Life Sciences xxx (xxxx) 123169

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

# New insights into the mechanisms and prevention of central nervous system oxygen toxicity: A prospective review

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ARTICLE INFO

*Keywords:*
Hyperbaric oxygen convulsions
Hyperbaric oxygen seizures
Hyperbaric oxygen therapy
CNS oxygen toxicity
High-pressure nervous syndrome
High-pressure neurological syndrome
Oxygen toxicity
Diving
Hyperbaric medicine
Paul Bert effect
Pressure reversal of anesthesia
Hypothesis

ABSTRACT

Hyperbaric oxygen therapy (HBOT) elevates the pressure of life-sustaining oxygen ($pO_2$), thereby saving lives. However, HBOT can also cause toxic effects like lung and retinal damage (peripheral oxygen toxicity) and violent myoclonic seizures (central nervous system (CNS) toxicity). The mechanisms behind these effects are not fully understood, hindering the development of effective therapies and preventive strategies. Herein, we critically reviewed the literature to understand CNS oxygen toxicity associated with HBOT to elucidate their mechanism, treatment, and prevention. We provide evidence that (1) increased $pO_2$ increases reactive oxygen species (ROS) concentration in tissues, which irreversibly alters cell receptors, causing peripheral oxygen toxicity and contributing to CNS oxygen toxicity. Furthermore, (2) increased ROS concentration in the brain lowers the activity of glutamic decarboxylase (GD), which lowers concentrations of inhibitory neurotransmitter $\gamma$-aminobutyric acid (GABA), thereby contributing to the onset of HBOT-derived seizures. We provide long-overlooked evidence that (3) elevated ambient pressure directly inhibits $GABA_A$, glycine and other receptors, leading to the rapid onset of seizures. Additionally, (4) acidosis facilitates the onset of seizures by an unknown mechanism. Only a combination of these mechanisms explains most phenomena seen in peripheral and CNS oxygen toxicity. Based on these proposed intertwined mechanisms, we suggest administering antioxidants (lowering ROS concentrations), pyridoxine (restoring GD activity), low doses of sedatives/anesthetics (reversing inhibitory effects of pressure on $GABA_A$ and glycine receptors), and treatment of acidemia before routine HBOT to prevent peripheral and CNS oxygen toxicity. Theoretically, similar preventive strategies can be applied before deep-sea diving to prevent life-threatening convulsions.

## 1. Introduction

Oxygen therapy (OT) encompasses a set of medical procedures for increasing the partial pressure of oxygen ($pO_2$) in inhaled gas, thereby increasing the supply of life-sustaining oxygen to the body. OT is indicated for numerous conditions, *e.g.*, lung disease and alveolar hypoventilation, poor tissue perfusion, carbon monoxide poisoning, gas gangrene, decompression illness, and arterial gas embolism, among others. [1,2] When a high oxygen supply is required, oxygen can be delivered in a hyperbaric chamber (hyperbaric oxygen therapy, HBOT), which further raises $pO_2$, facilitating oxygen uptake by the body. These forms of OT have become part of clinical routine and have helped save countless lives. [1,2]

HBOT is usually well tolerated by patients; the most common side effects include relatively rare traumas in the ear and sinuses caused by pressure changes. [3,4] However, HBOT may also cause undesirable effects (Table 1). [1,3,5,6]

Prolonged exposure to hyperbaric oxygen increases concentrations of reactive oxygen species (ROS) in tissues, [14,21] damaging cells and tissues - especially lungs and retinas, but also other organs (**peripheral oxygen toxicity**, also called 'hyperoxic acute lung injury', 'Lorrain Smith effect', historically also 'chronic oxygen toxicity'). [1,4,6,10–12] This peripheral toxicity depends on both $pO_2$ and cumulative time of

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https://doi.org/10.1016/j.lfs.2024.123169
Received 6 March 2024; Received in revised form 19 August 2024; Accepted 20 October 2024

**Table 1**
Various types of high-pressure associated syndromes. The magnitude of peripheral oxygen toxicity primarily depends on $pO_2$ and time of exposure. In turn, CNS oxygen toxicity (CNSOT) occur stochastically; their risk increases with ambient pressure, $pO_2$ and time of exposure. Finally, high-pressure neurological syndrome (HPNS) depends on the breathing mixture composition,[a] ambient pressure and its rate of increase. The latter two effects have partly overlapped manifestations.

