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Toxic Effects of Hyperbaric Conditions

Ali Erdal Gunes

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Abstract

Hyperbaric oxygen therapy is highly safe in treatments based on internationally accepted treatment tables. However, in some long-term treatments, the internal adjuvant and the patient are exposed to some toxic effects. In the presence of compressed air environment, nitrogen can lead to drunkenness. Another cause of poisoning is oxygen. Oxygen shows toxic effects when inhaled in the high-pressure environment for long periods or above partial pressures on 3 ATA. The excess oxygen has a toxic effect on the lung and central nervous system (CNS). Oxygen poisoning can be seen in long-term oxygen therapy in intensive care, in closed or semi-closed circuit diving, in saturation dives, on decompressions on the surface, in recompression and hyperbaric oxygen therapy. The first goal during convulsion is to prevent trauma prevent the patient from biting his tongue during the seizure. However, in nitrogen narcosis, the first intervention should be to prevent the diver from diving deeper to reduce the effect of anesthesia. The lifeguard must prevent the unconscious movements of the diver, such as removing the regulator from his mouth and holding his breath. He must think that the dive is like a dream.

Keywords: hyperbaric oxygenation, toxic actions, neurotoxicity syndromes, acute lung injury

1. Introduction

Inert gases are shown to have an effect in the body without entering metabolic and chemical activities [1]. The inert gas, which is nitrogen, encountered with problems in sports equipped divers. For this reason, what is known as inert gas narcosis in diving medicine can be called direct nitrogen narcosis in this chapter [2].

Nitrogen narcosis, depth poisoning, depth drunkenness, nitrogen narcosis is also known by other names [1]. The nitrogen that the two nitrogen molecules bind with three bonds between

them constitutes 79% of the air we breathe [3]. The increase of the nitrogen pressure negatively affects the central nervous system (CNS). It is usually seen at depths of more than 30 m [4]. Nitrogen narcosis is characterized by decreased intellectual function and decreased neuromuscular transmission performance, a tendency to laugh, decreased attention and decision-making, emotional state, and impaired behavior. Nitrogen narcosis does not cause permanent damage to the body, but mental and motor deterioration can lead to serious problems in the underwater [2]. These effects increase as the partial pressure of nitrogen increases, but it is not related to the time remaining at the same depth [5]. These changes have been seen for centuries as they are known when diving with compressed air due to nitrogen pressure. Other inert gases with similar effects have been described (neon, argon, krypton, xenon, and hydrogen) [1].

In diving with compressed air, nitrogen narcosis is the most important factor limiting depth. When it is necessary to work deeper than 40–50 m, it is necessary to get help from gas with less narcotic effect such as helium. Nitrogen narcosis is responsible for most of the dive accidents and dive-related deaths.

The cause of acute toxicity of hyperbaric oxygen therapy is related to oxygen partial pressure [6]. Although oxygen is a necessary gas to survive, oxygen can show toxic effects at high partial pressures and long-term exposures. Oxygen poisoning can be seen in long-term oxygen therapy in intensive care, in closed or semi-closed circuit diving, in saturation dives, on decompressions on the surface, in recompression and hyperbaric oxygen therapy [7].

Oxygen intoxication is caused by reactions between free oxygen radicals and cell components [8]. Gamma amino butyric acid (GABA) has frequently been studied in studies conducted in this regard [9]. Excess oxygen causes the generation of uncontrolled stimuli in the central nervous system by reducing GABA outflows [8]. It is thought that seizures developing in 3 ATA and above hyperbaric oxygen therapy are related to this [10].

2. History

The poisoning caused by air inhalation in a high-pressure environment was first described by Junod in 1835 [2]. In 1861, Green made a dive with divers with 48 m of compressed air, observing that the divers developed to sleep, their decision-making powers were impaired, and they saw hallucinations. Paul Bert stated that divers were poisoned at high depths in 1878. In 1903, Hill and McLeod described the intellectual functions of tunnel workers as inadequate at 5.5 ATA pressure. In 1930, Damant reported that memory problems had developed in 10 ATA. In 1932, Hill and Phillips thought these effects could be claustrophobic or psychological. According to a report by the British Navy in 1933, the section entitled "Loss of semi-consciousness" states that divers who have dived at 60–106 m have received hand signals sent to them, but no one remembers it when it comes to the surface [1].

