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Possible causes of narcosis-like symptoms in freedivers

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ABSTRACT

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During deep-sea freediving, many freedivers describe symptoms fairly similar to what has been related to inert gas narcosis in scuba divers. This manuscript aims to present the potential mechanisms underlying these symptoms. First, known mechanisms of narcosis are summarized while scuba diving. Then, potential underlying mechanisms involving the toxicity of gases (nitrogen, carbon dioxide and oxygen) are presented in freedivers. As the symptoms are felt during ascent, nitrogen is likely not the only gas involved. Since freedivers are frequently exposed to hypercapnic hypoxia toward the end of the dive, it is proposed that carbon dioxide and oxygen gases both play a major role. Finally, a new "hemodynamic hypothesis" based on the diving reflex is proposed in freedivers. The underlying mechanisms are undoubtedly multifactorial and therefore require further research and a new descriptive name. We propose a new term for these types of symptoms: freediving transient cognitive impairment.

KEYWORDS: cerebral blood flow; diving reflex; hypercapnia; hyperoxia; hypoxia; narcosis

INTRODUCTION

During scuba diving, inert gas narcosis (IGN) is caused by an increase in the partial pressure of various breathing gases, with nitrogen considered the main contributor [1]. In 1826, French physician Jean-Daniel Colladon first described IGN-related symptoms while he was experiencing a 20-msw descent. At that time, he reported "a state of excitement as if I had drunk an alcoholic liquor" [2]. In 1935, American physician Albert Behnke suggested that this behavior could be linked to nitrogen gas by using different mixtures of breathing gases [3]. Since then, many studies have been conducted on IGN. However, the underlying mechanisms and management remain under debate, even in scuba diving [1]. Nevertheless, the IGN-related symptoms experienced in scuba diving are nowadays quite well identified, as they are shown to lead to both impaired neurocognitive function and physical performance decrement. Such a narcotic effect occurs from 10 meters of seawater (msw), with a maximal prevalence of around 30 to 40 msw in depth [4]. Symptoms include spatial and temporal disorientation, memory impairment, euphoria, hallucinations, mood changes, impaired neuromuscular coordination,

psychomotor and intellectual decrements as well as loss of consciousness, the latter occurring at pressures above 1,078 kPa [4]. Collectively, these symptoms influence the ability to make correct decisions and necessarily contribute directly or indirectly to the yearly 6% of fatalities in divers [1,5].

It is interesting to note that elite freedivers describe symptoms that are fairly similar to that of narcosis that we will call "narcosis-like" while in deep freediving. These symptoms are described in both published and unpublished testimonies of elite freedivers: Guignes, Zucchari, Boudhiaf, Streeter, Néry, [6,7]. Symptoms include hallucinations, the "feeling of dreaming" or "being in a dream," altered perception of time, numbness in the mouth, tingling in the fingers and toes, blurred vision, loss of memory leading to confusion and, occasionally, panic. The confusion could be compared with that of some freedivers practicing no-limit freediving (i.e., assisted-descent freediving with sled) who have reported suffering from short-term memory impairment, e.g., their inability to describe the bottom phase and part of their ascent.

In addition to memory impairment, the French freediver holding the no-limit record at that time reported a euphoric state while he was reaching the bottom camera. Schagatay [8] reported that among 24 divers involved in the same competition, 12 had "narcosis-like" symptoms, including dizziness and confusion. She noted that all these symptoms appeared at depths greater than 40 msw. Similar symptoms are also reported at depths of 50 to 60 msw during "shallow" training dives with bottom hanging (i.e., remaining static at depth). Taken together, it is worth noting that this clinical picture appears to be quite similar to the one extensively described by scuba divers. One of the main differences between scuba diving and freediving is the timing at which the onset of narcosis appears: the descent for scuba divers and the ascent (sometimes upward to the water surface [with no breaks]) for freedivers [6,7]. If the narcosis of the freediver was indeed due to high partial pressures of nitrogen (PpN_2), then symptoms would be expected during the descent and not during the ascent since this phase corresponds to reduced PpN_2. However, these symptoms could persist after surfacing in freedivers, as previously described following scuba diving [9-11].