| Phenomenon | Conditions for occurrence | Manifestations (signs and symptoms) |
|---|---|---|
| **Peripheral oxygen toxicity** [1,4,6,10–14] | Occurs deterministically above the threshold $pO_2$ of 0.5 ATA. Increasing $pO_2$ and time of exposure increases damage. | Slow onset of interstitial lung oedema, capillary endothelium damage, alveolar cell death, decreased lung compliance, retinal damage; vasoconstriction in some organs. It can be fatal within hours to days, depending on $pO_2$. |
| **Acute central nervous system oxygen toxicity (CNSOT)** [1,5,10,14–17] | Occurs stochastically above the threshold pressure of 1.6 ATA; the risk increases with $pO_2$, pressure, and time of exposure (Fig. 1). Other factors increase (CO poisoning, exercise, acidosis, *etc.*) or decrease (alkalosis) the risk. If left untreated, they quickly progress into more serious manifestations. | Sudden onset of various symptoms that may include visual disturbances (blurred vision, tunnel vision), ear symptoms (tinnitus, pulsing sound), nausea, changes of mental state (irritability, anxiety, euphoria), muscle twitching (especially in face), dizziness and clumsiness, confusion, tremors, loss of consciousness, muscle spasms, spastic apnoea, seizures and tonic-clonic convulsions, and death if left untreated. |
| **High-pressure neurological syndrome (HPNS)** [18–20] | Occurs deterministically, symptoms start occurring above 10 ATA. Manifestations increase with ambient pressure and rate of pressure increase. Some gases (*e.g.*, nitrogen and hydrogen) reverse HPNS if given enough time to distribute throughout the body (as described in *section 3*). | Headache, vertigo, nausea, fatigue, euphoria, tremors, oposoclonus, myoclonus, dysmetria, hyperreflexia, cognitive deficits, memory impairment, CNS hyperexcitability, and loss of consciousness.[a] Convulsions have been reported.[b] Usually fatal in divers. |

[a] As further discussed in *Section 3*, some gases can reverse HPNS if given enough time to distribute to CNS, and so the effect depends on the composition of the breathing mixture and the rate of pressure increase. [7–9].

[b] These lists of signs and symptoms are based on observations of deep-sea divers who breathe balanced mixtures of helium-nitrogen-oxygen or helium-hydrogen-oxygen. As discussed in *Section 3*, hydrogen and nitrogen have anesthetic (inhibitory) properties, and thus, they can diminish (some) symptoms of HPNS and excitation. Therefore, we observe only "residual signs and symptoms" in such divers. When no anesthetic gas is present (usually performed only in laboratory animals), other manifestations (including convulsions) have been observed.

exposure [1,22] (where increasing $pO_2$ increases the rate of tissue damage; $pO_2$ below 0.50 absolute atmospheres (ATA) are deemed safe in the long term (> 30 h). [1,6,22] If left untreated, peripheral oxygen toxicity can be fatal within hours to days. [14] Fortunately, antioxidants (ROS scavengers, such as vitamin C [23–25] and potentially others [14]) decrease ROS concentrations in tissues [25] and thus can mitigate peripheral oxygen toxicity. [14,23–25]

Moreover, ambient pressure above 1.6 ATA [1] can lead to poorly understood CNS oxygen toxicity (CNSOT, Table 1), characterized by muscle twitches, spasms and life-threatening violent tonic-clonic seizures (*grand mal*) and death if left untreated (an effect also known as 'Paul Bert effect', hyperbaric oxygen seizures'; historically also 'acute oxygen toxicity'). [1,5,10,15] These signs occur stochastically within minutes to hours (Fig. 1), [5] usually without prodromal symptoms, and cannot be safely predicted in advance. [1,4,26] Nevertheless, increased ambient pressure and oxygen concentration increase the likelihood of CNSOT and accelerate their onset (Fig. 1B).[1] [5,27,30] Under moderate ambient pressure (2.4 to 3.0 ATA), CNSOT are relatively rare in most patients (0.008 to 0.7 % incidence), [31,32] but very common in carbon monoxide (CO) poisoning patients (0.3 to 4.7 % incidence) for unknown reasons (further discussed in *section 1.4*). [30,31]

Because hyperbaric CNSOT are very dramatic and potentially life-threatening, [1] current guidelines for HBOT recommend avoiding pressures above 2.0 ATA during HBOT to mitigate the risk of convulsions as much as possible. [16,31] On the other hand, limiting the total pressure in HBOT decreases the $pO_2$ in tissues, [26] thereby lowering the efficacy of HBOT. [26]. Thus, increasing the safety and efficacy of HBOT requires eliminating the risk of HBOT-associated convulsions, [1] which has been difficult because CNSOT is still poorly understood. When these convulsions occur, they can be often [1] mitigated by lowering the $pO_2$ and/or the ambient pressure to a normal level, [1,4] but administering benzodiazepines [31] or anesthetics [12] can help in some [31] cases as well. However, quickly lowering the total pressure can cause barotrauma (dysbarism), decompression sickness, and gas embolism and, therefore, is not always possible (especially in divers). [1].