In 1935, Behnke and his colleagues described the currently accepted theory of nitrogen narcosis. Narcosis is caused by an increase in partial pressure of nitrogen, which is an inert gas. The

enthusiasm (euphoria) developed at the 30-m compressed air dive; accompany slowing of the mental capacity and deterioration of the nerve-muscle communication. Attention was paid to the fact that this effect was further enhanced by the depth of the dive. At diving, drowsiness occurs at 90 m and loss of consciousness occurs at 90–140 m. Behnke and Yarbrough reported that this effect could be reduced by replacing nitrogen to helium in the dive inhalation gas [1].

According to the Deep Dive Committee Report in 1933, this was also related to the accumulation of carbon dioxide during the dive. In 1941, Case and Haldane showed that, when carbon dioxide was mixed in the diving air, the mental symptoms became more intense. However, In some studies clearly denied the carbon dioxide theory. They showed evidence of narcotic symptoms despite normal levels of carbon dioxide in the alveolar air. In subsequent years of studies has been found that direct anesthesia is responsible for the nitrogen between the air and dive with helium/oxygen [2].

3. Etiology

It is thought that the mechanism of nitrogen narcosis is the same as general anesthesia with volatile gases. All inert gases that produce anesthetic effects behave in the same way. These gases are composed of simple molecules with no structural properties and do not show chemical changes in the body [3].

Many researchers have attempted to understand the physical behavior of these gases and have found a close relationship with the oil dissolution feature. According to the Meyer-Overton hypothesis, there is a parallel between the dissolution of anesthetics in oil and potency of the narcotic effect. It stated that when the gases pass through cell oils at a certain molar concentration, they will show an effect of narcosis. In this case, the inert gas molecule affects the cell membrane function in the brain. However, there are some discrepancies in terms of the physical properties of the inert gases and their narcotics abilities (**Table 1**). For example, argon is two times more narcotic than nitrogen. However, their fat/water solubility ratios are similar. However, despite all these incompatibilities, narcotic behavior is parallel to physical characteristics in general [5].

According to Henry's Law, as soon as the partial pressure of nitrogen increases, it begins to dissolve more in the body and in the plasma. Nitrogen cannot be used by the body like oxygen. When we breathe compressed air during diving, many molecules enter our bodies and quickly dissolve in our bodies due to the height of the environmental pressure. When we dive 15 m sea water, the nitrogen partial pressure will double up. With the increase in depth, the narcosis signs will begin to appear. As is known, anesthetic symptoms occur when diving is 15 m or more, and we briefly explain it with the Martini Act (**Figure 1**) [4].

The dissolution hypothesis in oil has been tried to be understood by the concept of critical volume. Here, in order to develop the effect of narcosis, the inert gas must affect on the fat part of cell membrane to swell. In human studies, it has been confirmed that gas has a positive correlation with oil solubility by developing slightly to moderate narcosis.

Gases	Molecular weight	Volume	Solubility in oil at 37°C	Separation coefficient (oil:water)	narcotic effect
Helium	4	2.370	0.015	1.70	0.23
Neon	20	1.709	0.019	2.07	0.28
Hydrogen	2	2.661	0.040	3.10	0.55
Nitrogen	28	3.913	0.067	5.25	1.00
Argon	40	3.218	0.140	5.32	2.33
Krypton	83.7	3.978	0.430	9.60	7.14
Xenon	131.3	3.105	1.700	20.00	25.64