Mechanisms

The underlying mechanisms contributing to such symptoms are therefore most likely different between scuba divers and freedivers, implying that nitrogen is not the main and/or the only factor involved. Different theories have been reported to explain narcosis in scuba divers. Biochemical-based theories on toxicity and dissolution of gases are the hypotheses generally reported for air diving. As it is difficult to objectively and accurately measure narcosis [12], the effects are usually studied indirectly through inhalation of different anesthetic gases [13]. Anesthetic potency correlates with lipid solubility (Meyer-Overton theory) [5], implying that the IGN site is located on a lipophilic (fat-soluble) part of the cell membrane. Due to their lipophilicity, nitrogen (N_2) and inert gases bind to membranes. This phenomenon triggers the membrane to swell beyond a given critical volume, ultimately leading to narcotic effects according to individual susceptibility (i.e., concentration threshold) [1,4]. Since pressure affects narcotic potency in a linear fashion and N_2 narcosis remains with decreasing pressure (ascent phase), the contribution of an inert gas to narcosis is, in our view, unlikely in freedivers. Besides, neurochemical-based data revealed a decrease in hypothalamic neurotransmitters (norepinephrine and dopamine) following exposure to gas mixtures [14]. At the present time, no evidence supports these mechanisms in freedivers. We therefore advocate another way to characterize such symptoms: "freediving transient cognitive impairment," or FTCI.

Neurochemical hypotheses

Based on available animal models [15], neurochemical studies have been carried out on the effects of inert gases and pressure on the basal ganglia, particularly on the nigrostriatal pathway

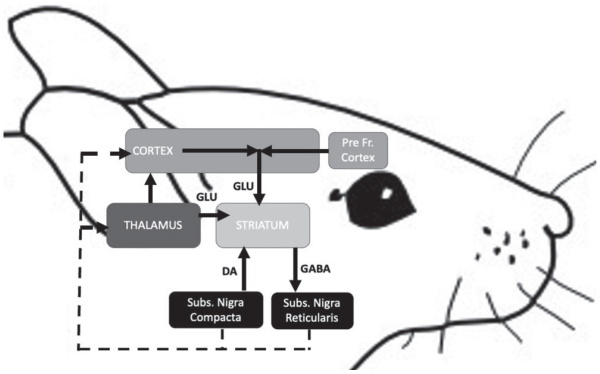

Figure 1. Main striatal projections of awakening and vigilance (redrawn from Vallée (Vallee et al., 2011)). The black matter pars reticulata (SNr) projects onto the thalamus via GABAergic neurons (GABA). The thalamus rich in glutaminergic neurons (Glu) projects onto the cortex and striatum. The combination of these two pathways corresponds to an inhibitory circuit. The cortex, mainly the prefrontal cortex (PFC), projects onto the striatum via excitatory neurons (glutamate). Finally, the substantia nigra pars compacta (SNc) projects onto the striatum using dopamine (DA). However, the effect on the striatum (inhibitor or exciter) depends on the type of receptor: D1-like (direct; inhibitory route) or D2-like (indirect route crossing the subthalamic nucleus not illustrated: excitatory). Dotted arrows indicate inhibitory action, while solid arrows indicate excitatory action.

(Figure 1). These studies are carried out on male Sprague-Dawley rats, bioinstrumented under general anesthesia, with voltametric electrodes in the striatum, and cannulas implanted bilaterally in the substantia nigra, either reticular or compact part as well as in the striatum, in order to subsequently receive a microdialysis probe. These structures are involved in the regulation of locomotor and cognitive processes disturbed by pressure or narcosis. This research focuses on the effects of the latter on monoaminergic (dopamine, serotonin) and amino acid (GABA, glutamate, aspartate) neurotransmissions and their interactions at the level of the basal ganglia. At the level of the striatum, the pressure is responsible for an increase in the release of dopamine [16-18], serotonin, glutamate and aspartate, although with different kinetics for these last three substances [19-21].

