathophysiology.

Spiess et al[22] in 1986 compared the effects of equal volumes (10 ml/kg) of hetastarch vs. FC-43 in rabbits given air emboli into the carotid artery. One group was given a uniform bolus of air, and survival rates were only 2/5 for the hetastarch group, but 5/5 for the FC-43 group. Another group received an air infusion until the EEG was flat bilaterally; survival was only 3/10 for the hetastarch group, but 10/10 for the FC-43 group.

Spiess et al[23] in 1987 compared the effects of FC-43 vs. hetastarch (20 ml/kg) in dogs given arterial air emboli into the coronary arteries in dogs. Hetastarch treated dogs all had ischemic ST-T changes on ECG, 6/10 had ventricular dysrythmias or conduction defects, and 3/10 died within 5 minutes. FC-43 treated dogs showed only 1/10 with ST-T changes, no dysrythmias or conduction defects, and no deaths.

Menasché et al[24] in 1985 compared FC-43 to saline in rats with air injected into carotid arteries. IVPFC treated animals tolerated over three times more air injection before electroencephalogram flattening and had less of a drop in intracerebral oxygen tension.

Cochran et al[25] in 1997 compared the effects of air emboli (5 ml/kg) introduced during cardiopulmonary bypass in swine. The control group used a standard crystalloid solution in the priming solution and the experimental group included 10ml/kg of an IVPFC (Oxyfluor™, 40% perfluorodichlorooctane) in the priming solution. In the control group, 3/5 animals suffered cerebral infarcts (histological examination) versus 0/5 animals in the IVPFC group. Additionally, the IVPFC group maintained or increased cerebral blood flow and the electroencephalogram showed less change and more complete recovery.

Two other studies have shown benefit of IVPFC in venous air embolism.

> Spiess et al[26] in 1986 compared FC-43 to three other volume expanders in rabbits with a continuous infusion of air into the femoral vein (.25 cc/kg/min). Animals treated with IVPFC and 100% inspired oxygen showed significantly longer survival, and increased total volume of air tolerated before death, and arterial and pulmonary venous oxygen levels were consistently higher, and central venous pressures were consistently lower.
>
> Tuman and Spiess et al[27] in 1986 compared hemodynamic parameters in dogs given either hetastarch or FC-43 prior to a nonlethal venous air embolism (.75 cc/kg/min for five minutes). All parameters showed less severe detrimental effects in IVPFC treated animals.

Thus, multiple studies in both large and small animals consistently demonstrated impressive benefits of IVPFC combined with oxygen in DCS, AGE, and VGE. It is notable that these models all used a very severe insult, and a valid critique of studies to date is that the IVPFC was either given prophyllactically or very shortly after the decompression insult or gas embolism. More research needs to be done to determine the magnitude of benefit with delayed administration and milder insults that more closely approximate most cases of human DCS.

Evidence of Benefit in Other Conditions Relevant to DCS/AGE

Fluosol DA™ was also studied for use in stroke[8,28], spinal cord injury, myocardial infarction, and wounds with vascular compromise, and its ability to raise tissue oxygen tensions is well documented. Since Oxygent™ is an improved emulsion with a higher concentration of oxygen carrying PFC and even smaller average particle size than Fluosol DA™, its ability to deliver oxygen to these compromised tissues should be even greater. Other active areas of research are the use of Oxygent™ during cardiopulmonary bypass[29,30,31] and for sickle cell anemia[17].

Although the manufacturer is currently focusing research efforts on its primary indication rather than oxygen delivery to areas of compromised circulation, it is expected that similar studies will be performed with Oxygent™ after FDA approval for use during surgery.

Safety Profile of IVPFC

Any therapeutic decision is based on an analysis of potential risk versus anticipated benefit. Thus, the safety of IVPFC emulsions is a prime concern. Fortunately, there is extensive data regarding safety of many formulations of IVPFC, including Oxygent™. Prior experience with Fluosol DA™ is also relevant.

Oxygent™ has been extensively studied in multiple animal models as well as human trials. To date, Oxygent™ has been administered to over 400 humans in closely scrutinized trials monitored by the FDA. There have been no permanent injuries or life threatening side effects. Side effects include a short lived febrile response 4 to 6 hours after administration

and a transient drop in platelet count 2 to 3 days post administration with no effect on platelet function or bleeding time. The mechanisms for each of these side effects has been extensively studied and are related to physical properties of the emulsion and to normal clearance of the emulsion from the blood by phagocytic cells of the reticuloendothelial system[2]. The actual PFC molecules, which are volatile liquids, diffuse into the bloodstream and are distributed in body lipids and eventually eliminated through the lungs. Although complete elimination of PFCs from the body takes place over a protracted time, no adverse effects have been associated with prolonged tissue retention.

Current safety studies have shown[2,7]:

No evidence of complement activation
No immunogenic or allergic reactions
No changes in immunoglobins or immune complexes
No impairment of cell-mediated immunity
No systemic detection of TNF or IL-1
No platelet activation
No impairment of platelet aggregation
No prolongation of bleeding time, PT, or PTT
No clinically significant effects on fibrinogen
No hemodynamic effects or vasoconstriction
No abnormal change in liver function (ALT, AST, LD)
No effect on pulmonary function

At his time, it appears that the risk of administration of Oxygent™ compares favorably to the risk of administration of other synthetic plasma volume expanders such as Dextran™, Hespan™, or albumin solutions (all of which have been advocated for use in DCS). The emulsion carrier is egg yolk phospholipid, similar to solutions used in parenteral nutrition and also in the commonly used anesthetic propofol, and has an extensive record of safety.

Flousol™ was extensively studied prior to FDA approval in 1989. Clinical use showed occasional complement-mediated adverse reactions which have been attributed to the synthetic emulsifying agent, Pluronic F-68[4]. These reactions were characterized by mild fever, dysphoria, muscle pains, and nausea. Symptoms were transient and did not lead to any sequelae. Additional concerns included transient decreases in white blood cell counts, and prolonged retention of the perfluorocarbon in the reticuloendothelial system. It was withdrawn from the market due to poor sales for its primary indication, and difficulties with administration[32], not because of safety problems.

Possible Potentiation of Oxygen Toxicity

Because of its oxygen carrying capability, it is of concern that a patient given IVPFC could develop oxygen toxicity of the central nervous system or other organs at an accelerated rate if hyperbaric oxygen therapy was subsequently provided. Review of prior experience and studies currently underway at Navy Medical Research Center indicate a slight shift in the dose response curve to oxygen and shortened time to onset of symptoms, but the effect is not as pronounced as originally anticipated. Swine given IVPFC and then given oxygen at 2.8

ATA showed the same rate of CNS oxygen toxicity as control animals[33]. This concern deserves additional study, but should be manageable by adjusting HBO pressure and oxygen concentration, or restricting the use of IVPFC to situations where HBO therapy is not immediately available.

Conclusions

When considered cumulatively, the evidence is compelling that IVPFC is very likely to have beneficial effects in DCS and AGE. The evidence shows that IVPFC delivers oxygen to tissues with disrupted circulation, enhances the resolution of inert gas bubbles, and speeds elimination of inert gas from the body. Multiple animal experiments in different species show direct benefit in models of DCS, AGE, and venous gas emboli. Studies in models of related conditions further strengthen the direct evidence. Safety studies have not yielded any evidence of major problems, but some transient side effects have been documented

As stated earlier, a therapeutic decision is based on an estimate of the likely benefits of the therapy, the risks of the therapy, *and the risk of not providing the therapy and allowing the disease process to continue*. It is the opinion of this author that in some specific situations, there is ample evidence to support the administration of IVPFC with 100% oxygen to patients afflicted with DCS or AGE. The main factors to consider are (1) the severity of the DCS/AGE insult, (2) the availability within a reasonable time of access to Hyperbaric Oxygen Therapy.

IVPFC would not be recommended at this time for a mild case of DCS where there is little risk of permanent disabling neurologic injury, nor would its use be recommended at this time if the patient could be taken to an HBO facility within approximately 6 hours, the time interval that appears to be critical for initiation of HBO with a high chance of success. It would have to be considered an "experimental therapy" and given with the appropriate consent. It should be considered analogous to a Class IIa therapy in the American Heart Association's classification of therapeutic interventions, "a therapeutic option which is acceptable, of uncertain efficacy, may be controversial, and for which the weight of evidence is in favor of its usefulness and efficacy." At the least, it should qualify as a class IIb, "…a therapeutic option that is not well established by evidence but may be helpful and probably not harmful".

The evidence is not yet definitive; there is much more research which needs to be done. The use of IVPFC is the single most fertile area for future research into therapy for DCS/AGE. The unfortunate reality is that this research is expensive, logistically difficult, and time consuming. The funding sources for such work are extremely limited, and at the present time, the pharmaceutical company holding the patent for Oxygent™ (Alliance Pharmaceutical Corporation, San Diego, CA.) is allowing only very limited experimentation for any indication outside the scope of the primary indication for which it is applying to the FDA. Other IVPFC preparations may be promising, but are several years behind Oxygent™ in the FDA approval process.

Actual controlled human studies in the treatment of DCS or AGE would be ethically difficult to perform, since DCS or AGE would have to be experimentally induced to have any

meaningful controls. Intentionally inducing either condition would be hazardous and unlikely to be approved by oversight committees. Altitude-induced DCS might offer an experimental model with an acceptable risk. Alternatively, human studies should be performed to study the safety of administering IVPFC after hyperbaric exposures (without inducing DCS), and the physiology of its effects on oxygen delivery, venous gas emboli, and inert gas elimination could be further detailed. The funding available to support such research is very limited, and thus it will likely take several years for evidence that would satisfy the most critical among us, and FDA approval will probably never be sought due to the expense of the process (it is notable that no therapeutic intervention for DCS/AGE, including HBO, has been formally approved by the FDA).