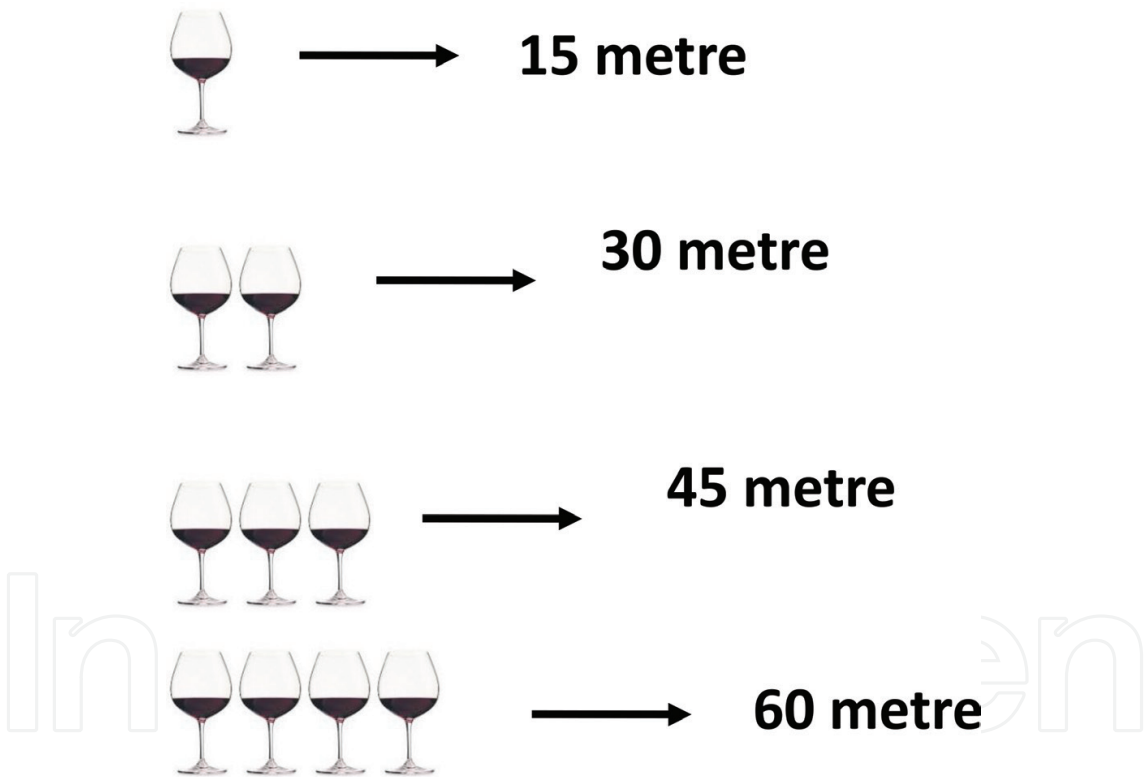**Table 1.** Narcotic effects and physical properties of some gases.

Figure 1. Martini Yasası.

In general, although these physical theories refer to the fatty part of the cell membrane, it has been shown that this narcotic effect is due to specific receptors and influences synaptic transmission. Some studies have shown that cell membranes are resistant to narcotics and cell membrane proteins and lipoproteins are responsible for this.

Many studies have focused on the cause of stimulation in the central nervous system. Stimulant-inhibitory synapses, molecules, and receptors are the basis of this effect. Among them, gamma-amyno butiric acid (GABA) is the most important inhibitory molecule. GABA is an important inhibitory neurotransmitter which made from glutamine after a series of reactions in the central nervous system (**Figure 2**). GABA receptors have been shown to be responsible for the formation of nitrogen narcosis [8].

The most important of the stimulating molecules is dopamine. Nitrogen accumulation increases the levels of dopamine, causing cortex and thalamus stimulation, which are brain regions (**Figure 3**). Nitrogen accumulation causes a reversal of uptake and an increase in dopaminergic levels. This situation leads to stimulation in the thalamus and striatum, which is the inhibitor center. This explains some neuromuscular disorders belonging to nitrogen narcosis [9].

In order to explain the acute toxic effects of hyperbaric oxygen therapy, it is necessary to focus on enzyme metabolism. High pO_2 values disrupt the function of enzymes, especially those containing sulfurized sulfhydryl groups. This effect of free oxygen radicals is widely accepted [7].