Conversely, a reduction in dopamine levels is observed in the event of exposure to nitrogen, nitrous oxide [22-24] or argon [23,25] illustrating, at least at the striatal dopamine level, the antagonistic effects of pressure on narcosis. These changes are related to the action of a particular neurotransmitter, i.e., gamma-aminobutyric acid (GABA), as demonstrated by studies using GABAa or GABAb receptor agonists injected into the substantia nigra pars reticulata (SNr) or pars compacta (SNc) [26].

The injection of muscimol, the main psychoactive alkaloid of mushrooms of the Amanita group and agonist of the GABAa receptor, does not induce any modification in the release of striatal dopamine at atmospheric pressure. Under pressure with respiration of a helium-oxygen mixture, the injection of this molecule, either into the SNc or into the SNr, blocks the increase in dopamine induced by the pressure [26,27]. At atmospheric pressure, the injection of baclofen, a GABAb agonist, induces a decrease in the release of dopamine in the striatum. Under pressure, this injection into the SNc blocks the increase in pressure-induced dopamine release. When baclofen is injected into the SNr, the reduction in dopamine levels persists. Furthermore, locomotor hyperactivity, a sign of high-pressure nervous syndrome (HPNS) in rats correlated with changes in dopamine levels, is reduced by activation of GABAb receptors and increased by activation of GABAa receptors [26-28].

The similarity between the effects obtained with injection of GABA into the SN (decrease in the release of dopamine at the level of the striatum) and those obtained with nitrogen under pressure suggests that nitrogen acts directly on the GABAa receptors of dopaminergic neurons of the nigrostriatal pathway. This means that: i) the pressure activates the GABA receptors of the GABAergic neurons of the substantia nigra pars reticulata and the substantia nigra pars compacta which are then inhibited; ii) GABA release in the substantia nigra pars compacta and thalamus decreases, which activates dopaminergic neurons in the substantia nigra pars compacta and glutamine neurons in the thalamus, resulting in an abundant release

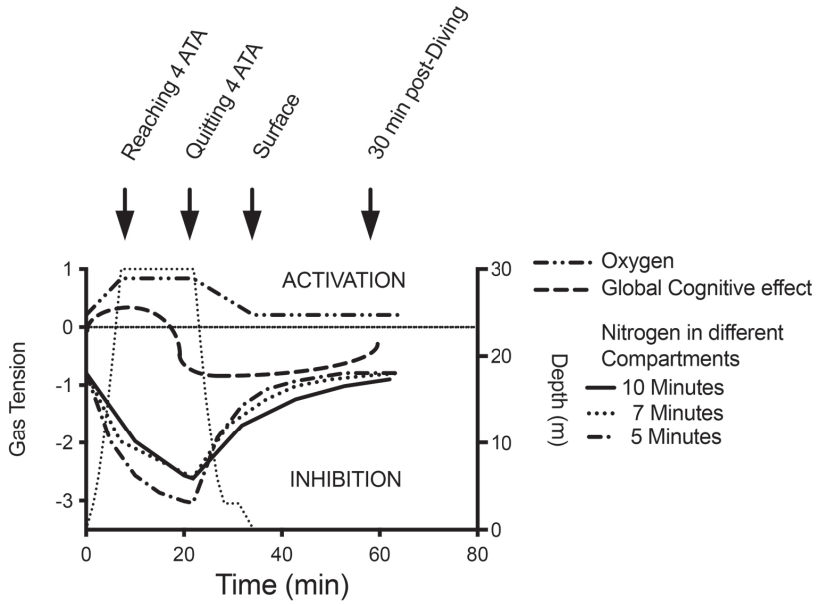

Figure 2. Tentative model of narcosis components in a scuba dive performed at 30 meters, for 20 minutes, with "remanent" narcosis (adapted from Balestra et al., 2012).

of dopamine in the striatum; iii) the activity of the thalamocortical pathway and, consequently, motor activity is increased.