If Oxygent™ (or another IVPFC preparation) becomes widely available, there will be a time when a physician will be faced with a patient afflicted with potentially crippling DCS or AGE distant from a hyperbaric chamber, and that physician will be faced with the difficult choice whether to administer Oxygent™ and oxygen in hopes that it could be beneficial, or withhold it because it is not "FDA approved" or "proven" for that indication. I feel that there is sufficient evidence to support giving Oxygent™, an oxygen-carrying plasma substitute that has been shown to be safe in other situations. The additional benefits described above are a bonus.

I suggest that it is the responsibility of the Undersea Medicine community to promote conscientious debate, and provide expert opinion, recommendations, and advocacy for further research so that the first physician to use IVPFC for DCS/AGE will not have to defend that difficult decision on his own.

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DISCUSSION 11:

Dr. Thalmann: As far as O_2 toxicity goes, you're right about the arterial PO_2 but the venous PO_2 will rise, because perfluorocarbons have a higher solubility for O_2, so to me oxygen tension in the brain will probably go up, so there's a good chance that may in fact increase O_2 toxicity. Second, I am not sure if your classification is premature, and the reason is that in all the studies that you quoted the animals were pre-treated before the insult. I don't think it's fair to say you can use this stuff in DCS and AGE after the insult because we don't know if it would work.

Dr. Latson: Does any other therapeutic regimen that we've classified as a class "2" during this meeting have any better data?

Dr. Thalmann: I don't know what you mean by better data, but yes, sure it does because most of the other therapeutic regimens that we have talked about have been investigated after the insult. In other words, they were used for treatment.

Dr. Latson: In the studies I cited with DCS and AGE it was given after surfacing. That's the same as the studies that show benefits from fluids, heparin and everything else.

Dr. Thalmann: I guess that didn't jump out at me because towards the end you were saying that you could go back and look whether these would be effective after symptom development.

Dr. Latson: In the studies cited it was given soon after the insult to see if it can prevent decompression sickness.

Dr. Thalmann: I say we're jumping the gun because generally we treat after symptoms arise;, we don't treat after the dive. That's not to say that it might not be beneficial, but I think it warrants more of a demonstration of efficacy there. In Dromsky's study, when I look there's a small number of pigs. I'm going to contest that 6 out of 15 is not significantly different from 4 out of 15, whereas the death rate was the same.

Dr. Latson: The death rate did not reach statistical significance.

Dr. Thalmann: So before I go around waving a flag at that one, you're right that there was no CNS DCS, but the death rate was the same. You have to investigate why the pigs die and what was going on. How long does this stuff stay in the circulation and what is its clearance rate? if you do the injection of it how long is it around before it is eliminated and how is it eliminated, by what mechanism?

Dr. Latson: Its half-life is about 6 hours and I did say that the elimination is through the lungs. It's a volatile liquid at body temperature. Once it comes out of it's emulsion particle it's eliminated via lungs. A small amount is taken up by the reticuloendothelial system.

Dr. Thalmann: So one might conjecture that it could be given prophylactically during missions where you might expect a high risk of AGE or DCS.

Dr. Latson: I'm not advocating that.

Dr. Thalmann: What I'm saying is we need some dose-response information, in other words how is the efficacy of this stuff related to its concentration in the circulation.

Dr. Latson: I absolutely agree that there is a tremendous amount more research to do. The questions are not at all definitive answered, and in fact my plea is to focus research dollars on this. My fundamental question is, if I had a patient in front of me who, if I did nothing, would probably end up quadriplegic or paraplegic or with a lot of neurological residual, with this drug for which there is significant evidence indicating that it might help, I have got to soul search about whether I would administer it.

Dr. Thalmann: Making a personal decision is quite different from making a corporate decision.

Dr. Latson: Absolutely.

Dr. Bove: Have any of these fluorocarbons been through phase 1?

Dr. Latson: Yes, they've been through phases 1, 2, and 3.

Dr. Bove: Do you feel comfortable in giving them prophylactically?

Dr. Latson: I'm not advocating giving them prophylactically. The only situation in which I'm advocating perfluorocarbon administration at the moment is in a neurologically crippling case when you have no hope of getting into a chamber and it's all you've got to give.

Dr. Molé: Given that the perfluorocarbon is an excellent carrier of nitrogen, giving it before a dive wouldn't make a lot of sense because that would be loading up the tissues that much faster. What sort of modifications to treatment tables would you anticipate? Would you still use air breaks or a general shortening of total treatment time?

Dr. Latson: We need more research to answer those questions. I think we probably have to use a reduced level of pressure, maybe 1½ or 2 atmospheres instead of 2.8, or a reduced inspired oxygen fraction, in order to maintain cerebral oxygen partial pressure below seizure thresholds. I think we need to study that in animals first, and then we need to do some very careful controlled human studies, in which we expose people to different pressures with perfluorocarbon on board, and see where we start getting CNS oxygen toxicity.

Dr. Farr: If the perfluorocarbon were administered without pre-oxygenation, wouldn't that increase the nitrogen load?

Dr. Latson: Pre-oxygenation is a possibility. I'm not positive if the preparation that will be marketed will already be pre-oxygenated. It could be pre-oxygenated by putting it through a membrane oxygenator, which might not be practical to be in the field.

Dr. Southerland: Could you make a comment about perfluorocarbon's CO_2-carrying ability?

Dr. Latson: It carries CO_2 very efficiently and that's been well documented.

Dr. Southerland: I thought the investigators at Buffalo were using a version that does not require an emulsifier.

Dr. Latson: There are multiple versions of perfluorocarbon perforations that are under investigation. I chose to look intensively at Oxygent™ (Alliance Pharmaceutical Corp, San Diego, CA) because it is the one most likely to be on the market soonest. I think this group should be prepared to recommend what should be done when it does reach the market. It may be premature to make a firm statement, but I am trying to stir up some debate and some action on it.

Dr. Goodman: Has there been any pathology?

Dr. Latson: They did some pathology, but I'm not aware of the results as of yet.

Dr. Chimiak: One of the situations this might be useful for is deep blow-up, which notoriously leads to very significant problems. This may be your number one choice besides recompression.

Dr. Latson: But my argument for using it after symptoms occur, based on the studies that we've got, is that we employ recompression after symptoms occur. The primary mechanism by which we think hyperbaric oxygen therapy works is increased oxygen delivery, enhancement of nitrogen elimination and possibly other effects such as on white cell adhesion. Oxygent™ provides those same therapeutic benefits and until we administer it to a human with symptoms of decompression sickness, we'll never know. We can do animal studies until the cows come home but we'll never know until somebody has the nerve to give it to humans.

Dr. Butler: To partially answer your well-founded speculation about whether or not this will increase oxygen toxicity, there may be some parallels to be drawn between the potentiation of oxygen toxicity that is seen with CO_2 intoxication, because with CO_2 elevations you don't change the PO_2, but because of cerebral vasodilatation you increase the oxygen dose and increase oxygen toxicity.

Dr. Thalmann: I'm assuming that using this to treat DCS and AGE currently is an off-label indication, and with the human trials conducted is the company amenable to supplying it for human trials?

Dr. Latson: Not at this point, and it's my understanding that if you try to conduct a human trial on a drug that's been FDA approved, you have to make a reapplication after application to the FDA and so again, I don't think there are deep enough pockets in the people who are interested in decompression research to do that, and that's why I'm pessimistic about it.

Dr. Thalmann: We asked this question here at Duke, and the word that came back is the physicians here can use any drug that's FDA

approved for any indication that they see fit, whether it's on-label or off-label, in a clinical setting, but you can't do an experimental trial without FDA approval. So it seems that a lot of your arguments are going to be moot, unless the company is willing to participate or give this stuff out to do some studies. That's the only way you are going to be able to establish efficacy. Simply having it available and having people give it here and there is only going to result in a bunch of sea stories.

Dr. Latson: Why do we impose a higher standard on this than on any other adjunctive therapy that we've proposed in this meeting?

Dr. Piantadosi: There's a little confusion about the physiology here and how this works. Anything that increases oxygen delivered to tissue is going to increase the PO_2 if the metabolic rate of the tissue stays the same. So for the brain, $CMRO_2$ is constant; when the tissue regulates its oxygen consumption, so when we increase O_2 delivery the PO_2 goes up. That's just the way that the systems have to behave: simple conservation of oxygen. CO_2, as Dr. Butler mentioned, is another issue here. You don't unload the oxygen from hemoglobin so also the PCO_2 in tissue goes up. So for those reasons the PO_2 in the brain is going to go up and the PO_2 at the cell is going to go up, and it's from the fact that both oxygen delivery and PCO_2 are increased. The amount that the PO_2 goes up is going to be affecting how much you increase the oxygen delivery. It's exactly a function of the dose. The last thing is that this is not innocuous stuff that you are proposing to give. We have worked with this a lot for many, many years. When you get it to awake people sometimes the blood pressure goes down, they don't like it, they feel bad. Next to the Duke Hyperbaric center there was a study going on with hyperthermia in cancer patients, and we were always running over there to treat hypotension.

Dr. Latson: Are you basing this discussion on the new preparations?

Dr. Piantadosi: It's egg phospholipid; it's the same problem. It goes all the way back 20 years. Some people do very poorly with it, so I think there are some reasons for not giving it until you go head to head with oxygen and fluids, which are much simpler to give. So my vote is not to give it, for both the physiological reasons and practical side effects.

LIDOCAINE (LIGNOCAINE)

Dr. Simon J Mitchell, MB ChB, DipDHM, PhD

Introduction

Lidocaine is a cationic amide compound belonging to the pharmacodynamic family of "sodium channel blockers". It is used clinically as an injectable or topical local anesthetic, and as an injectable antiarrhythmic agent in the prophylaxis of ventricular tachycardia and fibrillation[1]. Lidocaine readily crosses the blood brain barrier[2], has a high volume of distribution, and is rapidly metabolized by the liver. Metabolites undergo renal excretion[1]. The therapeutic index for lidocaine is relatively low and the therapeutic range for antiarrhythmic action is 6 – 21 μmol L^{-1}. Plasma levels are usually monitored during prolonged infusions to prevent toxicity, which may be manifest as cerebral irritability, bradycardia, atrioventricular block, or myocardial depression[1].

