3 Oxygen Toxicity

3.1 CENTRAL NERVOUS SYSTEM TOXICITY

Oxygen is necessary to maintain homeostasis[1] in the human body, but under hyperbaric conditions it causes central nervous system toxicity and toxicity in lung tissues, general toxicity in the other tissues, as well as other side effects.

The Polish Navy has maintained, until recently, the rules for fixing exposure time and maximum allowable oxygen partial pressure during a dive (Kłos R., 2000). They corresponded to the applicable provisions of the US Navy in the 1960s – Table 3.1 (Kenny J.E., 1973).

The manual released by the Ministry of National Defense in 1981 distinguishes between routine and exceptional exposures, where the boundary between them runs at a pressure of 0.175 *MPa* (Przylipiak M., Torbus J., 1981). Currently, during dives performed with closed circulation apparatuses where oxygen is used as a breathing medium, the Polish Navy accepts the recommendations by the US Navy (US Navy Diving Manual, 2008; US Navy Diving Manual, 2016). This monograph proposes amendments to some of these recommendations (see Chapter 5).

3.1.1 Central Nervous Syndrome

Oxygen toxicity impact on the central nervous system is called the *Paul Bert effect*; sometimes the acronym *CNS* for central nervous syndrome is used, but for the purposes of this book, in order to distinguish it from the acronym used to define the central nervous system (*CNS*), *CNSyn* will be used.

TABLE 3.1
Oxygen partial pressures and exposure time limits according to the regulations in force in the Polish Navy.

Maximum oxygen partial pressure	Allowable exposure time
[MPa]	[min]
0.130	240
0.145	150
0.160	110
0.175	75
0.190	45
0.205	25
0.220	10

According to some sources, in the recent years no significant advances in the knowledge of oxygen toxicity *CNSyn* have been made (Bitterman N., 2004). Still, many researchers refer to classical studies carried out during the Second World War by Kenneth Donald that were updated and published with the new findings compiled (Donald K.W., 1992). The most commonly used scenarios of combat exposure to oxygen were developed in the 1920s (Butler F.K., Thalmann E.D., 1984; Butler F.K., Thalmann E.D., 1986a; Butler F.K., Thalmann E.D., 1986b).

The phenomenon of oxygen toxicity of *CNSyn* is difficult to study because of the complex interaction of many factors, which include age, gender, individual predisposition and current mental and physical condition (Donald K.W., 1992). Toxicity is a phenomenon affecting many organs important for maintaining homeostasis. Frequently the biochemical systems theory is used to explain the phenomena of oxygen toxicity, assuming the adverse effects generated by the free radicals[2] and other metabolites that manifest as *CNSyn* symptoms (Torbati D., Church D.F., Keller J.M., Pryor W.A., 1992; Bartosz G., 2008).

During the oxygen exposures, hydrogen peroxide (H_2O_2) was observed in the human blood and its effect was tested on various brain areas (Bitterman N., 2004).

It is suggested that oxygen exposure has an effect on various neuroreceptors,[3] e.g. *GABA*[4] receptors, and that higher oxidized metabolic forms have an effect on enzymes[5] important for the human body, for example acetylcholine[6] (Bitterman N., 2004).

Mentioned among the methods used for reducing the risk of *CNSyn* is the introduction of air breaks that can be applied during oxygen decompression or hyperbaric treatment *HBOT*[7] (Clark J.M., Thom S.R., 2003).

During exposure to oxygen, an initial narrowing of cerebral blood vessels was recorded. This resulted in decreased blood flow to the cerebral cortex,[8] followed by an expansion of blood vessels. The moment at which this relaxation occurs seems to be the *CNSyn* threshold point, beyond which the *CNSyn* symptoms develop until an attack of convulsions.[9] Substances that reduce blood flow through the cerebral cortex can inhibit the development of *CNSyn* symptoms (Bitterman N., 2004).

3.1.2 The Mechanism of Central Nervous Syndrome

The *CNSyn* phenomenon will be briefly presented here using, as an example, the general biochemical theory of oxygen toxicity.

Biochemical transitions that utilize oxygen are the source of energy for higher forms of life on earth. The energy necessary to sustain life is obtained by the oxidation reactions occurring in cells. Bond energy released during the oxidation of carbohydrates, proteins and fats is stored in portions in phosphate bonds of guanosine-5'-triphosphate (*GTP*) and adenosine triphosphate (*ATP*) (Berg J.M., Tymoczko J.L., Stryer L., 2013). A simplified diagram of obtaining *GTP* and *ATP* in a cell is presented in Figure 3.1.

The major part of *ATP* is obtained from the cycle of the *respiratory chain*.[10] In the respiratory chain there occurs a combustion of hydrogen transported by such enzymes as nicotinamide adenine dinucleotide (*NAD*) from the *Krebs cycle*.[11] Oxygen is delivered to the respiratory chain by *cytochromes*.[12]

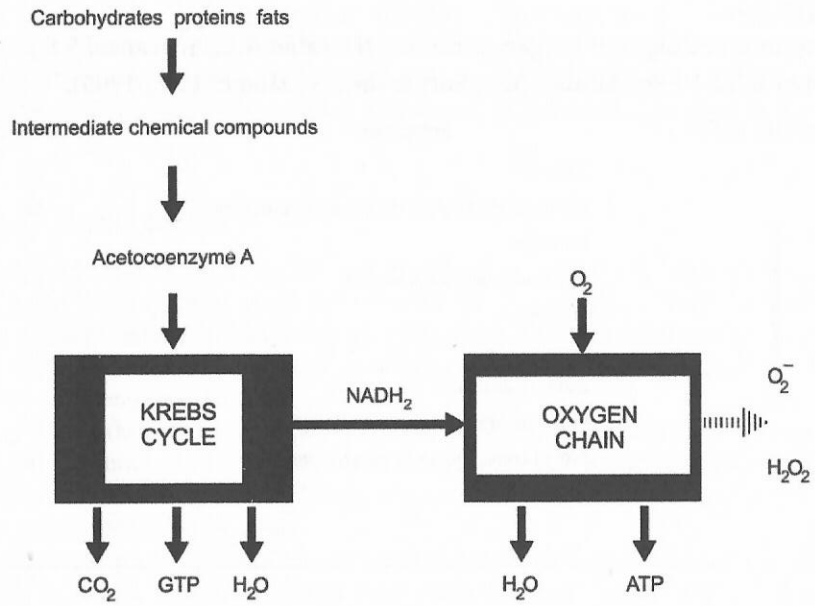


FIGURE 3.1 General diagram of *ATP* and *GTP* production.