At last, very high ambient pressure (> 10 ATA) can cause **high-pressure neurological syndrome** (HPNS; historically also called 'helium tremors' [33]), whose manifestations partially overlap with those of acute oxygen toxicity (Table 1). [18–20] HPNS is most ascribed to pressure-derived changes in function of cell receptors and channels, which leads to neurotransmitter imbalance CNS hyperexcitability. [20,34,35] HPNS can occur in deep-sea divers, but not in routine HBOT, which used much lower pressures (≤ 3 ATA) than those needed for occurrence of HPNS. Noteworthily, the presence of some gases in breathing mixtures (hydrogen, nitrogen, argon) and slow pressure increase (0.015 to 0.9 ATA per minute depending on current pressure) [36] can limit the risk of HPNS, further discussed in *Section 3*.

In this evidence-based prospective review, we briefly examine previously proposed mechanisms of CNSOT involving ROS and argue that other factors, primarily neurotransmitter receptor dysfunction, contribute to CNSOT. *In vitro* [37–40] and *in vivo* [41–45] studies have shown that γ-aminobutyric acid receptors A ($GABA_A$) [37–40], glycine [46,47] and *N*-methyl-D-aspartate (NMDA) [48] receptor functions are altered under increased pressure. Based on mounting, long-overlooked evidence, we postulate that CNSOT may also be attributed to these pressure-induced reversible alterations in the function of neurotransmitter receptors.

In line with our review-based mechanism, we suggest that a combination of antioxidants, pyridoxine, and inhibitory drugs (such as anticonvulsants / anesthetics / sedatives) may be administered preemptively before routine HBOT to prevent CNSOT. Moreover, in some patients, their blood pH should be monitored carefully, as acidosis severely increases the risk of CNSOT. Finally, we highlight the areas that should be investigated further to increase the safety and efficacy of HBOT and improve the safety of deep-sea divers.

### 1.1. ROS only partly account for CNSOT

CNSOT are most often attributed to the toxic effects of ROS. [3,4,13,49,50] ROS encompass a group of highly reactive oxygen-containing compounds that can be formed *in vivo* and damage tissues. Indeed, ROS concentration in tissues increases with $pO_2$, [51] which in turn can damage organs such as the lungs and retinas. [11,14,21] Thus, ROS is commonly accepted as a mechanism of peripheral oxygen toxicity. [14,21] In line with this hypothesis, antioxidants (ROS scavengers, such as vitamin C [23–25]) quench ROS [25] and thus mitigate oxygen toxicity in peripheral organs. [14,21]

[1] In extremely high pressure (6 to 10 ATA of pure oxygen), convulsions usually occur in mere minutes in mice [27,28] and humans [29]