In Vivo and in Vitro Evidence for Neuroprotection by Lidocaine

Studies of Direct Relevance to Dysbaric Disease

The hypothesis that lidocaine might be useful in treatment of neurological decompression illness (DCI) arose from *in vivo* investigations of cerebral arterial gas embolism (CAGE). Evans et al[3] pre-treated anesthetized cats with lidocaine (5 mg kg^{-1}) 5 minutes before a single bolus of 0.4 ml air to the vertebral artery. The mean sciatic/cerebral somatosensory evoked response (SER) in an untreated control group fell to 28% of baseline after embolism, recovering to 60% and 73% over 1 and 2 hours respectively. In the treatment group, the mean SER initially fell to 68% of baseline, recovering to 89% and 95% over 1 and 2 hours. Lidocaine also attenuated the increases in heart rate, blood pressure, and intra-cranial pressure recorded in the control group. The same authors subsequently used a modified CAGE model to investigate administration of lidocaine after the injury[4]. Cats received 0.08 ml increments of air to the carotid artery until the SER was reduced to 10% of baseline levels for a period of 5 minutes. Five minutes later, treatment group cats received lidocaine in a bolus and infusion regimen providing plasma levels of 8 – 16 μmol L^{-1} for the duration of the experiment. Mean control and treatment group SER recovered to 32.6% and 77.3% of baseline respectively over 100 minutes.

In a third experiment using feline CAGE, McDermott et al[5] reported SER recovery in three groups: no treatment; HBO only, and HBO plus lidocaine infused to achieve plasma levels of 8 – 16 μmol L^{-1}. The latter groups recorded significantly better SER recovery than the no treatment group, but the treatment groups were not significantly different from each other. While there was no additive benefit for lidocaine and HBO, conclusions about the efficacy of lidocaine alone could not be drawn since there was no lidocaine-only treatment group. Moreover, the same group published a superceding study that did show improved preservation of both the SER and cerebral blood flow when lidocaine was used adjunctively with recompression[6].

In the only study of lidocaine in treatment of DCI caused by bubbles formed from dissolved gas, Broome and Dick[7] reported no additive benefit for lidocaine administration as an adjunct

to recompression in a porcine model of spinal cord DCI. There were no untreated or lidocaine-only groups, which limits the conclusions that can be drawn. In addition, the outcome measure (running on a treadmill) may be insensitive to some of the potential sequelae to human DCI. Finally, the lidocaine infusion was maintained only for the 5 hours of recompression treatment, which may be insufficient if an anti-inflammatory action is important (see later).

Studies of Indirect Relevance to Dysbaric Disease

Neuroprotection by lidocaine has been reported in a steadily growing number of *in vivo* investigations of neurological injury unrelated to bubbles. The largest group of these is comprised of studies that have utilized various models of ischemic brain injury[8-19]. Since ischemia is one potential consequence of bubble formation in DCI, these studies are of some relevance to the present discussion. A neuroprotective effect has also been demonstrated for lidocaine in less directly relevant models of spinal trauma[20], cerebral irradiation[21] and cerebral fluid percussion injury[22,23]. It is notable that with the exception of 1 study, and the possible exception of 2 studies that are difficult to interpret, all those that demonstrated neuroprotection by lidocaine used a dose comparable to non-toxic doses in humans.

Two studies in ischemic brain injury did not show benefit[24,25], but one[24] was superseded by a subsequent study that did show benefit[12], and the other[25] can be disregarded because of problems with the model (D.S. Warner pers comm.).

Mechanistic Studies of Neuroprotection by Lidocaine

Potential mechanisms of neuroprotection by lidocaine include deceleration of ischemic ion fluxes, modulation of neuronal energy metabolism, modulation of leukocyte behavior, and modulation of hemodynamic parameters.

Deceleration of Ischemic Ion Fluxes

The pivotal early event in neuronal ischaemia is loss of intracellular ion homeostasis. The breakdown of the sodium/potassium pump that occurs with hypoxic energy failure leads to cell membrane depolarization and a vastly complicated chain of subsequent injurious events which include the elaboration of excitotoxins such as glutamate, and a rise in intracellular calcium[26]. Sodium channel blockade to prevent or decelerate membrane depolarization in hypoxic neurons is therefore a rational neuroprotective strategy[27], and there is abundant evidence of such activity by lidocaine when administered prophylactically. Astrup et al[28] and Lantos et al[29] showed that lidocaine in extremely high doses significantly decelerated potassium efflux from anoxic neurons. Astrup's study also showed that the effect of lidocaine was additive to hypothermia. These studies used unconventional doses of lidocaine that would abolish all EEG activity *in vivo*. However, others have shown that clinically relevant doses decelerate sodium influx[30] and neuronal depolarization[14,31,32] without altering pre-ischaemic electrical activity[30-32].

Since lidocaine delays or prevents intracellular sodium loading and anoxic depolarization, it is not surprising that it also ameliorates at least some of the associated secondary neurotoxic

events such as release of glutamate[15,33], and other excitotoxins[34], intracellular calcium accumulation[35-38] lipid peroxidation[39], and development of cerebral oedema[9,38].

Modulation of Neuronal Metabolism

In the context of neuroprotection, ischaemia is most appropriately regarded as an imbalance between energy supply and energy demand[27]. It follows that protection may be achieved not just by improving blood flow (energy supply), but also by reducing cellular energy demand. Another useful construct is the separation of neuronal energy demand into that required for electrical and synaptic activity ("activation metabolism"), and that required for basal cellular processes that must continue, even after abolition of functional activity ("residual metabolism")[40]. This is an important concept in the context of neuroprotection since residual metabolism corresponds to the energy necessary for preservation of non-functional but still viable ischaemic brain regions[27], such as the ischaemic penumbra of a focal infarction[41].

Lidocaine administration may affect both residual and activation metabolism in a dose dependent manner. Early studies demonstrated that lidocaine in unconventionally high concentrations reduced the oxygen consumption of rat brain cortex[42] and porcine brain mitochondria[43] *in vitro*, and both residual and activation metabolism *in vivo*[44]. Importantly, a significant reduction in the cerebral metabolic rate for oxygen has been demonstrated in dogs given conventional doses of lidocaine[45].

Modulation of leukocyte activity

Leukocytes may accumulate in the microcirculation of reperfused ischaemic tissue[46], especially where endothelium has been damaged by the passage of bubbles[47,48]. This can cause a secondary reduction in blood flow[47,48] and tissue damage through the release of inflammatory mediators[49]. There is substantial evidence that these processes may be favorably modified by lidocaine.

Stimulated leukocytes exposed to lidocaine in concentrations higher than conventional antiarrhythmic plasma levels exhibit reductions in superoxide release[50,51], oxygen consumption[50], lysosomal enzyme release[52], chemiluminescence[51,53], and bacterial killing[51] in vitro, and reduced leukocyte to leukocyte[54] and leukocyte to endothelium adhesion in vivo[54,55]. Since these investigations involved exposure to supranormal lidocaine concentrations, their relevance to clinical applications is in doubt. However, in other experiments utilizing conventional concentrations, lidocaine was found to reduce leukocyte superoxide release[51], leukocyte adherence[56], inflammation[56] and migration of leukocytes into inflammatory exudate[56,57]. Indeed, lidocaine was found to be a more effective inhibitor of leukocyte migration than methylprednisolone[56].

Modulation of hemodynamic parameters

Several authors have suggested that lidocaine may confer cerebral protection by favorable alteration of hemodynamic parameters[3,4,6,12,13]. Lidocaine in conventional doses does appear to preserve cerebral blood flow[6,9,12,13], reduce systemic hypertension[3,4,5,58,59] and reduce intracranial pressure[3,12,59] after brain injury, while having no clear effect on these parameters in the uninjured brain. There is little data describing the effect of lidocaine in

unconventionally high doses on post-injury cerebral hemodynamics. However, supratherapeutic doses appear to cause hypotension and reduce cerebral blood flow in the uninjured brain[19,24]. Thus, unconventionally high doses of lidocaine may be hemodynamically disadvantageous in brain injury.

The mechanism for lidocaine's effect on cerebral hemodynamics is not certain[59]. Lidocaine does reduce the release of catecholamines after brain injury[58]. This may explain its intracranial hypotensive effect when administered intravenously during endotracheal suctioning[60], endotrachial intubation[61], and craniotomy[62]. In addition, lidocaine has vasomotor effects, but its dose – response profile in the healthy circulation is complex. Both vasoconstrictive and vasodilatory effects have been observed depending on the dose of lidocaine used and the vascular bed being studied[63].

A Multiple Mechanism Neuroprotective Effect in CAGE

Based on these mechanistic studies, it seems plausible that lidocaine may achieve neuroprotection in bubble-induced injuries through a combination of the above processes. Indeed, given that CAGE is a "biphasic" injury characterized by transient ischaemia followed by leukocyte mediated inflammatory changes, lidocaine may be an "ideal" protective agent in this particular injury; first by sodium channel blockade during transient vessel occlusion, and then by ameliorating the secondary inflammatory changes after bubbles redistribute.