Cytochromes contain an iron atom capable of binding and donating oxygen. Then, a change in the valence state of iron takes place and cytochromes change from the oxidized form to the reduced form and vice versa. In a reaction of oxygen with $NADH_2$, water is produced and the reaction energy, which is stored in the phosphate bonds of *ATP*, is released. This is the main method of producing *ATP* that occurs in cell *mitochondria*[13] (Stryer L., 1997; Berg J.M., Tymoczko J.L., Stryer L., 2013).

When oxygen tension in tissues is high, oxygen may enter the respiratory chain in large quantities. Then the biochemical reactions lead to the formation of free radicals and H_2O_2. Responsible for this reaction are *redox enzymes*, which accelerate the *redox reactions*.[14] The resulting free radicals and H_2O_2 are potentially toxic to the cell,[15] but normally they should be deactivated[16] (Bartosz G., 2008; Nowotny F., Samotus B., 1971).

With a significant increase in oxygen tension, the production of toxic compounds rises and the biochemical protection system is not able to deactivate them, resulting in biochemical and physiological changes in the functioning of the body. They manifest themselves as *CNSyn*[17] symptoms. No cases of these symptoms occurring immediately after exposure of the body to oxygen have been recorded.[18] As a result of poisoning, some *CNSyn* symptoms were observed preceding an attack of convulsions. They included the following: restlessness, pale face, trembling lips and eyelids, nausea, cramps, dizziness, lack of coordination, visual and auditory hallucinations, narrowing the field of vision[19] and speech disorders (Table 3.2).

These symptoms are rarely noticeable before the onset of seizures[20] (Harabin A.I., Survanshi S.S., 1993; Brubakk A.O., Neuman T.S., 2003).

TABLE 3.2
Symptoms and signs of oxygen poisoning (Harabin A.L., Survanshi S.S., Homer L.D., 1994; Harabin A.L., Survanshi S.S., Homer L.D., 1995).

The degree of risk	Symptoms	Number of cases
	Nausea	75
	restlessness, dyspnea, insomnia, depression	12
	headache	5
	numbness, burning sensation	13
	dizziness	63
	cramps	335
	auditory disorder	7
	vision disorder	17
	loss of consciousness, speech disorder	16
	convulsions	91
Total		634

Generalized convulsions occur suddenly. The attack begins with the tonic phase usually lasting 30 *s*, during which the diver loses consciousness and stops breathing. This is followed by the clonic phase of uncoordinated movements of the entire body. The whole attack usually lasts about 2 *min*. After a long period of breathing oxygen in a hyperbaric chamber, where oxygen can be replaced with air, the allowable period of apnea, without causing harm to the poisoned diver, is about $t \in [5, 8]$ *min*[21] (Clark J.M., Thom S.R., 2003).

Factors that increase cerebral blood flow, such as immersion, hypothermia, workload, increase of CO_2 concentration and so on, increase the sensitivity to *CNSyn* symptoms (Vann R.D., 1993). Carbon dioxide can be present in the inhaled breathing medium or come from the so-called dead space.[22] Through the CO_2 tension receptors, the body increases the intensity of ventilation. The increase in ventilation rate is also accompanied by an increased density of inhaled breathing medium, increased breathing resistance and so on.

In norm-baric conditions, the excess of CO_2 could be more effectively eliminated than under hyperbaric conditions. Generally, under increased pressure CO_2 accumulates in the body. Initial hyperventilation leads to *hypocapnia*,[23] observed during exposure to oxygen, resulting in decrease of respiratory action. The defense mechanism that causes blood vessels in the brain to narrow leads to increased concentration of CO_2 in cerebral vessels in relation to peripheral vessels (see Chapter 2). Thus, CO_2 receptors in the initial phase cannot increase ventilation. This defense mechanism, however, has its drawbacks. The increased CO_2 concentration in cerebral vessels increases the concentration of hydronium ions (H_3O^+), which results in hemoglobin rapidly losing oxygen in blood and increasing its tension in plasma.[24] Because of this, brain tissue is exposed to higher oxygen tension π_{O_2}. It seems, however, that the body tries to compensate these effects with the enzymes that deactivate the free radicals produced.

During work, CO_2 emission from tissues to peripheral blood may result in the following: increase in ventilation, vasoconstriction at the periphery, which raises blood pressure, and expansion of cerebral blood vessels. This may increase the cerebral blood flow, potentially causing an increase in the O_2 stream flowing through brain.

3.1.3 Antioxidants

As already mentioned, during the increase of oxygen tension π_{O_2} in tissues, oxygen can enter the respiratory chain in increased volumes, resulting in the formation of free radicals and superoxides. It is assumed that under normal circumstances, they are deactivated by antioxidants. One effective antioxidant is melatonin.[25] Its action has been widely reported.

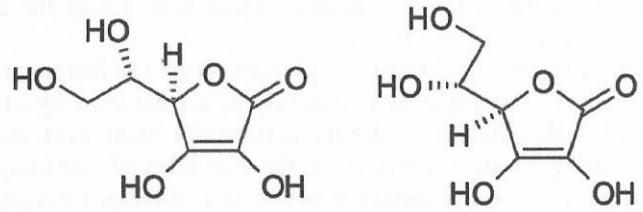
However, the activity of melatonin is spread over time and does not result in shifting the threshold of *CNSyn* occurrence (Swiergosz M.J., Keyser D.O., Koller W.A., 2004). Additional intake of melatonin causes somnolence, so its use is limited only to the time scheduled for rest.