Nitrogen acts directly on the GABA receptors of the dopaminergic neurons of the substantia nigra pars compacta, inhibiting them and reducing dopamine release. Dopamine inhibits the GABA neu rons of the substantia nigra pars reticulata by activating the inhibitory D2 receptors on their surface. As there is less dopamine, the inhibition is lifted and the GABA neurons are activated, blocking the dopamine neurons of the substantia nigra pars compacta and the glutamine neurons of the thalamus. This reduction in dopamine release in the striatum would explain some of the symptoms of nitrogen narcosis.

Several experiments have investigated narcosis persistence post scuba diving. In scuba divers, perceived post-dive fatigue is decreased and critical flicker fusion frequency (CFFF) is increased after diving with nitrox 30 [30% oxygen) compared to diving with air [10,11]. The same experiment was repeated with an underwater CFFF measurement. The results showed an increase in brain arousal at 33 meters, followed by a decrease in the CFFF after 20 minutes at the bottom and persisting up to 30 minutes after surfacing. This effect was directly eliminated by breathing pure oxygen for 15 minutes [9]. Consequently, narcosis and HPNS would result from a balance between these different chemical modifications, those of the pressure on the nigrothalamic GABAergic pathway and those of the gas on the nigrostriatal dopaminergic pathway, a bicephalic answer [29]. No experiments have been carried out with freedivers on this specific subject. It is difficult to say that freedivers follow the same pattern as shown in Figure 2.

The gas toxicity hypotheses

Compared to scuba diving, the air mixture contained in the lungs of a freediver while in apnea is not renewed. Thus, this fixed air mixture (composed of nitrogen, oxygen and carbon dioxide) is subject to pressure gradients of the environment while concurrently being consumed (for oxygen, O_2) or produced (for carbon dioxide, CO_2) during apnea. During descent, alveolar and arterial oxygen pressures increase, which may lead to transient

hyperoxia at the bottom [30]. However, this transient hyperoxia does not appear to be associated with any increased oxidative stress in freedivers [31,32]. While acute hypercapnic hyperoxia is known to boost free radical production in the caudal solitary complex of rat brain slices, it does not alter oxidative stress [33]. This is likely due to antioxidants and proteasomes removing damaged lipids and proteins to maintain cell viability during prolonged hyperoxia [34]. While arterial partial pressure of O_2 (PaO_2) increases during descent, arterial partial pressure of CO_2 ($PaCO_2$) is meanwhile only slightly increased owing to its: (i) much higher blood (and tissue) solubility compared to O_2; and (ii) its capacity to be buffered. At any stage of the descent, $PaCO_2$ appears therefore slightly increased, even during a constant-weight dive to 60 meters [35].

During ascent, the ambient pressure decreases, thus implying a substantial drop in PaO_2 to dramatic levels [35,36]. This transient hypoxic state may lead to the point of unconsciousness in freedivers [35,36]. Even without symptoms, these repeated hypoxic events may progressively alter neurocognitive functions. Billaut et al. [37] observed mild episodic memory dysfunctions that were positively correlated with years of dive training. After a diving session, overproduction of free radicals, oxidative damage to membrane lipids and decreased antioxidant capacity are associated with exposure to hypoxia, which in freediving usually occurs in the last few meters of seawater below the surface [37]. The possible long-term negative impact of reduced O_2 supply to the brain remains yet under question [37,39]. Whether apnea is performed using constant weight (i.e., with significant muscle activity) or assisted with a sled (i.e., with minimum muscle activity), $PaCO_2$ appears to be maintained to baseline levels or slightly increased during ascent [30,35].