Clinical Evidence for Neuroprotection by Lidocaine

There are four anecdotal reports of apparent benefit when lidocaine has been administered in clinical DCI or accidental CAGE. Drewry and Gorman[64] instituted a lidocaine infusion immediately after two recompression treatments failed to resolve the symptoms and signs of spinal DCI in a 34-year-old male diver. Complete recovery of all symptoms and signs occurred over the following 24 hours, prior to any further recompression therapy. Cogar[65] reported a case of rapidly progressive spinal decompression illness whose condition continued to deteriorate despite early institution of very aggressive recompression therapy. Progression of symptoms and signs was arrested with institution of a 24-hour lidocaine infusion. Despite an abysmal early prognosis, this patient went on to make a near complete recovery. Cogar also reported a second case; a 21-year-old male who presented with dense paraplegia 36 hours after diving. The prognosis for recovery of function in this setting is very poor[66]. On this occasion a 24 hour lidocaine infusion was begun concomitant with initiation of very aggressive recompression therapy, and the patient was able to walk from the recompression chamber after 53 hours of treatment. Mutzbauer et al[67] reported a small case series in which DCI cases treated with adjuvant lidocaine required fewer HBO treatments and less total HBO time to achieve similar outcomes when compared with retrospective controls. It is unclear how many of these cases had neurological disease. Mitchell et al[68] described a case of unequivocal CAGE following inhalation of helium from an unregulated cylinder, resulting in complete cortical blindness. This patient remained totally blind 6 hours after the incident and had MRI changes initially called "patchy infarction" in the occipital lobes. Despite the poor prognosis, after 4 hyperbaric oxygen treatments and a 48-hour lidocaine infusion the patient had complete restoration of vision and almost complete regression of the lesions initially detected on MRI.

Of less relevance to treatment of dysbaric pathologies is an uncontrolled series of patients with posterior fossa oedema following stroke[69]. The authors administered steroids, mannitol and lidocaine to reduce oedema prior to decompression surgery and concluded that lidocaine made a valuable contribution to management.

To date, the best evidence for clinical neuroprotection by lidocaine comes from a randomized double-blind study reported by Mitchell et al[70] who investigated cerebral protection in left heart valve surgery patients. These patients often suffer post-operative neuropsychological (NP) deficits, and the incidence of such deficits has been correlated against peri-operative exposure to cerebral emboli[71], many of which are bubbles[72,73]. Indeed, it has been argued that cardiac surgery is a useful clinical injury model for CAGE[74]. In the study, 65 left heart valve surgery patients completed 11 pre-operative NP tests, a self-rating inventory for memory, and inventories measuring depression and anxiety. These were repeated 10 days, 10 weeks and 6 months post-operatively. Patients were randomized to receive a 48-hour infusion of either a placebo or lidocaine in a standard anti-arrhythmic dose beginning at induction of anesthesia. A post-operative deficit in any test was defined as decline in performance by ≥ the group pre-operative standard deviation. In addition, sequential post-operative percentage change scores were calculated for each patient in all NP tests and the inventories for memory depression and anxiety. Forty-two patients completed all 3 reviews, 8 completed 2 reviews, and 5 were reviewed once. Significantly more placebo patients had a deficit in at least one NP test at 10 days ($p < 0.025$) and 10 weeks ($p < 0.05$). The lidocaine group achieved superior sequential percentage change scores in 6 of the 11 NP tests ($p < 0.05$) (there was no difference between groups in the other 5) and in the memory inventory ($p < 0.025$). The authors concluded that lidocaine appeared to have a cerebro-protective effect, unrelated to any effect on depression or anxiety, and at a level that was noticed by the patients.

Relevance of the Evidence to Treatment of DCI

While the overwhelming weight of evidence suggests that lidocaine is neuroprotective, the relevance of these studies to treatment of clinical DCI is much less clear. It is notable that lidocaine has been protective in all *in vivo* experiments involving CAGE, and in the only controlled study of human embolic brain injury. It could therefore be argued that in cases of DCI where CAGE is considered the most likely mechanism this justifies use of lidocaine either in the field as a first aid strategy, or as an adjunct to recompression. However, it must be acknowledged that in all of the relevant animal and human studies, lidocaine was administered either before or immediately following exposure to emboli. While immediate administration of lidocaine is possible in some clinical situations, such as in CAGE following submarine escape training, most clinical DCI scenarios would impose longer delays. No studies have addressed the effect of administration delay, and the maximum delay before benefit would decline or be absent altogether is simply unknown.

There is even greater uncertainty over the role of lidocaine in DCI caused by evolution of bubbles from dissolved gas, and which does not involve CAGE. The supportive data in this context is restricted to 3 case reports of apparent benefit in serious spinal DCI. While it is

biologically plausible that lidocaine's neuroprotective mechanisms may be relevant in such injuries, the data do not support any firm conclusions.

Optimal Neuroprotective Use of Lidocaine

With one exception, all *in vivo* studies demonstrating neuroprotection utilized conventional doses of lidocaine. In contrast, both *in vivo* studies that demonstrated no protection utilized doses considerably larger than used in conventional antiarrhythmic regimens. Although this may be coincidental, higher doses of lidocaine have been observed to selectively activate hippocampal neurons and increase metabolic stress[45,75,76] and this may predispose to ischaemic injury[5]. Moreover, the previously mentioned observation of reduced cerebral blood flow during administration of unconventionally high doses of lidocaine[24,45] is also suggestive of disadvantage from such regimens. Each of lidocaine's potentially protective mechanisms has been observed at conventional concentrations for clinical antiarrhythmic activity. Considered together, these observations suggest that the ideal neuroprotective plasma lidocaine concentration conveniently lies within the clinical reference range for antiarrhythmic effect.

Maturation of an ischaemic neural lesion, and particularly an ischaemia – reperfusion injury such as CAGE, will take place over many hours and will involve activation of leukocytes whose activities may be influenced by lidocaine. It follows that for optimal neuroprotection, lidocaine should be present in adequate concentrations for some time[8]. Since plasma lidocaine levels decline rapidly after a single bolus, a sustained infusion or repetitive boluses will be required. The infusion should begin as soon as possible following the injury, but there are no data that describe an optimal duration. It is notable that the trial by Mitchell et al[70] in cardiac surgery patients utilized a 48-hour infusion.

Conclusions

With respect to dysbaric disease, there is sufficient evidence (and sufficiently low risk) to justify expeditious lidocaine administration to divers suffering unequivocal CAGE. It is appropriate to use lidocaine as an adjuvant to first aid oxygen, and as an adjuvant to subsequent recompression, but not as an alternative to recompression (unless recompression is impossible to obtain). The infusion should follow a conventional antiarrhythmic regimen of 24 – 48 hours duration with a target plasma concentration in the lower half of the therapeutic range. The evidence is insufficient to consider this strategy a "standard of care".

There is insufficient evidence upon which to base a recommendation for routine lidocaine administration in DCI that does not appear to involve CAGE. However, in view of the favorable case reports and lidocaine's proven and potentially relevant neuroprotective activities, there is justification for its speculative use in serious cases of neurological DCI after appropriate patient counseling.

With respect to iatrogenic or accidental CAGE, there is sufficient evidence to justify prophylactic lidocaine administration in clinical settings where CAGE is invariable or highly likely, such as during open chamber left heart surgery. In reaching this conclusion,

lidocaine's status as a well understood and relatively safe drug has been considered, along with the Level IIa evidence in support of the indication.

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DISCUSSION 12:

Dr. Bove: We have gotten rid of lidocaine in cardiology for the most part because we now have oral sodium channel blockers, so one of the questions for Frank Butler would be whether an oral sodium channel blocker could be used in a prophylactic way because these could be given in a pretty harmless dose for people who are at risk.

Dr. Mitchell: That's a really good point. My only concern with that is that in parallel with research in lidocaine many of these studies looked at other sodium channel blockers, including some of the oral formulations, such as tocainide and mexiletene. Interestingly, they weren't found to be as efficacious as lidocaine. So, I don't think we can necessarily translate the benefit for lidocaine across to other sodium channel blockers. Particularly, those oral agents were tried I think for that very reason but not found to be as efficacious as lidocaine.

Dr. Thalmann: First of all I'm disappointed you said that 20-40% of treated cases have residual. Certainly there are series that have a much lower rate than that. Second of all you are using supra-normal doses may not be protective. In the first two studies I ran across with lidocaine, where they gave doses designed to flatten the EEG were ineffective and not protective. We have treated a severe case of DCS with lidocaine and it actually had no effect. So with the problem with sea stories is that you only hear the ones that work, which is why you do controlled studies, because you have to face up to the fact that sometimes it doesn't work. It's not to say that I don't agree that the data supports. It's just that it's not a miracle.

Dr. Mitchell: Actually the data do not support its use in decompression sickness, which is probably what you were treating.

Dr. Thalmann: I need to ask guys like David Warner and the other investigators that are into these neuroprotective drugs, why isn't there more interest in lidocaine in treating stoke?

Dr. Warner: I don't know the answer to that. I don't think it's anything negative it's just that there was a phase shift in science about 1986 or so when glutamate release was discovered and the anesthetics were largely abandoned. Actually they're very potent and protective drugs, but they really need to be on board at the time of ischemia. The neurology community largely took over brain protection research from the anesthesia community in the mid to late 80's and they look at a very different kind of patient than anesthesiologists do. So, considering the mechanisms that you propose for AGE, there would have to be a very narrow therapeutic window, which in some cases may be available to people with this disorder, but not when you are talking about hours later, which is more the case for the stroke community. I think that's probably why the drugs were abandoned, because the therapeutic window makes these drugs irrelevant. Do you agree with that Dr. Dietrich?

Dr. Dietrich: Yes, I think there are many neuroprotective drugs that have very potent effects when given prior to ischemic insult or immediately after. I think some of the sodium channel blockers are among those. I'm very interested in the effects of your drug on inflammation. Is there any concerning the mechanisms by which it decreases inflammatory response to injury?

Dr. Mitchell: That's a very good question. I think the most prevalent theory is that the interaction of white cells with their external environment involves some sort of stimulus-response coupling and the generation of action potentials involved in neuroelectrical activity and sodium channels. And by blocking sodium channels you prevent stimuli reacting with white cells. That's certainly the prevalent theory but I haven't read anything that I would consider plausible beyond that. So the answer is no, I don't know.