For example, the antioxidant defense system in the body can resist life to the oxygen pressure normally found in atmospheric air, or even slightly more. This value is 0.4–0.5 atmospheres (1 ATA at sea level, oxygen is approximately one-fifth in the air). Now, let's take a 30-m dive with air. In this case, total pressure will be 4 ATA, and if the oxygen forming partial pressure of air is $pO_2 = 0.8$ ATA, this value exceeds the antioxidant defense system of the body. The body is damaged acutely by oxygen at a depth of 30 m for a long time.
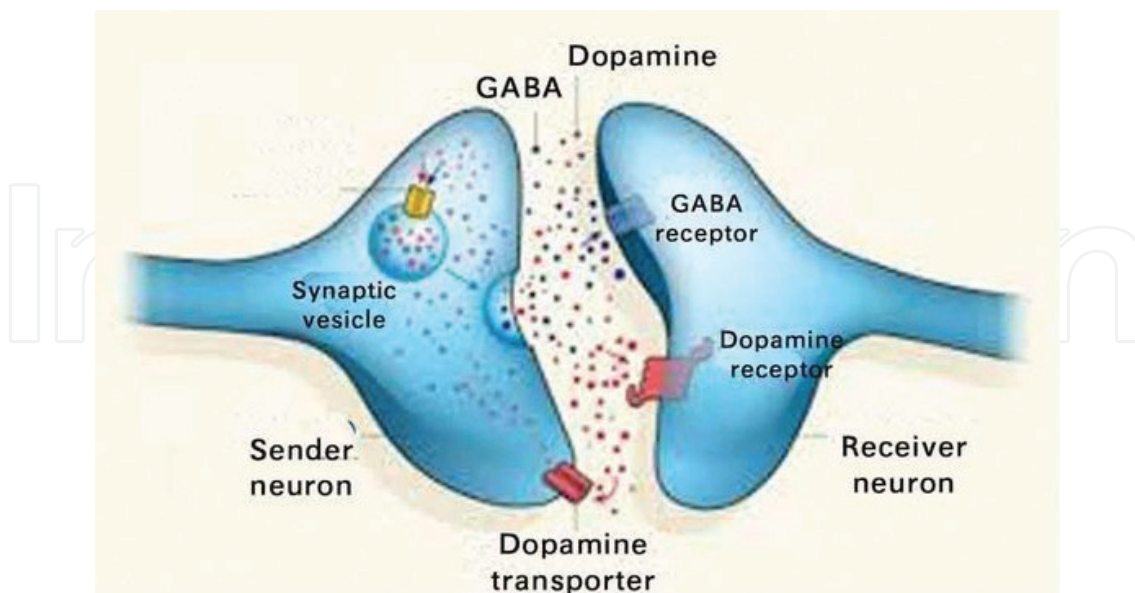

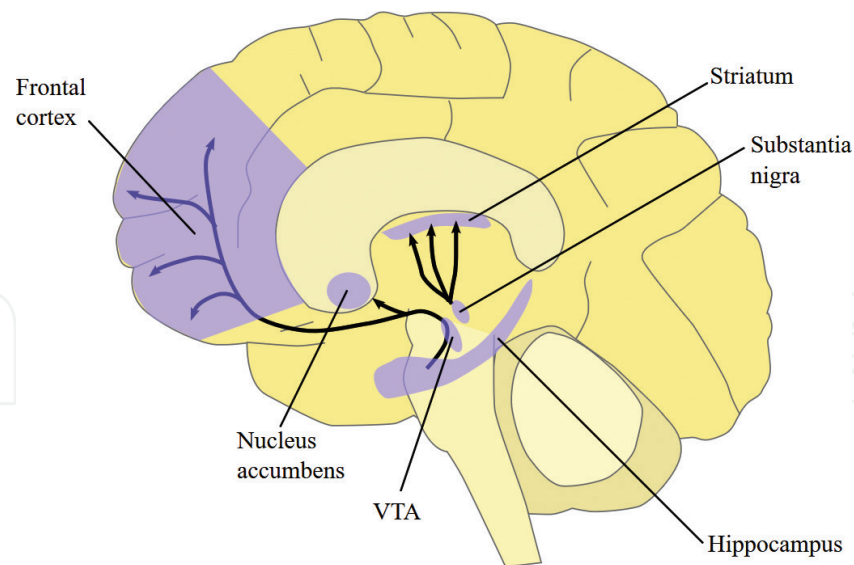**Figure 2.** GABA and dopamine metabolism.

Figure 3. Dopamine-induced thalamus and cortex.

4. Theories

• *Myer-Overton:* when inert gas is dissolved in the nervous system, the inert gas has an inhibitory effect on the nervous system.

• *Quastel-Metabolic:* at high pressure, inert gas disrupts cell metabolism. These sensitive cells are mostly found in the brain. The cells, which are consciousness formation, are the first to be affected.