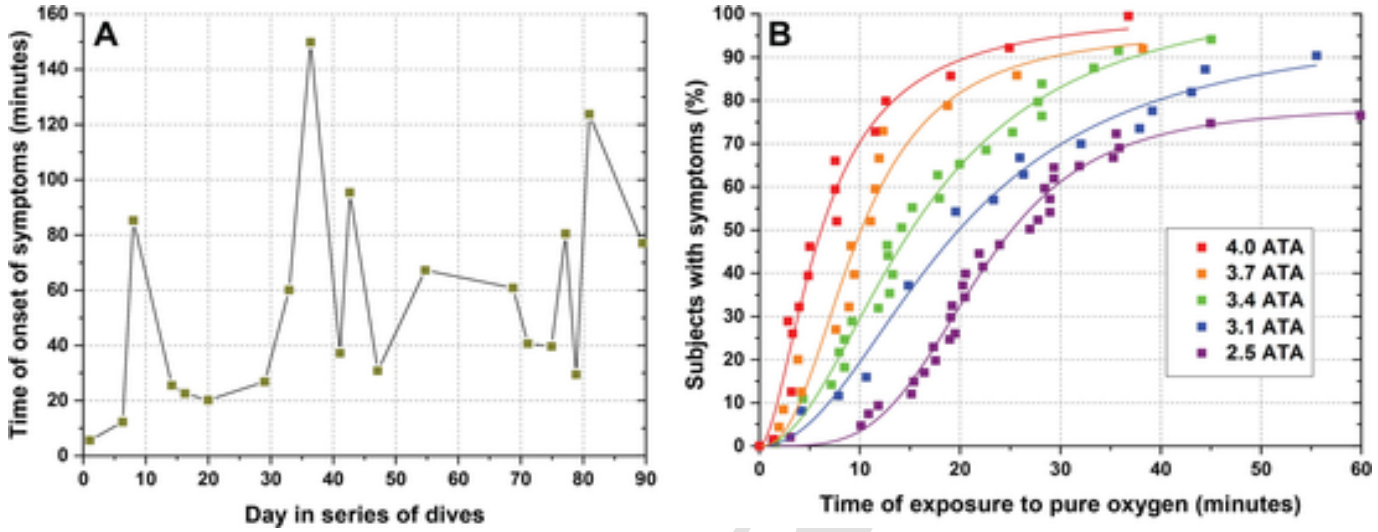


**Fig. 1.** (A) Time of exposure of a single diver to high-pressure oxygen (3.1 ATA) until symptoms of CNSOT occurred; the diver experienced a total of 20 exposures over 90 days under identical conditions. (B) Percentage of divers who developed symptoms of CNSOT as a function of exposure to 100 % oxygen under various pressures. Both plots were adapted from the literature [5] without any recalculations. Source data are available in the supplement of this study.
Notoriously, divers underwater are more susceptible to hyperbaric convulsions than patients in dry hyperbaric chambers under identical pressures. [5] The phenomenon is not well understood but is further discussed in *section 1.4*.

Moreover, ROS affect cellular receptors *via* covalent irreversible modifications, thereby altering neuronal function. [49,52–55] These irreversible cumulative modifications may be implicated in the CNS toxicity of HBOT, which would explain brain sensitization to oxygen after prolonged or repeated HBOT. However, CNSOT can be quickly mitigated by lowering the $pO_2$ to normal conditions, [36] which shows that irreversible modifications cannot be the only causative factor of oxygen-induced convulsions. While a few antioxidants (*e.g.*, disulfiram, glutathione, and caffeine) [1,17] have been shown to prevent or mitigate CNSOT, many potent antioxidants (vitamin E, [56] *N*-acetylcysteine, [56] allopurinol, [57] hypoxanthine, [57] superoxide dismutase [1]) have no effect, suggesting that ROS may play only a minor role in CNSOT. Moreover, some studies [58] have speculated that the effect of those few convulsion-protective antioxidants may be due to their own pharmacological effects, which may be completely independent of ROS scavenging activities. In other words, other mechanisms are needed to explain the acute CNSOT.

### 1.2. Neurotransmitter imbalance may directly lead to CNSOT

Some theories presume that HBOT can cause an imbalance of excitatory and inhibitory neurotransmitters and thus lead to convulsions. In line with these theories, compounds that excite CNS (thyroid hormones, epinephrine, among others) increase the chances of convulsions. [1] Indeed, numerous studies confirm that HBOT decreases brain concentrations of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the brain, [28,59–61] while leaving concentrations of excitatory amino acids (glutamate and aspartate) unchanged. [59] This decrease of GABA is usually ascribed to HBOT-decreased brain activity of glutamate decarboxylase (GD), [60–62] the main enzyme involved in the synthesis of GABA, [61] Further confirming this hypothesis; when GD activity was partially blocked pharmacologically, laboratory animals were more prone to CNSOT seizures. [63] The temporary decrease of GD activity during HBOT in the brain is not fully understood but is often attributed to ROS-induced deactivation of GD. [61,62] Noteworthily, administering pyridoxine (vitamin $B_6$) accelerated the normalization of GD activity (as its active form, pyridoxal phosphate, is a co-factor of GD). However, this normalization of the GD activity still takes *ca.* 1 to 2 h in rats. [63] Therefore, an HBOT-derived decrease in GD activity may offer a plausible explanation for CNSOT, and pyridoxine (or other forms of vitamin $B_6$) may help mitigate CNSOT. [64]

Nevertheless, even HBOT-derived decrease in GD activity cannot explain most phenomena seen in CNS toxicity associated with HBOT. For example, the return of GD activity to normalcy is relatively slow ( > 1 h in rats), [63],[2] during which the animals may experience multiple seizures, [63] which is in contrast with the fact that CNSOT usually cease within minutes [36] after the decrease of pressure to normal levels. In other words, although HBOT-induced decrease of GD may contribute to the onset of CNSOT, this mechanism does not explain why most hyperbaric oxygen convulsions are mitigated within minutes when $pO_2$ and/or pressure is returned to normalcy. Furthermore, while some studies say that administering pyridoxin protects against HBOT-induced convulsions, [64] other studies do not support this claim. [65] Therefore, an additional mechanism is needed to explain this sudden stop of CNSOT.

### 1.3. Elevated pressure reversibly alters the function of receptors, reversing anesthesia and contributing to CNSOT

Until now, most theories explaining the mechanism of CNSOT have overlooked that high ambient pressure can reversibly alter the function of cell receptors. For example, increased ambient pressure decreases the sedative and anesthetic effects of many medications *in vivo*. This phenomenon is commonly known as “pressure reversal of anesthesia.” Drugs' sedative and anesthetic potencies decrease linearly with ambient pressure [66] starting from *ca.* ≈ 2 to 4 ATA, [66,67] but drugs vary in their “pressure sensitivity” [37–39,66,68].[f] More specifically, increased pressure decreases the *in vivo* narcotic potency of many general anesthetics (methoxyflurane, [69] ethanol, [44,68–70] chloroform, [69,71] diethyl ether, [69,71] hexobarbital, [67] and nitrous oxide, [69,71,72] among others [66,69,71,72]); tranquilizers (chlorpromazine [69] and droperidol [69]); local anesthetics (lidocaine [69] and procaine [69])