Dr. Latson: First I just want to alert you that there is a large body of literature that I didn't have time to cover regarding the use of intravenous PFC's as a cardiopulmonary bypass prime solution to do the same thing that you are talking about. The answer is not in yet whether it's going to be helpful or not, but it's ongoing research and I think we should follow it very closely. Second, in your country when you did this randomized study of a drug for an indication that it was not approved, did you have to apply to your FDA equivalent in order to do it?

Dr. Mitchell: We went down that road and got approval. Since it was an established agent that was already in common use, we did have to get approval but it didn't involve anything that more

than writing a letter and saying that we were going to do it. They had no objections to that.

Dr. Latson: So when and if Oxygent™ comes on the market and gets FDA approval in our country, I assume that there's some equivalence between American FDA approval and that in some other countries.

Dr. Mitchell: All things that are FDA approved are approved in Australasia.

Dr. Latson: Do you think that it would be less cumbersome to do studies of arterial gas embolus or trials of therapy in DCS in Australasia?

Dr. Mitchell: Quite possibly.

Dr. Thalmann: On one of the studies you put up there, I think this was a Del Evans experiment, where he had a 1 ATA control with just lidocaine, and he compared that to typical HBO treatment. As I recall he showed that the lidocaine at 1 ATA was as effective as the HBO treatment, when using the evoked potentials.

Dr. Mitchell: I think that was the point I made that all of those studies where they combined hyperbaric oxygen and lidocaine, and compared it with hyperbaric oxygen, didn't have a lidocaine only group. I don't recall there being a study where there was lidocaine compared with hyperbaric oxygen.

Dr. Thalmann: If HBO and lidocaine are working via similar pathways, they may not be additive. The point about using lidocaine as first aid and until HBO is available is very reasonable.

Dr. Mitchell: Sure. Do remember too that the one lidocaine and hyperbaric oxygen study in cerebral arterial gas embolism that didn't show additive benefit was superseded by another study that did. With respect to your question about stroke, and why there hasn't been interest in testing lidocaine, one of the reasons I think is there is no money in it. I can tell you that from my own personal experience. We had interest from the scientists, but absolutely no interest from the manufacturer of lidocaine. If it was showed that lidocaine cured the common cold I don't think they would have been interested. I can tell you that it's not on the list of negative studies; there are no negative studies in which lidocaine has been looked at in stroke, apart from David's study, which I think was a global ischemia model.

Dr. Moon: Can you tell me if you think the use of lidocaine might increase the risk of CNS O_2 toxicity during hyperbaric oxygen therapy?

Dr. Mitchell: A good question, as one of the side effects of lidocaine is cerebral irritability. We anticipated that it might be a problem. It could be, but we have seen no evidence for it. I would say that in the course of our treatment of divers we've treated probably 50 or 60 patients with lidocaine and had no fits.

Dr. Warner: I would be surprised if that's a problem at all in the doses that you are giving, because it's actually a depressant initially, and only at higher doses does it become epileptogenic.

Dr. Mitchell: That's quite true; it has an interesting-dose response curve in that regard.

Dr. Massey: In the mid 1980's it was suggested that lidocaine be used when patients have had TIA's as a preventive measure, but I don't remember hearing what ever happened with it.

Dr. Flynn: I just want to follow up on what Thalmann was saying, Del Evans didn't do that comparison side by side, but if you look at the response to lidocaine alone on the surface versus recompression only, the magnitude of the response is virtually the same.

Dr. Mitchell: Are you interpolating between studies?

Dr. Flynn: Yes, interpolating between studies, and the model was exactly the same. So we weren't surprised when we didn't see an additional benefit of lidocaine because we already thought that we had the maximum response.

Dr. Thalmann: When we give lidocaine through a patient during a recompression treatment we noticed that whenever he was given 100% oxygen he became very nauseated. We wondered whether that was due to O_2 toxicity because whenever he went off oxygen the nausea went away. We ultimately discontinued the lidocaine and the nausea resolved.

Dr. Mitchell: When we use lidocaine in treating divers we aim for the lower half of the therapeutic range so, as David Warner pointed out, it may actually take away from the oxygen toxic effect.

CORTICOSTEROIDS IN DCI

Richard E. Moon, MD

Some anecdotal evidence suggests that corticosteroids may be of benefit in DCI[1-4]. In a retrospective analysis of a series of cases of AGE, Pearson and Goad observed that late deterioration was less common if corticosteroids had been administered. An analysis of outcome as a function of the single factor of corticosteroid administration did not show any benefit[5]. Similarly, unless given prophylactically, corticosteroids have not been shown to be of benefit in animal models of DCI[6-8], and even then the outcome variable was short-term (a few hours).

However, the Second National Acute Spinal Cord Injury Study did observe a benefit for intravenous methylprednisolone 30 mg/kg, given within 8 h of traumatic spinal cord injury, and followed by a constant infusion of 5.4 mg/kg/h[9]. At the 6 month follow-up there was a statistically significant difference in neurological function in corticosteroid-treated patients treated within 8 hours, compared to controls. The improvement appeared to be of marginal clinical significance, especially one year after injury[10]. A retrospective analysis of the data published later reported that patients who received methylprednisolone after 8 hours actually had a worse prognosis[10,11]. In the Third National Acute Spinal Cord Injury Study[12,13], the high dose 24-hour methylprednisolone regimen (24MP) was compared with an identical regimen infused for 48 hours (48MP) and a 48-hour infusion of tirilazad mesylate. This study did not include a placebo group. Patients for whom treatment was initiated within 3 hours of injury showed equal neurological and functional recovery in all three treatment groups. Patients for whom treatment was delayed more than 3 hours experienced diminished motor function recovery in the 24MP group, but slightly better motor recovery in the 48MP group at one year. Although the differences were not statistically different, there was a trend toward higher infectious complications and respiratory death in the 48MP group. Another randomized, prospective study of a 24-hour infusion of methylprednisolone showed no benefit one year after injury[14].

Although high dose methylprednisolone after spinal cord injury is considered standard of care a recent review of the literature concludes otherwise, that its use should be investigational[15].

These doses have not been tested in human decompression illnesses, but have been tested as a prophylactic regimen in pigs[16]. In those studies methylprednisolone treatment did not protect against severe DCS, and the treated animals had a greater mortality. Thus, corticosteroids are of no known benefit in the treatment of DCI and are not recommended.

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Dr. Flynn: I think that since there is almost no evidence that corticosteroids have any benefit, there is one aspect we haven't talked about, and that's augmentation of CNS oxygen toxicity which certainly the animal studies from years ago support, if there's no clinical benefit and there's a possibility of increasing our current therapeutic problem I think that's another reason not to use them.

Dr. Latson: Would you recommend altering the US Navy Diving Manual to take out the section on corticosteroids?

Dr. Flynn: Yes, I would.

Dr. Thalmann: As the data has become available to show that the efficacy of corticosteroids may not be what it was cracked up to be, and they have had undesirable side effects, we shouldn't be using them. I think that the statement that is in the Diving Manual should be taken out.

Dr. Moon: Claude, would you like to comment on CNS O_2 toxicity and corticosteroids?

Dr. Piantadosi: I agree with Ed Flynn, I think that they probably do increase CNS oxygen toxicity. Data come from a lot of different kinds of studies, including observations of protection of adrenalectomized animals from CNS oxygen toxicity. I am not sure there are good data on pulmonary oxygen toxicity, but I can tell you that the sicker folks are the more likely they are going to be to have a complication from this high dose methylprednisolone, particularly sepsis. This drug, which has been looked at in ICU patients in order to try to inhibit chronic pro-inflammatory processes, has gotten us into trouble every time. So, I really come down against the use of methylprednisolone in decompression illness.

Dr. Massey: When we have years of research with the drug in CVA's, and it was a mess. I agree that the degree of 'sickness' makes a big difference.

Dr. Moon: If you were heading up a panel to re-examine the issue of corticosteroids in spinal cord trauma, what would your take on the evidence be at this point?

Dr. Massey: At this point I don't think there is good evidence that it works very well. The data quoted in support of corticosteroids in trauma, reported effects that are very, very minimal.

Dr. Moon: Would anyone disagree with the concept that management of plasma glucose is a reasonable policy?

Dr. Butler: It's not so much that I disagree from any special knowledge, it's just that I think all the arguments that we've heard in favor of those two items being neuroprotective are in models that were not DCS or AGE. I don't know if there's good evidence for extrapolation from those models to the dysbaric situation. It seems like we ought to have that good evidence before we go out and impose something that's going to be somewhat of a logistic burden to accomplish.

Dr. Thalmann: The problem that Frank's hinting at is what's concentrated in number 2, if that recommendation comes out as a "have to" it incurs a huge expense in a lot of military chambers, particularly in remote areas. I think it would be reasonable in the Diving Manual to say that you should make every effort to prevent hyperthermia, along with a rationale, but not necessarily to make it a requirement. It would be nice have some experimental evidence to show that moderate hyperthermia, 1-1½ degrees above 37°C, was somehow detrimental in treating DCS. One of the things we have to remember is that most of the DCS we treat is not serious, is not life threatening. So this recommendation would only apply to a small percentage of treatments, which raises a real cost-benefit problem.

Dr. Moon: I hear you, but Frank is it not analogous to someone on the outskirts of a small remote town where the military is deployed getting shot, and not being able to be optimally taken care of in the context of a US teaching hospital only because there isn't a vascular surgeon immediately available. You may not have an air conditioning unit in a desert hyperbaric chamber, but does that necessarily mean that you have to engage the resources of the Department of Defense to put in air conditioning units in all tropical chambers? I'm just asking the question. If we came out with the recommendation that body temperature should be carefully controlled in the setting of severe neurological bends, would that, in practice, impact the military that much?