• *Clathrate:* under pressure nitrogen creates clathrate with protein and water. This formation disrupts neural transmission.

• *Iceberg:* when nitrogen gas dissolves in water, it creates molecules called icebergs. The iceberg also prevents the transmission of the nervous system like the same clathrate [4].

5. Pathophysiology

There are many variables that affect the susceptibility of the person to nitrogen narcosis. Diving health, deep diving experience, working conditions, environmental conditions are some of these. As the depth increases, the diver starts sign of the suppressing. Thinking problems, deterioration of time perception, deterioration of decision-making, memory problems, motor and mental functions, and the prolongation of reaction time are some of these [5].

When the diver starts to exit, the symptoms disappear quickly; sometimes, it does not remember what you are doing underwater during nitrogen narcosis.

There is no direct pathological change to acutely CNS oxygen poisoning in humans. In animal experiments, tissue death was demonstrated in the nervous system. Serious exposures can cause damage to the brain and spinal cord in the spinal cord. Even a 30-min dive with 4 ATA pure oxygen (30 m) can cause structural changes in the gray matter in the spine of front horn [7].

6. Clinical signs and symptoms

The mechanism of CNS oxygen poisoning is not fully known. Oxygen is believed to have evolved by the increase of pO_2 and the free oxygen derivatives affecting the CNS metabolism. As a rule, poisoning is seen when exposed to pO_2 pressure on 2 ATA and above [6].

Oxygen poisoning occurs more rapidly as the pO_2 pressure increases. According to Clark and Lambertsen's work; pO_2 1.7 ATA for 7 h, 1.8 ATA for 3 h, 2 ATA for 50 min and 3 ATA for 30 min showed signs of MSS poisoning [7].

Signs and findings are described in a wide range of fans. Nausea, vomiting, dizziness, ringing in the ears, incoordination, tunnel vision, irritability, pallor, sweating, heart rate slowing (bradycardia), lips, and hands twitching, eyes widening of the baby, hiccups, to remember the recent past, hallucination, confusion (confusion) are chief of the signs and findings. However, the most dramatic of these is the seizure, namely the convulsion. It is typical that consciousness is closed during convulsion [7].

The most common finding is a face twenty in the oxygen pressure on 2 ATA. The sign of paleness in the face is due to hyperoxia-induced vasoconstriction. Similarly, the loss of sensation in the fingers is the result of vasoconstriction [9].

Even though the depth is the same, being in the water reduces the resistance to oxygen poisoning considerably compared to being in dry air in the pressure chamber. Water and diving stress increase the susceptibility to oxygen poisoning. Also underwater, the signs mentioned above cannot be noticed, but the divers are noticed that they are poisoned when they have convulsions. Convulsions underwater are dangerous because they can lead to suffocation or barotrauma. Therefore, many authorities have determined the maximum depth of pure oxygen diving underwater to be 10 m. Other causes that reduce the threshold value of CNS poisoning are exercise, hypothermia, increased calm carbon dioxide levels [10].

Facial twitch usually results in convulsions. During convulsion, all body stimuli develop and the tonic phase called full contraction begins. During this time, breathing is interrupted. The tonic phase usually lasts 30 s and is accompanied by loss of consciousness. This period approximately takes 1 min, followed by the head, neck, trunk, and legs in large contraction followed by clonic phase. After the clonic phase, the contractures decrease and the respiration starts with hyperventilation, and after a while consciousness comes back. The diver does not remember any part of the event. The concentration of carbon dioxide has increased because of being held breath during the convulsion. However, contrary to normal epilepsy patients,

there is no reduction in oxygen reaching the CNS during respiration, as oxygen breathes at high pressure before the diver seizure [11].

When toxic effects of oxygen occur, it is necessary to reduce the partial pressure of oxygen inhaled immediately. In the pressure chamber, it is necessary to remove the oxygen mask or reduce the pressure. Diving depth must be reduced during diving. The diver must be brought to the surface safely. Reducing the pressure in the pressure chamber or rising in the dive is accompanied by lung barotrauma risk because it is kept breath during the seizure. After first aid, barotrauma should be controlled by drawing a chest radiograph [8].