An assessment of effectiveness of antioxidants depends on the test method. For example, a study in which healthy men exposed to hyperbaric oxygen had a diet enriched with *vitamins C* and *E* did not confirm any significant antioxidant capacities of these vitamins (Bader N., Bosy-Westphal A., Koch A., Rimbach G., Weimann A., Poulsen H.E., Müller M.J., 2007). Earlier studies conducted on mice infected with malaria[26] showed significant antioxidant activity of isoascorbic acid,[27] which is *isomer L* of ascorbic acid[28] (Rencricca N.J., Coleman R.M., 1979) – Figure 3.2.

The difference between the effectiveness of the optical[29] isomers of ascorbic acid was tested and proved to be significant. However, it was not taken into account in recent studies (Bader N., Bosy-Westphal A., Koch A., Rimbach G., Weimann A., Poulsen H.E., Müller M.J., 2007).

3.1.4 Oxygen Exposures

It is understood that O_2 shows no toxic effects on the central nervous system, when partial pressure p_{O_2} is equal to or less than $p_{O_2} \leq 0.1 MPa$[30] (Betts E.A., 1992) – the rationale for adopting this value is given in Chapter 4. During combat dives, oxygen partial pressure p_{O_2} often goes beyond this value.[31]



Form L Form D

FIGURE 3.2 Optical isomers of ascorbic acid.

TABLE 3.3
Partial pressure and time limits for oxygen exposure accepted by the US Navy in the early 1990s (US Navy Diving Manual, 1980).

Oxygen partial pressure	Standard exposures	Exceptional exposures
[*MPa*]	[*min*]	[*min*]
0.10	240	*
0.11	120	*
0.12	80	*
0.13	60	240
0.14	50	180
0.15	40	120
0.16	30	100
0.17	**	80
0.18	**	60
0.19	**	40
0.20	**	30

* times limited only due to L. Smith effect
** exposures prohibited during standard dives

In the 1970s, the US Navy changed the norms of oxygen exposure due to the risk of *CNSyn* symptoms appearing. The changes covered reduction in the partial pressure limits to $p_{O_2} \leq 0.20\,MPa$, division of the exposure type into standard and exceptional, and reduction in allowable time limits for each of the two exposure types. Accepted (until the early 1990s) oxygen exposure time limits during dives with oxygen are presented in Table 3.3 (US Navy Diving Manual, 1980).

In the 1990s, the US Navy changed the allowable oxygen exposure times for *CCR – SCUBA*[32] to allow for more flexible diving operations (US Navy Diving Manual, 2016). In 1991, NOAA[33] changed its rules concerning the partial pressure limits of oxygen during *Nx* exposures[34] (NOAA, 2001; NOAA, 2017). The amendment covered a longer time of stay under the allowable partial pressures of oxygen in *Nx* and determination of the maximum exposure time during the 24 *h* period (Table 3.4).

During deep dives, breathing resistance increases due to an increase in density of breathing medium. The breathing resistance may be accompanied by a rise in accumulation of CO_2 in the diver's body for the reasons described previously. With the increasing distance from the water surface, the possibility of providing assistance to or of a self-rescue of a diver/divers who has/have developed oxygen poisoning becomes more complicated. Therefore, the maximum permitted partial oxygen pressure for deep dives should be reduced.[35]

TABLE 3.4
Exposure time and partial pressure limits of oxygen in the *Nx* accepted by NOAA (NOAA, 2001; NOAA, 2017).

Standard exposures

Oxygen partial pressure	Exposure time limits		Maximum exposure time in 24 *h*	
[*MPa*]	[*min*]	[*h*]	[*min*]	[*h*]
0.16	45	0.75	150	2.5
0.15	120	2.0	180	3.0
0.14	150	2.5	180	3.0
0.13	180	3.0	210	3.5
0.12	210	3.5	240	4.0
0.11	240	4.0	270	4.5
0.10	300	5.0	300	5.0
0.09	360	6.0	360	6.0
0.08	450	7.5	450	7.5
0.07	570	9.5	570	9.5
0.06	720	12.0	720	12.0
Exceptional exposure				
0.20	*30*	*0.50*		
0.19	*45*	*0.75*		
0.18	*60*	*1.00*		
0.17	*75*	*1.25*		
0.16	*120*	*2.0*		
0.15	*150*	*2.5*		
0.14	*180*	*3.0*		
0.13	*240*	*4.0*		

NOTE:
– if in one of the dives the time of exposure has been reached or has exceeded the limit, the diver must rest for at least 2 *h* on the surface before next exposure
– if in one or more dives over a period of 24 *h* the maximum exposure time assumed for 24 *h* has been reached or exceeded, the diver must rest for at least 12 *h* on the surface before next exposure (Rutkowski D., 1990)

Similarly, when diving in caves or wrecks, because of limited access to the surface, the rules of deep dives should be followed. The distinction between the standard exposure and the exceptional exposure is related to the conditions of a particular dive. The exceptional exposure can be allowed only for the purpose of saving a human life or other important random events.

3.2 PULMONARY TOXICITY

Oxygen is toxic to the respiratory system. Oxygen toxicity was first observed during prolonged[36] breathing of pure oxygen at atmospheric pressure – and it was called either *Lorrain Smith effect*, from the name of the discoverer, or oxygen pulmonary toxicity (Shilling C.W., 1981; Brubakk A.O., Neuman T.S., 2003). The symptoms of pulmonary toxicity are very similar to *pneumonia*.[37] During dives outside the saturation dive protocol, this effect is minor compared to the *Paul Bert effect*,[38] but it is recommended that it should be monitored during oxygen dives (Shilling C.W., 1981; Brubakk A.O., Neuman T.S., 2003).