Dr. Butler: I think that's perfectly fair, as long as you say that you have no model-specific data to back that up, it's just your opinion, then I think it's fair to say. We would just need to say that we don't have any data for dysbaric models to back up a firm recommendation. To follow up on what Ed said, and discussed earlier, it's becoming evident that in addition to separating decompression sickness and gas embolism as a way to approach this, we also need to address specific indications within those categories. For example, his point was that you don't need to be measuring plasma glucose in somebody whose knee pain has just being treated satisfactorily with hyperbaric oxygen at 60 feet. If you take somebody who has a gas embolism, even if they are unconscious and you recompress them to 60 feet, and they wake up and say hello, do you really need to start a 48 hour lidocaine drip on that person? Similarly, we have to look at indications for DVT prophylaxis, which should only apply to patients with paralysis. In other words, there is a specific clinical indication for that disease classification.

Dr. Piantadosi: Dr. Massey and I were just discussing this. We don't see plasma glucose very high in most divers, notwithstanding the very occasional diabetic who goes diving and has a high glucose, and we don't see a lot of hyperpyrexia. So I think you could use these principles without putting specific guidelines in. You should be aware and pay attention to plasma glucose in sick folks, and you should be aware and pay attention to fever in people with significant brain injury, and not be so specific because we don't have data to give very specific treatment guidelines.

Dr. Farr: The question is to me is not, should I ensure that all the chambers around the world are cool, but rather, if I don't have a chamber should I then become interested in keeping that guy really cool? It's an issue for me not of whether to substitute active cooling for hyperbaric treatment when the latter isn't available.

Dr. Warner: I do not think you have sufficient evidence to justify the expense or potential risk of cooling the individual to below normothermia. Many would disagree with me, they think there is sufficient evidence, but on paper there isn't. So I don't think that's really a point of discussion at this stage, but treating fever is something that we can do without a lot of expense. Antipyretics, surface cooling procedures, water and a fan, do it pretty well. I just get this sense of dragging this poor soul out of the hot sea and throwing him into a chamber, which probably is the right thing to do, but not being aware of the fact that high body temperature and glucose can affect the outcome from acute central nervous injury in a pretty profound way. Increasing the awareness of these issues is probably the way to go at this stage. Without setting a protocol, making sure that the average person taking care of these people knows that treatment of fever and hyperglycemia might help.

Dr. Reed: It would be difficult to retrofit every chamber in the Navy with heavy duty cooling, but especially for operational diving, it would be helpful to recommend that hyperpyrexia is detrimental, and that putting a severely injured injury diver into a hot chamber is not a good idea. It would help in terms of operational planning. For example, putting the transportable chamber on the open deck of a ship in tropical waters in the summer may not be a good idea and perhaps some alternatives should be examined.

Dr. Latson: There are already guidelines in the Navy Diving Manual that specify maximum chamber temperatures and maximum time that a patient should be in a chamber at given temperatures to reduce heat stress.

Dr. Flynn: Actually those times are very, very stressful for patients. They are based on avoiding loss of consciousness from hyperthermia. That's exactly what we want to avoid.

Dr. Chimiak: Conversely, if you have a chamber in a cool environment, or you have the ability to cool the chamber actively, should you keep the chamber cold to the patient's discomfort, in order to keep that patient's core temperature on the low side. A chamber treatment may require 6 to 8 hours, which is a long time to keep the patient uncomfortably cold.

Dr. Butler: Another issue is that if you induce shivering in the diver then you increase his O_2 consumption, and quite possibly increase his likelihood of a CNS O_2 hit.

Dr. Thalmann: That's really true in a number of animal experiments we did. Individuals even in cold water can maintain their core temperature for quite a time, and getting someone to cool down can be a risky business, which is not that easy to do. It is reasonable to suggest that simple measures be in place to prevent a diver from raising his core temperature by avoiding a super hot environment and treating a fever. Those are things that can be

done, even in a chamber. Having a written principle may provide the diving medical officer a little push power to have the chamber situated in the best location.

Dr. Flynn: Let's say that the hypothermia problem is not coming from the environment, but rather from the patient who is having pyrexia. What would be the appropriate drug to use to bring the temperature down? We've talked about aspirin and NSAIDs, and why we may not want to use them. How can pyrexia be managed physically or do we have to use drug therapy for that?

Dr. Chimiak: I would use acetaminophen.

Dr. Moon: I'd like to spend just a few minutes on where we go from here. In talking to a few of the scientists in the last couple of days one priority everyone has mentioned is an animal model. Dr. Dietrich suggested that if one could take an animal model of bends and run through some of the kinds of experiments that have been described here that would be potentially enormously helpful.

Dr. Latson: The Naval Medical Research Center (formerly the Naval Medical Research Institute, NMRI) has spent years establishing the swine model of decompression sickness, in saturation mode and in spinal cord injury mode, has a standard through which to learn adjunctive therapies, and that's what they have done with steroids and perfluorocarbons and saline. I think that behooves us to look at the models that are established and see if they fit the bill, rather than going out and trying to restart a new model. I believe there is also a smaller rat model too.

Dr. Flynn: There is also a sheep model and a goat model.

Dr. Thalmann: I didn't think anyone implied that we need to make a new animal model. I think we just need to establish what animal models are available and which are useful. Right now the Navy is funding three animal models to look at DCS. I think that the problem that you're going to run into is the work load. If you just take say five different interventions that look promising, that's probably more work than one lab can do in a reasonable amount of time, considering the numbers of animals that would be needed to show an effect. Some of the models are not as good as others. I had some long talks with Drew Dutka about the spinal cord DCS models in dogs, using somatosensory evoked response as an end-point. He agreed that it was a very severe model, and that there is nothing that can be done to bring them back to normal. In other words, there is no treatment modality that would bring the evoked potentials back to normality. The degree of injury is important. The pig, sheep and goat models are better in that respect, because they do under certain conditions seem to recover.

Dr. Piantadosi: I'm going to take the other side here because the large animal models haven't been used a lot about to investigate mechanism. We still don't really know at the cellular or molecular level what is going on with this disease. We are not going to make progress with pigs, sheep and goats because we don't have the reagents and we can't change their gene expression in a reproducible way. So, I think it's worth a hard look at small animal models and getting clever about how to do the environmental exposures. I think we might then have a chance of learning a lot more about the molecular pathogenesis here. We all agree that bubbles start this process off, but after that I don't think we're going to be able to find a consensus about the pathophysiological sequence. So we need to have a way to look at how to load the inert gas up, we need to be able to bend the animal, we need to be able to look at the histology and then we need to be able to characterize the animal molecularly. Then we have to go back and change some things in the animal at the molecular level and distinguish between epiphenomena and true mechanisms. I think if we're going to get into modern pathophysiology and make a breakthrough in decompression sickness we're going to have to have a different approach on the basic level.

Dr. Flynn: One comment on the small animal models, they are really global ischemia type models; you have to produce a tremendous amount of gas in circulation before you see any effect. It's different from the large animal model where the spinal cord or the bone marrow may be selectively affected. In small animal models it's really a total volume of gas that's liberated in the circulation that is important. I think that can detract a lot from trying to do the kind of work that you are talking about.

Dr. Thalmann: I agree that the disadvantage of a large animal model is that it is very expensive. How you control the small animal model to give you the a graded response seems to be the challenge. The response in small animals seem to follow a step function, meaning that you have an okay rat or a rat that's completely wiped out. But

maybe using computer controlled valves, and getting ultra-precise in compression and decompression rates etc, that you could develop a small animal model with which spinal bends could be investigated. I think it's worthwhile to see if it can be done. I wouldn't necessarily throw it out a priori, but the problem with the past research has been the fact that very small errors in small animals produce big differences in outcome. I don't think we have been able to control the small errors, and it may be possible with a little bit of modern technology and some computerization that we can control the small errors to the point that we can make such a model useful.

Dr. Vann: There's another way that a small animal model may be made more useful as well, and that is with this new technique of microtomography, in which with rats they can see down to a resolution of a few microns. I think that has huge potential here for best showing the physiology and pathophysiology of where bubbles form, what thresholds are necessary. Such work could be done in combination with some pathology studies. It looks like a marvelous technique.

Dr. Thalmann: Four or 5 years ago, we sent a bunch of people from NMRI to Madison, Wisconsin to examine MRI as a technique. The problem with imaging very small lesions is that it took a long time. When we talked about imaging down to the kind of levels of interest, the time that it took was orders of magnitude longer than resolution times. It is like taking a picture with a very long shutter time. You get a blur and can't make any sense out of it.

Dr. Warner: We are not alone in this discussion. At present there is no cure for stroke, there is no cure for head injury, there is no cure for spinal cord trauma, there is no cure for spinal cord ischemia. All these domains are undergoing the same questioning, and until we find effective treatments, probably by accident some day, then we can look back and see what course of events led to that, can we apply a validity to any of these comments? They haven't said that. What is largely the case in these other domains, which is quite similar in some ways to spinal cord bends, is that it's a symphony of events. I do not know this research so I don't understand why you can't make a rat or mouse get decompression sickness; it doesn't make sense to me that you can't. They are very small creatures, sophisticated techniques probably would be required but they've been overcome in virtually every other model of CNS disease. I think that you really have to have both small and large animal models. The small animal model allows you to use large sample sizes and take advantage of the very robust neuroscience that's available for the rodent. Then take a large animal model, and I would suggest that the first step in a large animal model is to prove validity. I think that the best way to prove is to do an experiment where you create DCS and then you have one group that you make hot and one group that you keep normal temperature. Worsening of the injury in the hyperthermic group, which has been observed in virtually all other CNS injury models, would validate your model. If hyperthermia doesn't worsen the injury there is probably something wrong with the model. I agree entirely with Claude. We're just sitting here with archaic knowledge of the biology in this disease. How can you come up with a revolutionary intervention when you have no idea what you are dealing with? I just think you need to study the small animal model.