Therefore, the narcotic effect of CO_2 seems unlikely at this diving stage (i.e., during ascent). Alternatively, diving narcosis is most likely the result of a complex interaction between activities, environmental conditions, and gases. In addition, the interaction across gases should not be excluded, as N_2, O_2 and CO_2 are known to alter neurocognitive performance at different partial pressures [40]. At present, this interaction effect has been established only for divers using equipment to breathe different gas mixtures [40]. There are no direct links with what is known to be real "narcosis" as explained previously.

A hemodynamic hypothesis?

Human physiological response to static apnea triggers the so-called diving reflex. Its main effects are bradycardia and peripheral vasoconstriction, allowing blood to be redirected toward oxygen-dependent organs such as the heart and brain [41]. These hemodynamic adjustments have also been observed during constant-weight diving since the diving reflex is powerful enough to override the cardiovascular response to exercise [42,43]. All during apnea, vasoconstriction progressively induces an increase in stroke volume and mean arterial pressure [44]. Bain et al. [45] recently noted that toward the end of a deep apnea, freedivers were exposed to hypoxia and (mild) hypercapnia while displaying both increased blood pressure and cerebral blood flow. Hypoxia, and particularly hypercapnia, are known to increase cerebral blood flow, which can ultimately disrupt neuronal activity or at least dynamic brain self-regulation. During maximal apnea in elite freedivers, dynamic brain autoregulation is severely impaired with a concomitant decrease in cerebral oxidative metabolism [46]. A disruption of the blood-brain barrier has also been suggested [45]. During descent, lung volume decreases proportionally to the increase in pressure, thus promoting a redistribution of blood around the lungs called the blood shift [47]. This blood shift protects the lungs from being crushed while in the descending phase. A reciprocal mechanism, "reversed blood shift," is obviously expected during the ascent phase, although not clearly demonstrated. We hypothesize during ascent that: (i) the diving reflex together with diaphragmatic contractions support high cerebral blood flow; and ii) the blood shift attempts