3.2.1 Units of Pulmonary Toxicity

At the end of the 1960s, a pulmonary toxic dose unit of oxygen, known as *UPTD*,[39] *pulmonary oxygen toxicity Q*, was established as an equivalent to one-minute exposure at oxygen partial pressure $p_{O_2} = 0.1\,MPa$ (Harabin A.L., Homer L.D., Weathersby P.K., Flynn E.T., 1987).

3.2.2 Repex

The most commonly used system of protection against pulmonary toxicity is the method validated during the *Repex* program (Hamilton R.W., Kenyon D.J., Peterson R.E., 1988; Hamilton R.W., Kenyon D.J., Peyerson R.E., Butler G.J., Beers D.M., 1988). However, there are many other models described in the literature (Shykoff B., 2007; Arieli R., 2019). Intensive research in this area is associated with the development of technical diving and medical uses of O_2, but some research is also being carried out in military applications (Arieli R., Yalov A., Goldenshluger A., 2002).

In the Repex system, it is assumed that O_2 begins to be toxic to the lung tissue if it exceeds partial pressure $p_{O_2} > 0.05\,MPa$.[40] To calculate pulmonary oxygen toxicity Q Table 3.5 can be used, which provides minute doses of $\dot{\varrho}$ as a function of oxygen partial pressure p_{O_2}.

For example, breathing pure O_2 for $t = 30\ min$ under pressure $p_{O_2} = 0.15\,MPa$ exposes the diver to *pulmonary toxicity dose* Q of approximately $\varrho = \dot{\varrho} \cdot \tau = 1.77\,UTPD \cdot min^{-1} \cdot 30\,min \cong 53\,UPTD$. For the same purpose a functional dependency can be used (Hamilton R.W., 1989; Shykoff B., 2007):

$$\varrho = t \cdot \left(\frac{p_{O_2} - p_{O_2 max}}{p_{O_2 max}} \right)^{\frac{5}{6}} \tag{3.1}$$

where: p_{O_2} – oxygen partial pressure, t – time, $p_{O_2 max}$ pressure under which pulmonary toxicity symptoms are not observed $p_{O_2 max} = 0.05\,MPa$, $\frac{5}{6}$ – exponent for the best model approximating the experimental data.

The maximum safe doses of pulmonary oxygen toxicity Q depend on exposure time t in Table 3.6, and in Table 3.7 the average values of the vital lung capacity

TABLE 3.5
Values of minute dose of $UTPD \cdot min^{-1}$ of pulmonary oxygen toxicity $\dot{\varrho}$ as a function of oxygen partial pressure p_{O_2} (Hamilton R.W., 1989).

Oxygen partial pressure p_{O_2}	Minute dose of oxygen pulmonary toxicity $\dot{\varrho}$	Oxygen partial pressure p_{O_2}	Minute dose of oxygen pulmonary toxicity $\dot{\varrho}$
[*MPa*]	[$UTPD \cdot min^{-1}$]	[*MPa*]	[$UTPD \cdot min^{-1}$]
0.05	0.000	0.16	1.92
0.06	0.265	0.17	2.01
0.07	0.490	0.18	2.20
0.08	0.656	0.19	2.34
0.09	0.831	0.20	2.48
1.00	1.00	0.21	2.61
0.11	1.16	0.22	2.74
0.12	1.32	0.23	2.88
0.13	1.47	0.24	3.00
0.14	1.62	0.25	3.14
0.15	1.77		

TABLE 3.6
Allowable dose of pulmonary oxygen toxicity Q during a multiday oxygen exposure.

Exposure time	Allowable daily dose of pulmonary oxygen toxicity Q	Allowable total dose of pulmonary oxygen toxicity Q
[*dni*]	[*UPTD*]	[*UPTD*]
1	850	850
2	700	1400
3	620	1860
4	525	2100
5	460	2300
6	420	2520
7	380	2660
8	350	2800
9	330	2970
10	310	3100
11	300	3300
12–30	300	

TABLE 3.7
Reduction in the vital capacity of lungs after oxygen exposure and rest time required to eliminate this effect.

Maximum acquired pulmonary dose *Q*	Reduction of the vital capacity of the lungs	Minimum required time between exposures
[*UPTD*]	[%]	[*h*]
615	2	2
825	4	4
1035	6	6
1230	8	8
1425	10	10–12
1815	15	13
2190	20	20

reduction resulting from exposure to oxygen are given together with the average time required to compensate for this effect.

3.3 SOMATIC TOXICITY AND OTHER THREATS

Oxygen is used in a wide range of its partial pressures (Table 3.8).

Aviation and space medicine deals with *hypoxia*. Problems with hypoxia are also important for survival in the high mountains. For divers this phenomenon is important when diving in high-altitude waters. Acclimation before diving and decompression problems in these conditions are caused not only by the lower ambient pressure but also by reduced oxygen concentration C_{O_2}. Sometimes the oxygen content of C_{O_2} is intentionally reduced as in the case of type INERGEN fire extinguishing mixtures type[47] (Table 3.8).

The carcinogenic effect of O_2 accompanies not only diving activities but the very nature of the impact of O_2 on the human body (Bartosz G., 2008). There is a postulated theory which states that O_2 contained in the air and its long-term carcinogenic impact is responsible to a large extent for the effects of aging.[48]

Undoubtedly, hyperoxia and hypoxia are linked to a direct threat of loss of health and life.

3.3.1 Chronic Oxygen Toxicity

Chronic effects of breathing under increased oxygen partial pressure p_{O_2} are called general O_2 toxicity or oxygen somatic toxicity.[49] One of the described effects is a reversible reduction in the amount of hemoglobin and the number of red blood cells in the blood of saturation divers similar to the increase in their number after a long-term acclimation to hypoxia. These effects in healthy people are reversible but must be taken into account when planning dives or resting after the dive.

TABLE 3.8
The frequently used oxygen partial pressure ranges.