Dr. Hardman: You guys have already said most of what I was going to say. I think the biggest reason initially for using larger models is they more closely approximated the physiology of man in one respect, and the people who were using these models, including us, knew how to use them better. I agree with you, I think there need to be both. The biggest problem with the larger animal models is that you can't do large numbers of experiments with them unless you have a huge factory of people to help you do it. I did 200 animals over about a 6-year period. That took a lot of time, as I had other simultaneous responsibilities. It took a minimum of 20-40 hours of work time on each animal for me personally. The advantage of the small animal is that you can do some of these studies in larger batches, especially if they can be adapted to mice. There are so many possibilities with the transgenic models that would allow you immediately to tap into pertinent issues such as inflammation and some of the other things that we have been talking about. The big animal models I thought worked well to show qualitative differences and with sophisticated imaging, that's the next best way to follow what's happening. You also need to do some chronic experiments, and be in a place where you are allowed to do such experiments. Where I am I don't believe that I could do chronic experiments in big animals any more.

Dr. Thalmann: The reason that large animals were used was because we wanted to simulate human physiology, and we were trying to get something

close to the genetics of humans so that we didn't have to extrapolate too much. The problem with small animal models to date is that their kinetics are so wacky that we'd have to exercise much more precise control. It's not that they may not be useful, it's just that we need to have another look at establishing the kind of precision that we need. Rat models are used to investigate other diseases, and techniques for handling them are well developed. The question is whether the disease in rats reasonably mimics the human disease. A lot of the therapies we need are not for severe, fulminant, completely debilitating, paralytic decompression sickness. For a patient with DCS manifesting as mild leg weakness, if you have too severe a model any useful therapeutic effect could be masked.

Dr. Warner: That's a very good point but I think you can titrate the severity of the insult to get the degree of injury that you want to study. I'm not an expert on animal care policies but I know that we're allowed to create spinal cord ischemia in our mice, and I think if you have a complete paraplegia you need to account for body and bladder function in these animals and proper care. But if you can generate some sort of intermediate state, which is what we have settled into in our lab, there's plenty of literature coming out from many different institutions that that's quite allowed, and I don't think there's any real prohibition against that. I think you can adjust the insult to get the injury that you want to study.

Dr. Piantadosi: I don't view animal models any more as complete models of human disease. We look for aspects of the animal model of disease that tracks a particular aspect or particular mechanism that we think might be important in human disease. We make an observation about the disease; we break it up as much as we can and reduce it down as far as we can until you get some aspect that we can control or that we can gat a handle on. So I don't necessarily think we're going to find a mouse model that's going to mimic human spinal cord decompression sickness, but we ought to be able to injure the spinal cord in some way that you guys would say that aspect of the injury might be important in human bends, why don't you try to understand it? Maybe that would be a better way to think about this rather than trying to duplicate the human disease in a mouse.

Dr. Moon: Getting back to large animals for a moment, one of the advantages of large animals is that they scale a little bit better to humans and conceivably one could large animals to do the randomized control trial that one would like to do in humans. For example, if one wanted to look up the effect of fluid administration in decompression illness in pigs or goats you could do that. There are some survival models. Is there any feeling among the people in this room that there are burning clinical questions that could conceivably be answered by doing a large animal trial, expensive though it may be.

Dr. Butler: I think maybe the thing that comes closest to meeting that criterion is related to Gary Latson's work. There's a lot of unease with this group about PFC's, and I'm not sure why, because I thought it all looked pretty good. I think we need to figure out what we need to do to make a pretty definitive decision about PFC's, because if we're looking at increasing oxygen delivery to the tissues as useful in the pre-recompression phase it seems like that's out best bet. One thing I have to say about Gary's fundamental question, it's not "would you use it if you had it?" The question is, are you convinced enough that its going to work that are you going to give it to every diving medicine provider out in the field because you're convinced that he needs it? So if we were to do large animal studies it seems like that would be a place to start. The other place that I think that we need to do large animal studies is in decompression sickness with lidocaine. In Simon Mitchell's presentation I don't think he was implying that lidocaine isn't efficacious in decompression sickness, its just that it hasn't been modeled.

Dr. Thalmann: Speaking for myself, my discomfort with PFC's isn't that the data aren't great, but we have no experience with it. Regarding the other interventions, such as lidocaine and fluids, everyone has experience with them. In humans we know very well what the dosages and side effects are. In those terms, I don't think PFC's are ready to be made generally available. Perhaps after they are made available to major medical centers and some practitioners have some clinical experience with them, they may be ready for a wider distribution.

Dr. Butler: To answer your question about where we go from here, it seems like one of the things we need to do is it seems like you've done a very nice job of farming out the different aspects of care to different people, I think that we need to maybe formalize those subgroups and help them organize their recommendations much as Simon did, very specifically for what indications. I think we need to focus on the question of not just diagnosis but

clinical status. For example, do all gas embolism patients need lidocaine, or just the ones who don't get better or just give the ones that we can't recompress immediately. We need to gather the references about them so we can organize those into a final report. So that's a start that I think needs to be in the future as well.

Dr. Latson: I would encourage some of the basic scientists to familiarize themselves with the animal models that have been developed over the last decade at the University of Wisconsin, and other places, so that if they see a therapeutic intervention that they think is promising that whatever research they do is consistent with those animal models that already have some history. I agree with Dr. Thalmann, that probably the single biggest hurdle that we have to overcome with perfluorocarbons is familiarity. I think that when it becomes FDA approved and it gets used throughout the world in the first few years, familiarity will develop. At some point in time there's going to be a physician faced with a serious case when recompression therapy is not available, and he's going to have the nerve to go ahead and use it. I think that this group should do everything it can to muster the information and organize it and publicize it so that when that first physician uses it the first time in a case of spinal cord DCS or AGE, he has a firm foundation with which to argue why he used it. That's my goal, get the debate stimulated, get as much research as we can possibly accumulate, get it publicized and then stand by for that first case to happen. It's going to happen eventually, just like that first time somebody used lidocaine.

Dr. Moon: That brings us to human research. A number of planned randomized trials have stumbled for a variety of reasons, largely because there aren't that many cases of bends, particularly the kinds of bends that we're most interested here, the severe ones. I propose that randomized trials are not the way to go, not the way to spend limited resources. But, we will continue to observe bends. Dr. Butler has expressed an interest in doing some observational studies to look and dissect either causes for or reasons for failure to respond to recompression therapy. What ideas do people have about that? What do people think about observational studies?

Dr. Latson: I applaud any effort to further delineate why it doesn't work. I think I saw a draft of Dr. Butler's proposal to accumulate a large amount of laboratory data whenever you have a patient that doesn't improve rapidly, well don't really have a serious case that during or after treatment not delaying treatment but at some point during or after treatment try drug samples, get a variety of biological indicators and we started doing that at NEDU, but had a couple of projects that we have started doing on that road. I certainly applaud efforts to do that, I think it's absolutely what we need to do because we may stumble upon one marker that shows a difference between patients that get better and patients that don't and that may tip us off to where we need to go. So I completely support that.

Dr. Butler: I haven't seen anything in the last couple of days that suggests that it's a bad or unnecessary idea. If anything I have gotten the impetus to proceed with that. The second observational study that could be worth doing is that of divers who can't get to a chamber or who are not responding to recompression and are administered an adjunctive therapy, perhaps on the basis of what this Committee recommends We should be aggressive about following up on such cases. We can then start to build on this incredible diving practice and learn something from it.

Dr. Piantadosi: I want to go back to the fishing expedition a little bit and get your ideas about where to fish. The routine clinical chemistry tests that we do I don't think will give you what you're after. What you're telling me is that you want to look for new biomarkers and new disease markers. What are people's ideas on that? We need some brain or cord specific markers, and I don't know what are the good ones. Things like brain specific enolase and myelin basic protein may get a step closer, but even in the diseases where those things seem to be useful, it's a little bit dicey.

Dr. Goodman: I think it is a bit dicey, but to my mind some of the markers could be useful, such as NSE (nonspecific enolase), S100, which has been used in some cardiovascular studies of brain injury and maybe myelin basic protein. I don't think we'll have a high degree of specificity with these, but I think those would probably be the best first shot, because they're practical and commercially available. I don't think the turn around time is fast enough that you could actually use them clinically. For an initial study you could get rolling with cases of severe neurological decompression illness, and measure S100, NSE and myelin basic protein. I don't know of anything more specific that would be useful.

Dr. Butler: I think that when we want to further identify areas that we could potentially intervene and look first for markers in those areas. For example, consider reperfusion injury. If we found specific markers of oxidative damage, those popped up in a large majority of patients who did not respond to treatment, then that may lead us to be more aggressive in looking at an anti-oxidant intervention. If we thought a thrombotic mechanism was the preliminary cause of the failure to respond, then we might want to consider anticoagulation. If, on the other hand, we did MRI's, and in patients who didn't respond 80% of them had demonstrable spinal cord hemorrhages, we might conclude that anticoagulants are not a good idea.

Dr. Goodman: Just a question, do you folks collect and bank blood and CSF samples from these cases? Over the years in the trauma work that we've done we realized that we're either not smart enough or the techniques aren't available, so we squirrel samples away. Some day when something comes up, we can analyze them. So, it would seem to me that a reasonable consideration might be to take some biological samples, for example CSF and blood, from clear cut cases, store the samples. If we don't know what to do with them today, someday when we do we might be able to do something useful.

Dr. Warner: I think that's a really good idea, giving that we have a small population of patients to study and you don't know what to do with them yet, but time would be on your side then. An example of that is the apolipoprotein E story, which is a cholesterol transporting lipoprotein. There are different mutations of it that are established in the human genome, APOE ε2, APOE ε3 and APOE ε4. APOE ε4 was first recognized to be a predictor of early Alzheimer's disease then the people are looking at neurocognitive outcome after cardiopulmonary bypass realized that the constellation of neurocognitive deficits associated with cardiopulmonary bypass is similar to Alzheimer's disease. When they started genotyping their patients they found a relatively good correlation between genotype and outcome after bypass[1]. Since then there has been huge amount published on this, demonstrating as association between genotype and outcome in such conditions as dementia pugilistica (boxing injuries)[2], head trauma[3], cardiac arrest[4] and stroke[5]. In almost all forms of acute brain injury, if you have the genotype that is more sensitive to stress, your outcome would be worse. That's just one gene, so, who knows 5 years from now what we'll be thinking? If you start collecting these samples, particularly in a way that would preserve the genome, then you can genotype these patients and perhaps establish that a fraction of your non-responders are in fact not related to therapy, but rather the patients' genotype. I think it would be a very good idea. It's not terribly expensive to obtain and store the samples and it would be a very wise expenditure of dollars.