Although the sensitivity of nitrogen narcosis is quite different from person to person, all the divers who dive at depths of 60–70 m demonstrate clinical signs of nitrogen narcosis. Firstly, high cognitive functions are affected. The main symptoms of these are judgments, decision-making, close memory, learning, concentration, and attention. The diver may feel very good and can over-confidence himself as a light alcohol drinker. Along with increased nitrogen partial pressure at higher pressures, diminished hand strength and progressive deterioration of mental performance, intellectual fixation, hallucinations, and finally lethargy/blunting and coma. Some divers may experience a disorder in the form of tunnel vision, but they cannot be aware of the danger because of the perception disorder [1].

Tension, cold, tiredness, soothing medicines, alcohol and medications that affect the central nervous system may cause exacerbated narcosis. The effects of nitrogen narcosis are likened to the intake of alcohol. Alcohol and nitrogen narcosis symptoms are often associated, especially as enthusiasm and motor coordination develop. Even with a somewhat sarcastic approach, the nitrogen narcosis is assessed with a criterion called the Martini law. According to this law, every 50 feet of depth leads to equivalent effects on a glass of martin. Enthusiasm, joy, laughter at 10–30 m; increased self-confidence, fixed idea at 30–50 m; loquaciousness, dizziness, hysterical seizures at 50–70 m; delayed response to stimuli, loss of concentration, mood swings at 70–90 m; hallucinations, and loss of consciousness develop over 90 m [3].

The nitrogen narcosis effect is affected within a few minutes when you descend into depth and is not related to the dive time. Initially, fast diving increases the anesthetic effect, but this effect is rapidly returned when ascending to surface [3].

Other causes that increase the degree of nitrogen narcosis need to be considered. Alcohol, fatigue, tension, cold, oxygen, and carbon dioxide changes increase the effect of narcosis, limiting the diver's ability in underwater. Experimental studies have shown that alcohol and underwater exercises increase the effect of narcosis. Increased carbon dioxide and nitrogen pressurized diver have been shown to reduce performance. In certain periods and long dives, divers can develop some adaptations against to the narcotic effect of nitrogen [4].

Despite the fact that it is not a realistic and appropriate guide for the formation of nitrogen narcosis, scientific studies are carrying out. It is useful to monitor the performance of the diver in simple tasks, tests that can be reached to narcotic sensitive individuals, the use of low narcotic gas mixtures during diving and reduction of other factors affecting narcosis in depth, achieve a safe dive operation without encountering this effect. Since these tests are not used in the selection of the sportive diver or mixed gas is not used in sportive diving, the depth of the dive is reduced or terminated when anesthesia develops. It is also necessary to

pay attention to the other factors, which increase the influence of nitrogen narcosis mentioned in the previous paragraph. The effects of nitrogen narcosis are roughly measured by two methods. First of these, the behavioral approach measures the fulfillment of the assigned task, which measures arithmetic, memory, and handicraft. The other is a measure of some neurophysiological parameters [5].

(A) Behavioral approach

The behavioral approach is examined in three main categories: cognitive ability, reaction time, and skill. Cognitive competence is the most frequently affected by nitrogen narcosis, but skill competence is least affected.

In this study, conducted on open water divers, anxiety, and a decrease in the success of the task were observed. The anxiety status was determined by measuring plasma cortisol and urine noradrenaline. The intellectual function, arithmetic, and memory capacity of open dives were found lower than the coastal diving in open sea diving. The cause of this decline is depending on stress of the open sea diving.

The effect of nitrogen narcosis on behavior has been studied by psychologists. They defined this as a slow process model. In this model, they saw slowed activation with anesthesia, increased reactivation duration. The least affected hand is skill because less cognitive function is needed for skill.

(B) Neurophysiological changes

Neurophysiological tests are needed to evaluate some subjective values, to achieve low performance and to provide objective evidence. These are the information that is obtained by drawing the electroencephalogram of the brain after diving with compressed air in the cabin. First, findings of high stimulation in the cortex of the brain have been reached. This situation includes voltage increases in the basal rhythm of the brain.

The measurement of the functions of the central nervous system can be done by examining the cortical potentials, evoked from the exposed inert gases in the brain. The low response to stimulus is an experimental measure of the effect of nitrogen narcosis.