[2] >1 h even when pyridoxine is administered; under normal conditions, the recovery may be even longer, but the data is missing in literature.

and other drugs that depress CNS (diazepam [69] and morphine [69]).[3] This effect is reversible and mainly depends on the total pressure rather than $pO_2$ (but a minor effect of $pO_2$ was also described [44,67]). [70] The pressure reversal of anesthesia is likely caused by a reversible decrease in the function of glycine and $GABA_A$ receptors [46,47] and likely other receptors, too. [18,34,48]

The effect of pressure on the function of receptors is best understood in GABA and glycine receptors. Both glycine and $GABA_A$ receptors are heavily regulated by endogenous and exogenous allosteric modulators. [73–75] However, increased ambient pressure induces changes in $GABA_A$ and glycine receptors, decreasing their sensitivity to many allosteric modulators (Fig. 2). Although high pressure (12 ATA) does not decrease GABA-mediated chloride currents directly (Fig. 2A), [39] it does reverse the activity of both positive (ethanol, [39,68] pentobarbital, [37,68] diazepam, [38,39,41] flunitrazepam, [37,68] and zolpidem [38]), and negative (Ro15–4513, [38] and 6,7-dimethoxy-4-ethyl-$\beta$-carboline-3-carboxylate (DMCM) [38]) allosteric modulators, as shown in Fig. 2. By contrast, some allosteric modulators are resistant to high-pressure effects on their activity. As a case in point, the activity of 3$\alpha$-hydroxy-5$\beta$-pregnan-20-one is not reversed under high pressure (12 ATA, Fig. 2D). [68] As with $GABA_A$ modulators, the activity of positive allosteric modulators of glycine receptor (ethanol, [76,77] butanol, [77] and propofol [78]) can also be reversed under high pressure (12 ATA). Although the pressure used in these studies (12 ATA) is much higher than that commonly used in HBOT, even low pressures ($\approx$ 2 to 4 ATA) can partially reverse anesthesia *in vivo*, [66,67] and alter the functions of receptors *in vitro*. [79] Thus, these pressure-induced changes in neurotransmitter receptor activity may trigger pressure reversal of anesthesia.

The mechanism of how pressure affects GABA-mediated chloride flow remains unknown. [80] Original hypotheses assumed that pressure induces changes in receptors, which changes the receptors' affinity towards allosteric modulators, but these hypotheses have yet to be confirmed. However, available data show that the affinity of positive allosteric modulator flunitrazepam towards GABA receptors is not affected by pressure, [37] even though flunitrazepam-induced GABA-mediated is decreased by pressure (Fig. 2C). Noteworthy, the effect of pressure on cell receptors does not have to affect receptors directly but may alter the surrounding structures of receptors and thereby affect the receptors. For example, caveolae rafts are pressure-sensitive [81,82] and ROS-sensitive [83] and are often associated with receptors (even G-protein coupled receptors). [84] Consequently, pressure can alter cell signaling and communication pathways. [81,82] Nevertheless, current data on the effect of pressure on ionotropic receptors *via* caveolae rafts and other pressure-sensitive structures are very limited and should be investigated in future studies.

Increased ambient pressure may also affect other receptors and channels, [35] but the sensitivity of most receptors and channels to increased pressure has yet to be studied. For example, recent studies have shown that increased pressure alters the structure [34] of some [48,85] *N*-methyl-D-aspartate (NMDA) receptors, [85] one of the main excitatory receptors in the brain, thereby reversibly increasing their calcium current [48] and facilitating their excitatory function. [34,48,85] Thus, increased pressure may affect many receptors and disrupt the excitatory-inhibitory balance in the CNS, further contributing to the reversal of anesthesia.

Regardless of the actual mechanism, we argue that pressure-induced changes in the function of receptors may explain not only the pressure reversal of anesthesia but also high-pressure-induced excitations - both HPNS and CNSOT. Even relatively low pressures ($\leq$ 4 ATA) increase neurons' excitability *in vitro* [79] and *in vivo*. [66] Increased pressure disrupts the excitatory-inhibitory balance of neuronal communication in CNS, ultimately increasing the risk of CNSOT (Fig. 2). [85] In that sense, high pressure resembles both mechanism and clinical manifestations of $GABA_A$/ glycine receptor antagonists or NMDA agonists (convulzants), [86,87] and, therefore, may be treated similarly (*i.e.* administration of inhibitory drugs, such as anesthetics [88] or sedatives [89,90]). Further confirming this hypothesis, administering convulzants (*e.g.*, strychnine, a glycine receptor antagonist) lowers the pressures needed to start hyperbaric convulsions. [91] Considering this mechanism, facilitating the inhibitory systems [27] of the CNS or inhibiting the excitatory systems [92] of the CNS may prevent hyperbaric symptoms.