Oxygen partial pressure [*MPa*]	Specification
0.010	extinguishing gases type *INERGEN®* – it is safe to breath in limited time a mixture of nitrogen, argon, carbon dioxide and oxygen in which oxygen partial pressure falls down to the level of 0.008 *MPa* under condition, that partial pressure of CO_2 will be 0.005 *MPa* (Fire Research, Test, Development and Education Centre, 1993)
0.012	lower limit of safety due to hypoxia
0.016	first symptoms of hypoxia
0.021	normal oxygen partial pressure in atmospheric air
0.035–0.040	typical saturation exposures
0.050	maximum oxygen partial pressure during saturation dives and the beginning of the lung oxygen toxicity[41]
0.10	pure oxygen breathing on surface
0.16	the most commonly accepted upper limit of safety for nitrox dives out of the saturation zone[42] (Hamilton R.W., 1989; NOAA, 2001)
0.20	treatment table *CX*-30 [43] worked out by Comex in 1986 (Comex Marseille, 1986)
0.24	suggestion to use *Nx* 0.4 at a pressure of 0.6 *MPa* in the treatment of diving diseases (Rutkowski D., 1990)
0.25	the upper limit of permitted combat dives with oxygen[44] (Butler F.K., Thalmann E.D., 1986b)
0.28	20 *min* test of oxygen tolerance (NOAA, 2001) and oxygen treatment tables[45]
0.30	suggestion to use *Nx* 0.5 at a pressure of 0.6 *MPa* in the treatment of diving diseases[46] (Rutkowski D., 1990)

Other more dangerous effects are *paresthesia*[50] and avascular necrosis of bone. However, their direct relationship to diving may be difficult to demonstrate clearly (Hamilton R.W., 1989).

3.3.2 The Chemisorption of Oxygen in the Middle Ear Syndrome

An unpleasant effect observed after oxygen dives may be collapse of the tympanic membrane resulting from chemisorption of O_2 from the middle ear cavity.

During change in dive depth, the diver is forced to equalize pressure in the middle ear cavity through the *Eustachian tube*. Multiple change of depth in the course of diving can cause a significant increase in O_2 concentration in the gas space of the middle ear. Even with minor symptoms of cold Eustachian tube, the channel has a reduced patency, and even trained divers[51] are, then, forced to perform strenuous

Valsalva blowout.[52] The oxygen locked in the ear canal undergoes diffusion through the membrane of the oval window of the inner ear where it is absorbed and consumed,[53] resulting in a reduction of pressure in the middle ear and an increase in the outside force exerted on the eardrum.

If this phenomenon happens during a rest period, the diver will wake up with a headache resulting from the strain of the tympanic membrane. Typically, a congestion of the tympanum occurs, i.e. effusions into external and middle ear and increased release of ear wax in the outer ear. It is accompanied by irritating weakening of hearing sensitivity. Usually there is no perforation of the tympanic membrane. This may occur as a result of earlier injuries that reduce the membrane's flexibility and creates scarring.

Another dangerous effect can be an excessive accumulation of dissolved oxygen in *perilymph*,[54] which may be accompanied by its movement resulting in symptoms similar to those of neurological disorders, which occur during a decompression sickness (Farmer J.C., Thomas W.G., 1976). There are recorded cases of irritation of the ear labyrinth causing its increased activity during oxygen decompression or during hyperbaric oxygen treatment. This effect is associated with moving of the *lymph* due to differences in tension of gases dissolved in it. Such cases have been rare during diving operations in Poland. However, there are credible descriptions of such problems in the international literature (Strauss R.H., 1976).

3.3.3 Oxygen Blindness

Constriction of cerebral blood vessels as physiological effects associated with exposure of brain tissue to high partial pressure of oxygen can be especially dangerous for eyesight.

During hyperbaric oxygen therapeutic procedures[55] cases were recorded of constriction of carotid artery feeding the retina *CRAO*[56] leading up to full blockage[57] and in effect to blindness. Quick restoration of circulation resulted in restored vision (Anderson B., Saltzman H.A., Barbee J.Y., 1965).

It has been also noticed that a disturbing percentage of newborn babies after a long stay in an incubator with an atmosphere enriched with O_2 irreversibly lost their eyesight (Bartosz G., 2008). For this reason, clean air is now used in incubators.

Visual disturbances associated with exposures to high oxygen partial pressure have been studied since the beginning of scientific investigations on diving (Donald K.W., 1947). It has been repeatedly confirmed that oxygen under high pressure has an adverse effect on eyesight (Clark J.M., Thom S.R., 2003).

3.3.4 Oxygen Blackout

A wide range of the literature deals with the phenomenon of oxygen blackout related to hypoxia during breath-holding dives. The issue of hypoxia occurring while returning to the surface during such dives will not be discussed here. In relation to oxygen combat dives, the term oxygen blackout is usually understood as loss of consciousness by a diver after switching from breathing oxygen to the atmospheric air after the combat mission. One of its reasons may be the already

mentioned physiological defense reaction involving the cerebrovascular constriction that results in reduced cerebral blood flow. It is usually accompanied by peripheral vasodilatation, which can lead to *hypothermia* induced by the cooling effect of the aquatic environment.

In hyperbaric conditions, oxygen tension occurs at a higher level in the peripheral blood. Hence, oxygen receptors in the glomerulus will decrease the respiratory rate and reduce the blood flow. Rapid switching to breathing air – which contains less O_2 and is usually combined with the need to get the job done[58] – before the relaxation of cerebral vessels and before increasing cerebral blood flow may cause the phenomenon of hypoxia. In addition, the pressure reduction related to ascent is accompanied by a decrease in the partial pressure of O_2, which reduces respiratory stimulation as in the case of hyperventilation. If this effect occurs in water, the diver runs a risk of choking with water or drowning, but in most cases it only leads to temporary confusion and loss of concentration (NSO, 2020).