Dr. Flynn: Actually all the divers at NEDU were recently screened for apolipoprotein E genotypes, which were then correlated with history of decompression sickness and outcomes. Although I wasn't personally involved in that study, I understand it was negative. It's just a small group of about 60 or so people, but at least that thought process is underway.

Dr. Warner: That's a good sign but usually it takes more patients than that because the ε2 and the ε4 alleles are relatively uncommon. Thus it's necessary to get a large sample size.

Dr. Flynn: The thought was to generalize this to all Navy divers, but of course then there are ethical issues about identifying someone's genotype and whether some would be disqualified from diving because of a potentially bad outcome. In a recent study at NEDU we have looked at S100 protein, IL-1, IL-6 and a number of other markers such as D-dimer, and we don't see much of anything. In the goat work in the UK some mild elevations in S100 protein have been observed, and they've also looked at endothelin-1, which seems to show a little more promise. We haven't looked at that yet but we have all the samples.

Dr. Piantadosi: You could collect all kinds of cells from the blood. Lymphocytes can be banked. These days we can even look at sloughed endothelial cells in peripheral blood.

Dr. Hardman: The Honolulu heart study has been going since 1965, in which tissue, including brains, and blood have been stockpiled. I have also set up a network in Hawaii to try to get every death with due to decompression illness, and I have received I think three cases since I have been there, in 24 years. Setting up a brain bank would not be a small undertaking. A big bank of cases would be needed, and whereas I don't think any one institution would get those very quickly, if everybody participated, you could acquire a large number of cases in a

reasonable amount of time. You need to stockpile blood and cerebrospinal fluid routinely, if you can. The truth is that you would be on a fishing expedition, but some useful progress has come out of such studies in other diseases, such is in cancer of the stomach. For example, it was discovered that there are serum markers that are elevated before the cancer declares itself.

Dr. Moon: Before he left Dr. Dietrich suggested that once tissue is placed in a block the chemistry is fairly even over years, and he wondered whether it might be fruitful to do some immunohistochemistry on spinal cords that have been stored.

Dr. Hardman: It's true. In the bank that we have we have tried to get cases in under 6 hours after death. I have a team of people who try to get the cases done within 6 hours. I think that out of 450 cases now we have about 300 that are under 12 hours, and probably 100 of those are under 6 hours. The delays are due to the administrative logistics are involved. Cases of decompression illness are going to be so rare that you're going to have deal with a pathology community that doesn't know what this disease looks like, especially with respect to the spinal cord. Thus they don't examine it even though they should. So it means that a pathologist familiar with the disease has got to talk to them when this happens. I do try to go over the cases when I'm home when this happens. But I can tell you I've gone to 80 scuba deaths and only two turned out to be due to decompression illness. They remainder had other things such as equipment failure and drowning, but not decompression illness.

References (Discussion 13)

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4. Schiefermeier M, Kollegger H, Madl C, Schwarz C, Holzer M, Kofler J, et al. Apolipoprotein E polymorphism: survival and neurological outcome after cardiopulmonary resuscitation. Stroke 2000;31:2068-73.
5. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. Stroke 2002;33:1190-6.

American Heart Association Guidelines for Clinical Efficacy

Class 1: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class 2: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class 2A: Weight of evidence/opinion is in favor of usefulness/efficacy

Class 2B: Usefulness/efficacy is less well established by evidence/opinion

Class 3: 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

Level of Evidence A: Data derived from multiple randomized clinical trials

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies

Level of Evidence C: Consensus opinion of experts

UHMS Guidelines for Adjunctive Therapy of DCI

Aspirin		
	Class	**Level**
AGE (no significant inert gas load)	2B	C
DCS: pain only/mild	2B	C
DCS: neurological	2B	C
DCS: chokes	2B	C

NSAIDs*		
	Class	**Level**
AGE (no significant inert gas load)	2B	C
DCS: pain only/mild	2B	B
DCS: neurological	2B	B
DCS: chokes	2B	C

* *The only evidence thus far available applies to the use of tenoxicam, a nonselective inhibitor of cyclooxygenase (COX). NSAIDs are not currently recommended for use in the field. Use of nonselective COX inhibitors, because of their effect on platelet function, could engender some risk for combat divers who may be required to return to action after treatment of an episode of decompression illness.*

Anticoagulants, Thrombolytics, IIB/IIIA Agents*		
	Class	**Level**
AGE (no significant inert gas load)	2B	C
DCS: pain only/mild	3	C
DCS: neurological	2B	C
DCS: chokes	2B	C
DCS with leg immobility (DVT prophylaxis)	1	A

* *Routine therapeutic anticoagulation or use of thrombolytics or IIB/IIIA antiplatelet agents in patients with neurological DCI is not recommended, due to concern about worsening hemorrhage in spinal cord or inner ear decompression illness. Use of these agents may also be risky in combat divers who may be required to return to action after treatment of an episode of DCI.*

Low molecular weight heparin (LMWH) is suggested for all patients with inability to walk due to leg weakness caused by neurological DCI. Enoxaparin 30 mg, or its equivalent, subcutaneously every 12 hours, should be started as soon as possible after injury.

If LMWH is contraindicated, elastic stockings or intermittent pneumatic compression are suggested, although their effectiveness at preventing DVT is probably less than LMWH.

Repetitive screening for DVT while withholding anticoagulants until clot is identifiable is a strategy likely to be less efficacious than routine LMWH administration.

These guidelines are extrapolated from observations in patients with traumatic spinal cord injury. Neither the efficacy nor the safety of these guidelines in neurological DCI has been specifically confirmed in patients with DCI. 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.

Surface Oxygen*		
	Class	**Level**
AGE (no significant inert gas load)	1	C
DCS: pain only/mild	1	C
DCS: neurological	1	C
DCS: chokes	1	C

** 100% O2 administration can be safely administered for 12 hours with air breaks; thereafter, at the discretion of the rec eiving physician.*

Fluid Therapy*		
	Class	**Level**
AGE (no significant inert gas load)[§]	D5W 3 LR/crystalloid 2B Colloid 2B	C
DCS: pain only/mild	D5W 3 LR/crystalloid 1 Colloid 1	C
DCS: neurological	D5W 3 LR/crystalloid 1 Colloid 1	C
DCS: chokes	D5W 3 LR/crystalloid 2B Colloid 2B	C

** For intravenous administration, lactated Ringer's solution or other glucose-free isotonic crystalloid is suggested, unless otherwise indicated. Patients who have been immersed for prolonged periods may require additional fluid because of immersion-induced diuresis.*

[§]The pathophysiology of the lesion (pulmonary barotrauma vs. in situ gas formation) is not the issue. The different recommendations for fluid therapy in 'AGE' vs. 'DCS' apply to an isolated cerebral lesion without significant hypovolemia (e.g. hypovolemia due to immersion diuresis, perspiration or bubble-induced endothelial damage and extravasation of plasma).

Corticosteroids*		
	Class	**Level**
AGE (no significant inert gas load)	3	C
DCS: pain only/mild	3	C
DCS: neurological	3	C
DCS: chokes	3	C

** Corticosteroids are not recommended for the treatment of decompression illness.*

Lidocaine[§]		
	Class	**Level**
AGE (no significant inert gas load)	2A	B
DCS: pain only/mild	3	C
DCS: neurological	2B	C
DCS: chokes	3	C

[§] There is insufficient evidence to support the routine use of lidocaine for DCI, and it is not a standard of care. In order to make a recommendation for the routine use of lidocaine at least one human trial in decompression illness is required to demonstrate safety and effectiveness.

If it is to be used clinically, evidence suggests that an appropriate end-point is attainment of a serum concentration suitable for an anti-arrhythmic effect (2-6 milligrams/liter or micrograms/milliliter). 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 could 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. Experience with the use of lidocaine in other settings indicates that ataxia and perioral paresthesias are common. More serious toxic effects such as seizures can also occur.

Body Temperature:

Many Committee members felt that for patients with evidence of brain or spinal cord damage, the available evidence is sufficient to recommend aggressive treatment of fever. However, there are no animal data in dysbaric models or human DCI data to support a firm recommendation. When treating victims of neurological DCI, whenever practical, hot environments that may cause elevation of body temperature above normal should be avoided.

RESEARCH PRIORITIES FOR INVESTIGATION OF DECOMPRESSION ILLNESS

Human studies

- Development of consensus and guidelines for diagnosis of DCI/severity
- Systematic search for and evaluation of outcome in cases of decompression illness not recompressed, and compare with conventional treatment
- Detailed clinical investigation of fresh serious DCI cases
- Perfluorocarbon trial
- Trial of surface O_2 vs. recompression for pain-only bends
- Anti-platelet therapy trial
- NSAIDs trial
- Lidocaine trial

Animal studies

- Development of small animal model neurological DCI with long term outcome
- Development of large animal model neurological DCI with long term outcome
- Use of acute animal model of neurological DCI to test interventions (e.g. lidocaine, perfluorocarbons, mild hypothermia)
- O_2 toxicity with perfluorocarbons

Committee Priorities for 2003 and 2004

- Organize and hold a workshop directed toward the development of consistent guidelines for diagnosis of DCI and assessment of its severity (2003)
- Organize and hold a workshop to re-evaluate expected results from human trials currently underway in stroke and head injury (2004)
- Update the adjunctive treatment guidelines in the light of new developments and feedback from the diving medicine community (2003 and 2004)

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