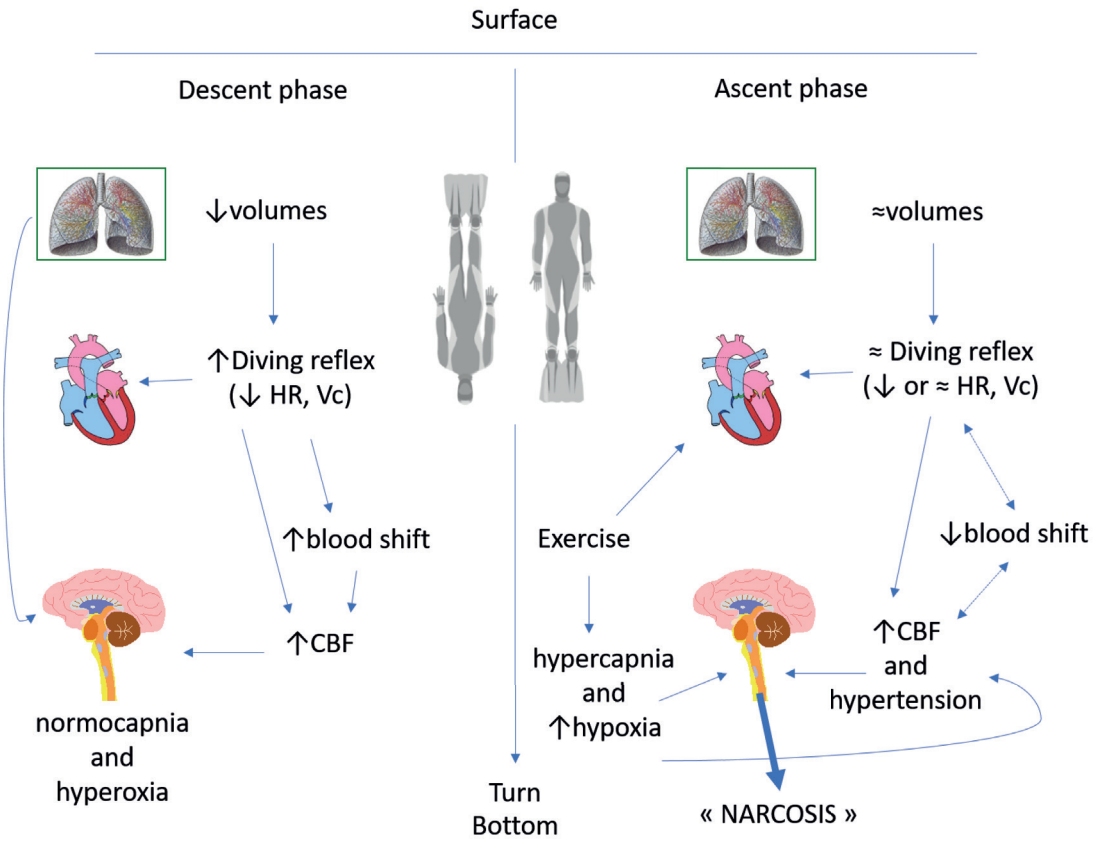

Figure 3. Proposed mechanisms of narcosis in freedivers. During the descent and from the beginning of the apnea, lung volume decreases (due to increased ambient pressure) while the diving reflex is triggered. Blood therefore gradually moves from the periphery to the thoracic cavity (blood shift) which increases cerebral blood flow. The freediver becomes hyperoxic but remains normocapnic at this stage. During ascent, increased muscle activity raises carbon dioxide production, placing the freediver into a state of hypercapnic hypoxia. Cardiovascular responses induced by increased muscle activity challenge the diving reflex which may nevertheless remain predominant (depending on both intensity and training level). Cerebral blood flow then further increases owing to hypercapnic hypoxia, which would in turn impair cerebral function and explain narcosis symptoms experienced by freedivers. CBF: cerebral blood flow; HR: heart rate; Vc: peripheral vasoconstriction.

to reverse (decrease) despite vasoconstriction-induced high venous return and pulmonary expansion. Taken together, these mechanisms might contribute to the high cerebral blood flow during ascent, which could in turn impair neuronal activity and explain narcosis symptoms experienced by freedivers.

Additional factors

Several additional factors should be mentioned as possible contributors to narcosis in scuba divers. These include hypothermia, hyponatremia, hypoosmolality, metabolic acidosis, anemia and advanced age. In addition, opioids and benzodiazepine decrease the required concentration of the narcotic substance, while hyperthermia, younger age, amphetamines, cocaine and chronic alcohol abuse increase it [5]. Considering the freediving context, hypothermia and age are likely the most pertinent factors to retain in the development of narcosis. Recently, the speed (of descent and ascent) has been considered a key factor since this

parameter increases the risk of syncope [48] and possibly blood redistribution through a decreased diving reflex. During constant-weight diving using fins, divers experiencing syncope had longer dive times (197 seconds vs. 167 seconds) together with a faster first dive phase, i.e., the active phase (1.24 m • s^{-1} vs. 1.06 m • s^{-1}) [48]. Authors suggested that the higher speed could increase air (O_2) consumption, which would reduce lung volume. Reduced lung volume may therefore induce blood movements, thus increasing cerebral blood flow.

CONCLUSIONS

Based on the present narrative, a proposition of mechanisms involved in the freediver "narcosis" is summarized in Figure 3. During the descent and from the beginning of the apnea, lung volume decreases while the diving reflex is triggered. Therefore, blood gradually moves from the periphery to the thoracic cavity, increasing cerebral blood flow. The freediver becomes hyperoxic but remains normocapnic at this stage. During ascent, increased muscle activity raises carbon dioxide production, placing the freediver into a state of hypercapnic hypoxia. Cardiovascular responses induced by increased muscle activity challenge the diving reflex, which may nevertheless remain predominant. Cerebral blood flow then further increases owing to hypercapnic hypoxia, which would in turn impair cerebral function and explain "narcosis-like" symptoms experienced by freedivers. Therefore, the term narcosis would be inappropriate. We propose: freediving transient cognitive impairment, or FTCI.

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