Some hypotheses suggest considering the toxic effect of increased CO_2 tension in the cerebral vessels, but in the light of the experiments *in vivo* it appears that the effect of hypercapnia on oxygen blackout is limited. This is because the recorded increase in CO_2 tension is, in normal conditions, tolerated asymptomatically (Lamberdsen C.J., Kough R.H., Cooper D.Y., Emmel G.L., Loeschcke H.H., Schmidt C.F., 1953). Although increasing the tension of CO_2 in the cerebral vessels significantly affects the drop of O_2 in hemoglobin, the effect is not significant in the case of oxygen blackout but rather in the case of the described earlier O_2 toxic effect on brain tissue. It seems that the mechanism of oxygen blackout during the oxygen mission may be associated rather with decreased CO_2 tension in peripheral vessels causing lack of sufficient stimulation for the respiratory center.[59]

3.3.5 Oxygen Bends

Animal studies have shown that the occurrence of decompression sickness (*DCS*) symptoms may be caused by compression while using pure oxygen followed by rapid decompression (Donald K.W., 1955; Bennett P.B., Elliott D.H., 1993; Brubakk A.O., Neuman T.S., 2003). However, the course of oxygen-induced *DCS* in this way was much milder than *DCS* induced after the same air exposure (Donald K.W., 1992). *DCS* induced in such a way usually does not require hyperbaric treatment since it undergoes spontaneous compensation in time (Vann R.D., 1989). Although the phenomenon of oxygen bends is possible, it does not pose a significant risk during a normal diving operation with the use of O_2 as breathing medium. It can have a negative impact on the air transport in divers after exposure, for example during a recovery of special group/section.

3.4 OXYGEN TOLERANCE TEST

The procedure of oxygen tolerance test (*OTT*) used in the armed forces is described in Appendix 2. The description covers only the most important information on the purpose and method used to conduct the test.

3.4.1 National Practice

In the armed forces when qualifying candidates for diving with an artificial breathing medium, it is recommended that they undergo selection tests in a decompression chamber: a pressure test and an oxygen tolerance test, or both tests simultaneously. A single oxygen tolerance test should be repeated with an interval of at least a week and pressure tests are recommended to be run as often as possible, especially when Polish Navy divers are to be advanced in ranks, and before the periodic medical examination (Szefostwo Ratownictwa Morskiego, 2007).

3.4.2 International Experience

Discussions of whether to use the *OTT* have been held since the beginning of systematic research into the use of O_2 as breathing medium (Clark J.M., Thom S.R., 2003). The fundamental problem in obtaining a conclusive *OTT* result is the considerable and significant variability in both individuals[60] and groups[61] (Donald K.W., 1947). The same studies found, however, that divers exposed to oxygen poisoning in a decompression chamber and submerged in water showed higher resistance to *CNSyn* while submerged in water. This proves that the test performed in a chamber provides useful information (Donald K.W., 1992). Initially, *OTT* has been used in several countries, but at the beginning of the century it was only the armed forces of Germany and Poland that used it for initial screening.

In 2000, the US Navy conducted an analysis of the results of 6250 *OTT*s in 1976–2000 that involved candidates for combat diving. During this period only six candidates were rejected, hence the benefits to cost ratio was found to be negative and it was recommended that the screening tests in the US Navy[62] be cancelled (Walters K.C., Gould M.T., Bachrach E.A., Butler F. K., 2000). The most important reason, however, for the recommendation to discontinue the screening was the introduction by the US Navy of a new procedure for purging the respiratory volume of the *oxy – CCR SCUBA* with oxygen. As a result of this action, the diver practically breathes $74\%_v O_2/N_2$ which, when enriched with O_2 during a dive, should not exceed $85\%_v O_2/N_2$ (Harabin A.L., Survanshi S.S., Homer L.D., 1994; Walters K.C., Gould M.T., Bachrach E.A., Butler F.K., 2000).

3.4.3 Test Procedure

A candidate for the *OTT* should have an updated medical certificate and prior to the start of *OTT* should be familiarized with the way the test will be conducted and the rules of behavior inside the hyperbaric chamber.

Before entering the chamber, divers undergoing the *OTT* should answer some questions regarding their general well-being and should be examined by a physician. The scope of examination can be extended but not by elements that could significantly overload the diver on the day of such an examination.[63]

The hyperbaric chamber for running *OTT*s should be prepared appropriately for such tests. The candidate goes through the *OTT* accompanied by an attendant who closely monitors the behavior and who runs the commissioned tests (see Appendix 2).

The tested candidate and attendant enter the chamber, which is then pressurized up to the equivalent of a depth of 18 mH_2O. During the compression process, they breathe the chamber air. After reaching the depth of 18 mH_2O, the tested diver should be again briefly instructed in the use of the oxygen inhaler. Then he puts on the inhaler mask, fits it closely and starts breathing O_2 for 30 *min* at rest and in recumbence. The period of time from the start of compression to the start of breathing O_2 should be no longer than 15 *min*. Breathing takes place in the low resistance open system with the discharge of exhaled medium out of the chamber.[64]

During the *OTT* an attendant, who is breathing the chamber air, monitors the candidate and, at 5 *min* intervals, carries out measurement of breathing rate, heart rate and blood pressure of the diver undergoing the *OTT*. The attendant should, at all times, monitor the tested diver for any symptoms of *CNSyn*. If such symptoms are noticed, the subject should make the diver stop breathing oxygen from the inhaler and as soon as possible make him breathe the chamber air.

During the *OTT* the hyperbaric chamber should be ventilated, preventing concentration of O_2 inside the chamber from rising above $C_{O_2} < 25\%_v$ CO_2 partial pressure of the chamber air should be less than $p_{CO_2} < 1\,kPa$.

After 30 *min* of O_2 breathing, the tested diver removes the mask and for two minutes breathes the chamber air pressurized to the equivalent of 18 mH_2O. Then decompression takes place. The recommended decompression speed should not exceed 10 $mH_2O \cdot min^{-1}$ because of the presence of the attendant. If, in accordance with the Polish Navy air decompression table, decompression stops are not required for the attendant, it is recommended that a 1 *min* stop be made at a depth of 3 mH_2O, which is considered to be a safety stop.