7. Treatment

When acute poisoning statements are made during treatment in the pressure chamber, the patient should be given air to breathe deeply. If necessary, the treatment table can be changed by the underwater physician. In case of unconsciousness, stomach contents should be prevented from escaping to the lungs (aspiration).

The first goal during convulsion is to prevent trauma [7]. The tongue should prevent the patient from biting the tongue during the seizure. It should be known that naturally depends on the dive, the lack of oxygen (hypoxia) does not occur. It is necessary to wait until the tonic phase of the convulsion is finished. Otherwise, the diver may be exposed to lung barotrauma.

If oxygen poisoning develops in the pressure chamber treatment;

• Stop diving, remove the mask.

• If convulsion develops, it will prevent damage to itself and its surroundings.

• Tongue bite is blocked by attendance.

• Enables hyperventilation with air in the pressure chamber.

• The sedative drug can be started with the recommendation of the underwater physician.

• If symptoms have disappeared after interruption of treatment within 15 minutes, it will be resumed from the same point of treatment.

• If necessary proceed to non-deeper treatment tables.

The first intervention should be to prevent the diver from deeper to reduce the effect of anesthesia. The lifeguard must prevent the unconscious movements of the diver, such as removing the regulator from his mouth and holding his breath. He must think that the dive is like a dream, and he should try to go to ascend from the depth.

The diver must be closely followed when he comes out of the water. There is no treatment to be done when the anesthetic effect is passed. During close follow-up, hypoxic findings, drowning, sudden outbreaks, etc. should be considered and examined for secondary problems. The underwater physician should be consulted if such cases are found to be present.

8. Prevention

When medications that prevent convulsions are used before the dive, the convulsion is under control, but cell damage is still present. This causes the diver to reach uncontrolled depths and be exposed to more toxic effects. The only safe approach is to make diving plans at depth limits. This limit depends on the partial pressure of the oxygen, the duration of the dive and environmental factors.

Underwater physicians test the candidates who are susceptible to CNS oxygen poisoning. The oxygen tolerance test can be done by oxygen breathing in the hyperbaric oxygen therapy device at 2.8 ATM for 30 min. Although this test is susceptible to positive ones, there is no clinical validity of the "oxygen tolerance test." Tolerance can vary from person to person or from day to day in the same person [9].

In the simplest case, it is necessary to avoid high partial pressures of inert gases during diving. It is important to be aware of the circumstances of air diving and know that performance and decision-making authority will be affected at depths of over 40 m. In professional diving, it is necessary to use less narcotic gases such as helium to increase the depth of safe diving. It is known that the adaptation of the dive with the daily dives against nitrogen narcosis. Some studies have shown that although some personal adaptations can occur, reaction times do not benefit from repeated dives.

To prevent nitrogen narcosis, some mixed gases are used in professional dives. Diving is planned here by creating a mixture of oxygen with nitrogen, helium or helium/nitrogen. The aim here is to reduce the narcotic effect by reducing the partial pressure of the nitrogen. However, it is necessary to pay careful attention to oxygen poisoning since oxygen increases partial pressure in such diving. As helium increases heat transfer, divers must be careful against the hypothermic effect. Due to such effects, only professional divers are allowed to mix gas dives.

Amphetamines reduce the narcotic effect that causes the prolongation of the reaction period, so they are not used in diving. The diver should be aware of the risks in the underwater environment. Also, increase narcotic efficacy, drugs that suppress the central nervous system, such as alcohol and antihistamines. These drugs create a synergistic effect with nitrogen, accelerating the reduction of performance and decision-making.

9. Return to diving

When the symptoms disappear, and the diver feels ready, the dive may return. It should be noted here that nitrogen is a secondary health problem that will develop in a diver who is forced to exit during narcosis. If necessary, the diver should be re-examined [2].

In diving accidents, the treatment of hypoxic injuries is more important than oxygen poisoning. Therefore, priority should be given to the treatment of diving accidents. In the treatment of decompression, air or gas mixtures can be used in the pressure chamber to reduce the most toxic damage. Vitamin A, C, E, selenium, and so on to reduce oxygen poisoning. Antioxidant products can be used in hyperbaric oxygen therapy or before diving [7].

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