### 1.4. Acidosis accelerates convulsion onset by an unknown mechanism

Acidosis significantly accelerates the onset of CNSOT and subjects' death. [93] Accordingly hypercapnia, [1] diving [94] and physical activity, [5] high or low ambient temperature, [5] compounds that increase body metabolism rate (cortisol, [1] thyroid hormones, [1] and epinephrine), [1] and other states that lead to acidosis significantly accelerate the onset of convulsions. In line with that, alkalemia caused by administration of bicarbonate [93] or Tris buffer [93] decelerates both the onset of convulsions and the death of test animals. [93] Moreover, carbon monoxide poisoning is often accompanied by acidemia, [95] which may explain the enormous susceptibility of CO-poisoning patients to CNSOT. [30,31] Furthermore, divers are prone to acidosis, [94] which may explain their higher relative risk to CNSOT. [5].

The mechanism by which acidemia increases the risk of CNSOT remains unknown, as changes in pH can affect virtually every metabolic and signaling pathway. Acidosis increases the excitability of neurons *in vitro*. [96] Noteworthily, acidosis alters the function of some surface proteins, including excitatory [97] and inhibitory receptors. [98,99] Therefore, just like increased ambient pressure, acidosis may lead to neurotransmitter effect imbalance, which may facilitate the onset of convulsions. Moreover, previous studies speculated that hypercapnia increases brain blood flow, thereby facilitating CNSOT by a mechanism that is not yet explained. [93] Nevertheless, future studies should enlighten the role of acidosis in CNSOT in more detail. But - regardless of the actual mechanism, acidemia dramatically increases the risk of CNSOT. Therefore, any preventive strategies should also pay attention to blood pH, especially in high-risk patients, such as those with metabolic acidosis and CO poisoning.

### 1.5. Seizures result from four main pathophysiological pathways

HBOT-associated convulsions may result from multiple pathological pathways that HBOT affects (Table 2 and Fig. 3). Our proposed mechanism of (3) the direct effect of pressure on cell receptors does not exclude the remaining proposed mechanisms of CNSOT, such as (1) ROS-induced changes in receptors, (2) decreased GABA synthesis, or (4) the role of acidosis. Instead, these mechanisms are complementary to one another. The mechanisms (1) and (2) involve cumulative irreversible changes of receptors and enzymes, which take time to form and remedy (until a new receptor or enzyme is synthesized). Therefore, mechanisms (1) and (2) can explain the long-term increasing chance of convulsion occurrence with prolonged or frequent exposure to HBOT (Fig. 1B), but they do not explain the sudden onset and termination of convulsions with changes of ambient pressure. In contrast, increased pressure directly alters the function of receptors (3). These alterations in receptor function manifest immediately and cease upon a decrease in pressure. In that sense, direct hyperbaric changes in receptors' function may explain convulsions' sudden onset and termination with increasing and decreasing pressure. High pressures ($>$ 15 ATA) can cause a severe

[3] High pressure did not significantly affect the narcotic potency of a few drugs within the pressure ranges of *in vivo* studies (*e.g.*, zoxazolamine up to 4 ATA [67] or gaboxadol up to 12 ATA [68]). However, these findings may be caused by the low "pressure sensitivity" of these drugs and too low range of pressures in the studies to produce significant changes in anesthetic potencies *in vivo*.