The first test in a series of *OTT*s positively completed should be repeated after a minimum of a week-long break. Only the positive results of the second *OTT* provide a basis for considering the successful completion of *OTT*s. Such a proceeding is related to the earlier mentioned variability of individuals in O_2 tolerance under hyperbaric conditions (Donald K.W., 1992). Frequently, the *CNSyn* symptoms detected during the first *OTT* are not confirmed in the second *OTT* (Butler F.K., Knafelc M.E., 1986).

If during the *OTT*[65] the diver convulses the test is terminated, deemed failed and is never repeated. The failed diver can only be authorized for dives with air as breathing medium.

When during the *OTT* the candidate experienced symptoms of malaise, his/her breathing rate dropped below four breaths per minute or other than seizures symptoms of *CNSyn* occurred, the *OTT* should be interrupted and repeated after a minimum gap of one week. Recurrence of symptoms or signs of *CNSyn* are subject to the same rules as those applicable for cases of seizure occurrence in the tested diver. If the diver during the repeated *OTT* shows no *CNSyn* symptoms, this is regarded as successful completion of the first stage of *OTT* and the second test is performed after a minimum gap of one week. If the third exposure goes without comment, the diver passes *OTT*. If, however, during the third *OTT* the diver shows even the slightest sign of *CNSyn*, they should be treated as if they have experienced a seizure.

If the first test is successful, and during the second one malaise symptoms or symptoms of *CNSyn* other than seizures occur, the *OTT* may be repeated twice at gaps of at least one week. If, while repeating *OTT*, symptoms of *CNSyn* occur, the

diver should be treated as if they have had seizures. After each *OTT* the diver should remain in the vicinity of decompression chamber for around one hour.

3.4.4 The Role of Oxygen Tolerance Test

Due to shortages of qualified physicians specialized in diving medicine, there is an ongoing discussion concerning regulations applied to diving military units in view of the necessity to lower costs. Given national economic problems and practices in other countries, it seems that resigning from *OTT*s is one of the first permissible steps in this regard.

The *OTT* would have been abandoned a long time ago if there were no common conviction shared by the Polish Navy divers about its usefulness and the rationale behind its implementation. Owing to the positive *OTT* results, the divers have built a sense of security and confidence in their own abilities. A negative result was not used to judge them as unfit for diving. It only imposed limits on their powers to take risks. Additional theoretical and practical training that accompanied *OTT*s consolidated the need for self-control and strengthened the knowledge of *CNSyn*. It must therefore be concluded that the psychological effect was more important than the effects of screening.

It seems that the psychological effect of *OTT* is completely overlooked in the undergoing discussions. Its importance is confirmed by continued employment of psychologists in military units despite the fact that divers are now specially selected professional service members. When it comes to military divers, the psychological effects are marginalized, although a significant reduction in the population of active military divers is recorded, which is balancing on the edge of capability to maintain combat readiness. Probably there are many reasons for this state of affairs. They have one common denominator, i.e. a decrease in the ethos of service, understood here as the standards and values that make up the character of a diving professional, which in turn defines their identity and uniqueness. Not without significance is the effect of lowering the standards of medical service, which also reduces the attractiveness of service in a diving unit. The higher incidence rate of *CNSyn* symptoms recorded in NATO navies prompted some countries to consider reintroducing *OTT*s.[66] That might stop the growing concerns of divers and their defection to other types of service.

Because of the need to rationalize costs, the expenditures incurred by the diving service must be reduced. However, this should not deprive divers of maintaining their feeling of security. It seems that introducing such a pragmatic[67] way of tackling the problems mentioned can only be achieved through organizational changes.

Young and fit candidates, following thorough medical examination during the recruitment, can undergo the selection tests during mandatory training while the medical staff can be used as primary care physician[68] medical diving supervisors and members of recruitment commission. This will allow implementing comprehensive care[69] and will contribute to enhancing the service ethos and strengthening the sense of security among divers. It will also allow for more efficient use of physicians serving in diving units, who also provide a range of psychological services.

3.5 SUMMARY

Oxygen exhibits toxicity to the human body. However, during oxygen dives and in most combat dives it is its neurological form, *CNSyn*, that plays the most important role. This chapter deals with the biochemical view on *CNSyn* associated with the formation of free radicals and forms at a higher oxidation state that can potentially be toxic to the human body. It also includes some considerations concerning the biochemical protection mechanisms against these harmful products, which protect the diver's body from *CNSyn* only to a limited extent.

NOTES

1 The ability of a living organism to retain constant equilibrium of, for example, blood composition or temperature, by proper coordination and regulation of life processes.
2 Group of atoms, generally short-lived, that has unpaired valence electrons – free radical valency.
3 Nervous receptor.
4 Two types of *GABA* receptors binding *γ-amino butyric acid*:
   - receptor $GABA_A$ regulates the influx of chloride ions into the cell, hindering the formation of action potentials responsible for providing information in the nervous system
   - receptor $GABA_B$ regulates the flow of potassium ions and calcium to neutralize the effect of chloride ions and regulate the release of neurotransmitters.
5 The majority of these are proteins, macromolecular chemical compounds regulating the processes of life.
6 Neurotransmitter that converts the electrical signal to a chemical signal at the synapse and that plays a fundamental role in the rapid conduction of nerve signals.
7 Hyperbaric oxygen therapy; sometimes HBO is used as the acronym.
8 Observed as the defensive response to an increase in partial pressure of oxygen (see Chapter 2).
9 Tremor.
10 Electron transport chain.
11 $NADH_2$ – hydrogenated *NAD*.
12 *Cytochromes* are proteins present in cell mitochondria, exhibiting features of biocatalysts involved in the transport of electrons.
13 Mitochondria are surrounded by a membrane structure present in the plasma of most cells with a nucleus, which is where, as a result of cellular respiration, the majority of *ATP* in a cell is produced.
14 Oxidative-reductive.
15 For example, they can cause the inactivation of many enzymes.
16 For example, by vitamin E, catalase, peroxidase, etc.
17 Of these symptoms, convulsions are most often mentioned.
18 The whole biochemical processes described above require time to produce enough radicals to cause DCS, therefore the delay described is indirect evidence of the correctness of the reasoning.
19 Called tunnel vision.
20 However, it is advisable to familiarize divers with them; sometimes trained divers can quickly recognize the beginnings of poisoning, thus preventing severe *CNSyn* symptoms (Harabin A.L., Survanshi S.S., Homer L.D., 1994).

21 Because of good oxygenation of the body.
22 For example, from parts of a diving apparatus with limited gas exchange.
23 Hypocapnia, also hypocarbia, is a state of reduced, below the norm, partial pressure of CO_2 in blood.
24 Together with a decrease in the *pH* value, the capacity of hemoglobin to bond oxygen is reduced – as in the Bohr effect described earlier.
25 Melatonin is a hormone regulating circadian rhythms, including sleep and wakefulness.
26 Infection results in a significant production of oxidants by protozoa of malaria.
27 Or *E315*, which is a permitted antioxidant used in the food industry to prevent undesirable oxidation processes, extending the shelf life of foods.
28 Which is vitamin C.
29 Frequently observed differences in biochemical activity of optical isomers.
30 NOAA tables adopted this threshold as 0.06 *MPa*.
31 An additional complication is that the oxygen partial pressure during the dive may change in a fairly wide range.
32 Independent closed circuit diving apparatus with oxygen as breathing medium: *Closed Circuit Rebreather* (*CCR*) – *Self-Contained Breathing Apparatus* (*SCUBA*).
33 National Oceanic and Atmospheric Administration.
34 These changes were preceded by more than 10 years of medical research on dives with nitrox mixtures as breathing medium and *Repex* program (Hamilton R.W., 1989; Hamilton R.W., Kenyon D.J., Peyerson R.E., Butler G.J., Beers D.M., 1988; Hamilton R.W., Kenyon D.J., Peterson R.E., 1988).
35 Often in this type of operation, the stress factor that can significantly increase the cerebral blood flow similarly to the other aforementioned factors is neglected.
36 More than 24 *h*.
37 Symptoms include dry cough, increased breathing resistance, problems with taking full breaths, etc.
38 Paul Bert is considered the first to have described *CNSyn* (Shilling C.W., 1981).
39 Unit of pulmonary toxic dose – *UPTD*, cumulative pulmonary toxic dose – *CPTD*, oxygen tolerance unit – *OTU*.
40 A prolonged stay in the atmosphere, in which the oxygen partial pressure exceeds the $p_{O_2} > 0.05\,MPa$, is limited for the diver's safety.
41 Lorrain Smith effect.
42 The most commonly accepted safety limit for dives using diving apparatus.
43 Use of heliox *Hx* 0.5 at pressure 0.4 *MPa* (Comex Marseille, 1986).
44 Short exposures.
45 Optimal conditions for "washing out" the body from nitrogen.
46 Effective reductions in the size of gas bubbles at the decompression disease.
47 It is worth mentioning that *hypoxia* and *hypercapnia* partially cancel each other out in the atmosphere of INERGEN.
48 For example, the carcinogenic effects of oxygen occurring during long, multiple oxygen exposure were described (Groöger M., Öter S., Simkova V., Bolten M., Koch A., Warninghoff V., Georgieff M., Muth C.M., Speit G., Radermacher P., 2009).
49 Somatic means concerning the body: bodily, physical.
50 Distortion of tactile sensation involving the wrong location of stimuli, and distortion of their experience, as tingling, numbness, prickling sensation, etc.
51 Who do not have problems with equalizing the pressure through swallowing saliva or moving the lower jaw.
52 Blowing out breathing medium from lungs to nose with closed mouth and squeezed nostrils.

53 Physical absorption combined with chemical reaction is chemisorption.
54 The fluid filling the bony labyrinth of the inner ear.
55 Therapeutic procedure often used for general and local tissue oxygenation against anaerobes, after respiration poisoning, to secure the grafts, frostbites, burns, post-radiation damages, osteomyelitis, safeguarding the slow-healing wounds, sudden deafness, etc.
56 Central retinal artery occlusion – *CRAO*.
57 Blockages often concern the main artery branches supplying the retina and can be seen as a partial problem with visual acuity; similar symptoms manifest many cardiovascular diseases, including systemic hypertension, inflammation of the arteries and diseases such as syphilis.
58 For example, associated with the need to remain on the surface of water, going to the shore, leaving the area, counter-action against waves.
59 Any lack of stimulation of the nervous system causes perturbations of conduction of signals, which results in exclusion of control leading to cessation of breathing.
60 Symptoms of *CNSyn* were induced in one diver once or twice a week for a period of 90 days and significant differences in tolerance to increased partial oxygen pressure as a breathing medium were observed (Donald K.W., 1947).
61 Symptoms of *CNSyn* were induced in 36 divers and significant differences in the tolerance time to oxygen partial pressure at .. were observed (Donald K.W., 1947).
62 One has to be aware that to serve in special forces, only candidates with special physical qualities and who are healthy and young are selected; hence, it should be assumed that the threat to the wider population is bigger than that observed during the tests.
63 For example, physical performance tests.
64 Breathing work $W < 0.3\ J \cdot dm^{-3}$ and the maximum instantaneous inhalation resistance $\Delta p < 2.5\ kPa$.
65 The first or the second.
66 Underwater Diving Working Group NATO Standardization Agency Meeting, Istanbul 2011.
67 Understood here as an approach taking into account the logical relationship with the problematic situation.
68 As a substitute for psychologists.
69 Practice shows that the divers in the units may also be subject to other occupational diseases associated not only with diving, for example disorders of the spine associated with running high-speed boats.

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