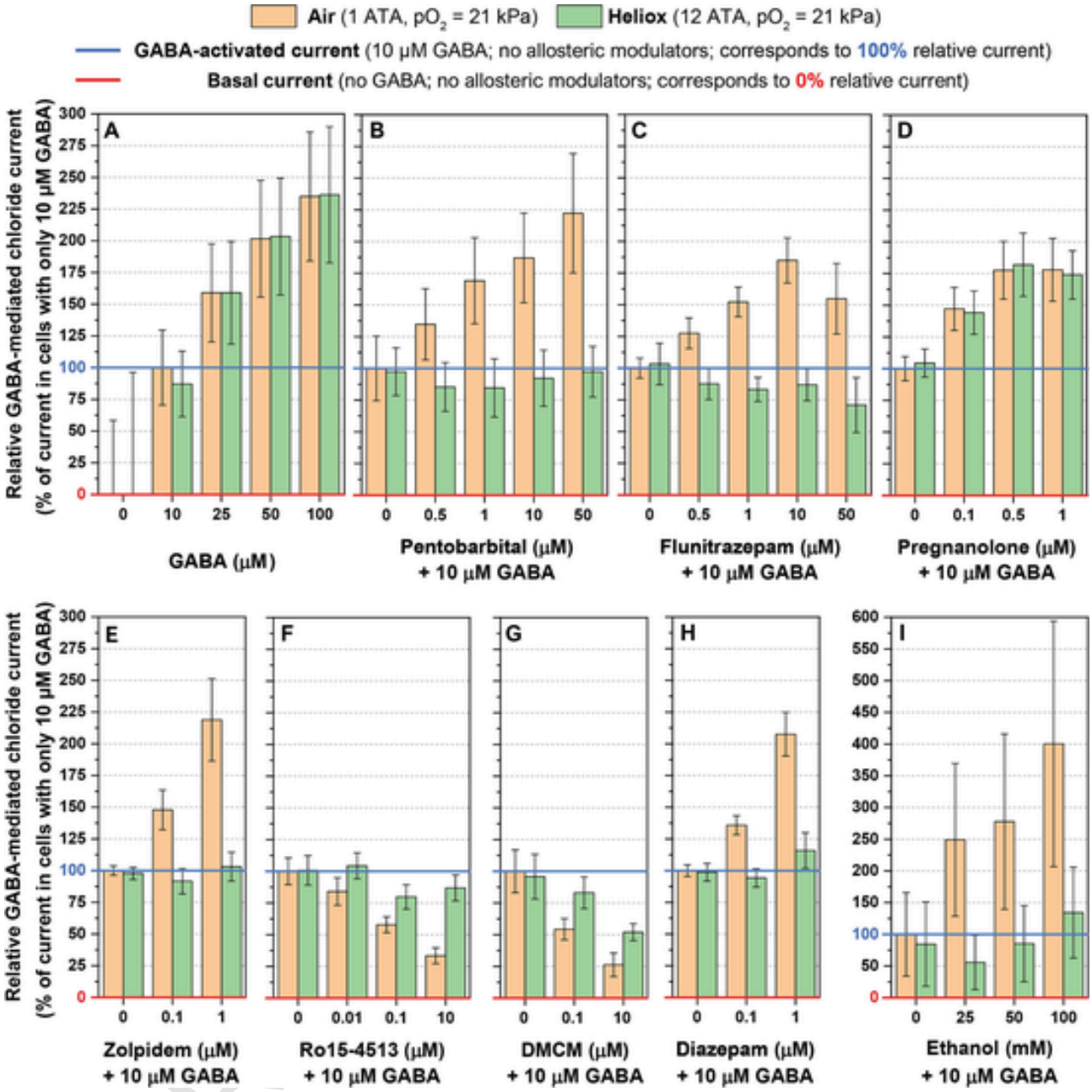


**Fig. 2.** (**A**) Relative GABA-mediated chloride flow in brain tissues *in vitro* as a function of concentration of GABA. Effect of various positive (**B**, **C**, **D**, **E**, **H**, and **I**) and negative (**F** and **G**) allosteric modulators on GABA-mediated chloride currents in brain tissue *in vitro* under normal (air, 20.9 % of $O_2$; pressure 1 ATA.; $pO_2$ = 21 kPa) and high pressure (heliox mixture; 1.7 % $O_2$, 98.3 % He; pressure 12 ATA.; $pO_2$ = 21 kPa). Data compiled from previous studies, [37–39] recalculated, and expressed as mean ± standard error. Source data and recalculation methods are available in the supplement of this study.

enough neurotransmitter imbalance to cause tremors or even convulsions on its own (HPNS), but even relatively low pressures (≈ 2 to 4 ATA) [79] may serve as a 'tipping point' in a CNS that is already altered by ROS generated by hyperbaric oxygen and thus trigger the convulsions. Nevertheless, mechanism (3) alone does not easily explain the increasing chances of CNSOT with time of exposure and frequency of HBOT, nor does it explain why increasing partial pressure of oxygen shortens the typical onset of convulsions. Additionally, (4) the effect of acidosis on receptors explains why CO poisoning, exercise, low temperatures, diving, and other factors that increase body metabolism rate may facilitate the onset of CNSOT. Combining these four mechanisms may explain most clinically and experimentally observed factors that affect the onset of CNSOT (Fig. 3). Moreover, this complexity of the mechanism underlying the CNSOT may explain (a) why so many seemingly unrelated internal and external factors may increase or decrease the risk of convulsions, (b) why each preventive strategy has only a limited effect on its own, and (c) why some studies come to conflicting conclusions about the efficacy of specific treatments (*e.g.*, [64] *vs* [65]) depending on their experimental conditions.

### *1.6. Additional pathophysiological pathways may be involved, too*

Some factors that have been linked to increased or decreased risk of CNSOT are not explained by either mechanism (1), (2), (3), or (4).

**Table 2**
List of four main pathophysiological mechanisms that lead to CNSOT, their pathophysiological mechanisms and their possible remedies.

| # | Mechanism | Pathophysiological consequences | Remedy |
|---|---|---|---|
| 1 | ROS-induced irreversible alterations of cell surface receptors | Increasing cumulative chance of hyperbaric convulsions as a function of $pO_2$ and time of exposure | Lowering $pO_2$, time of exposure or administering ROS scavengers |
| 2 | Decreased activity of GD | Increasing cumulative chance of hyperbaric convulsions as a function of $pO_2$ and time of exposure | Lowering $pO_2$, time of exposure or administering pyridoxine |
| 3 | Pressure-induced changes in surface receptors | Reversible pressure-induced changes in receptors; may serve as a tipping that triggers convulsions | Lowering pressure, administering inhibitory drugs |
| 4 | Acidosis-induced changes in surface receptors (?) | (unknown, reversible acidosis-based changes of receptors may be involved) | Monitoring of blood pH and preventing acidosis |

Some studies show that ammonia [60] or nitrogen monoxide (NO), [58,100,101] among others [79] may be involved in the onset of convulsions by altering the brain function in other ways (*e.g.*, NO-mediated transient increase of cerebral blood flow may predispose to convulsions [58,101]). Both these molecules can also alter the function of receptors. [102,103] Specifically, NO belongs to 'reactive nitrogen species' (RNS), an analogue of ROS. Therefore, just like ROS, NO or other RNS may react with proteins and receptors and irreversibly alter their function (nitrosative stress). [104] However, it is not clear whether these changes in concentrations of small molecules truly contribute to convulsions or are just an independent consequence of a deeper underlying mechanism that increases both (a) subjects' sensitivity to HBOT and (b) the content of these molecules. Therefore, future research should enlighten the role of these endogenous molecules in CNSOT towards finding the best preventive treatment.

### *1.7. Low doses of inhibitory drugs prevent HBOT-associated convulsions*

In line with the observation that CNSOT occur *via* a neurotransmitter imbalance, a pre-emptive administration of numerous direct and indirect GABA activators (anticonvulsants / sedatives / anesthetics / hypnotics / anxiolytics / tranquilizers) have been shown to delay or even prevent HBOT-associated seizures and death in laboratory animals. Specifically, these include phenobarbital and other barbiturates, [27,105] diazepam and other benzodiazepines, [27,105] chloroform, [12] baclofen, [105] carbamazepine, [106] chlorpromazine, [1] and antagonists of excitatory amino acids, [107] and vigabatrin [108] (anticonvulsive inhibitor of GABA degradation [109,110]), among others. [68,91,111,112] Although pre-emptive administration of these compounds strongly limits CNSOT in animal models, they are not routinely administered in clinical practice before HBOT to prevent CNSOT. Administering sedatives and anticonvulsants to test animals significantly prolongs their survival, [27,105] which indicates that these compounds prevent convulsions rather than simply masking them. Accordingly, pre-emptively administered sedatives may enable exposure to higher $pO_2$ during HBOT and/or decrease the necessary intervals between sessions (developing new hyperbaric treatment schedules), thus increasing HBOT efficacy. Low doses of inhibitory drugs may be particularly beneficial to patients with a high risk of convulsions (*e.g.*, carbon monoxide poisoning patients [30]). Therefore, clinical trials should verify if administering various inhibitory drugs may increase the safety and efficacy of HBOT therapy.

### *1.8. Effective preventive therapies may encompass multiple compounds*

A combination of sedatives, other drugs, antioxidants, and pyridoxine may be the best preventive therapy to reduce the risk of CNSOT and peripheral oxygen toxicity. HBOT causes many alterations in the organism, which may ultimately lead to convulsions and peripheral toxicity (Fig. 3). Pre-emptive administration of inhibitory compounds (*e.g.* anesthetics, sedatives, or tranquilizers to counter the effect of the pressure-altered function of receptors, discussed in *section 1.3*), [27,105] some antioxidants (to scavenge ROS; discussed in *section 1.1*), [1,17] pyridoxine (to boost synthesis of GABA; addressed in *section 1.2*), [64] and blood pH adjustment (*section 1.4*) [93] can prevent CNSOT and reduce mortality in animals or humans. The efficacy of most of these strategies was shown only in animal models and is yet to be verified in humans. However, as all these drugs are approved for human medicine and have minimal side effects (especially in a single-dose administration), their pre-emptive administration before HBOT should be considered, especially in high-risk patients. While these compounds may have limited efficacy alone, their concurrent administration may have a more profound protective effect due to the complex multi-pathway mechanism of CNSOT. Moreover, antioxidants (such as vitamin C [23–25]) can reduce peripheral toxicity of HBOT, [11,51,113] which is yet another benefit to the patient. Thus, combining multiple compounds and maintaining adequate blood pH may prevent acute HBOT-associated toxicity to CNS and peripheral organs.

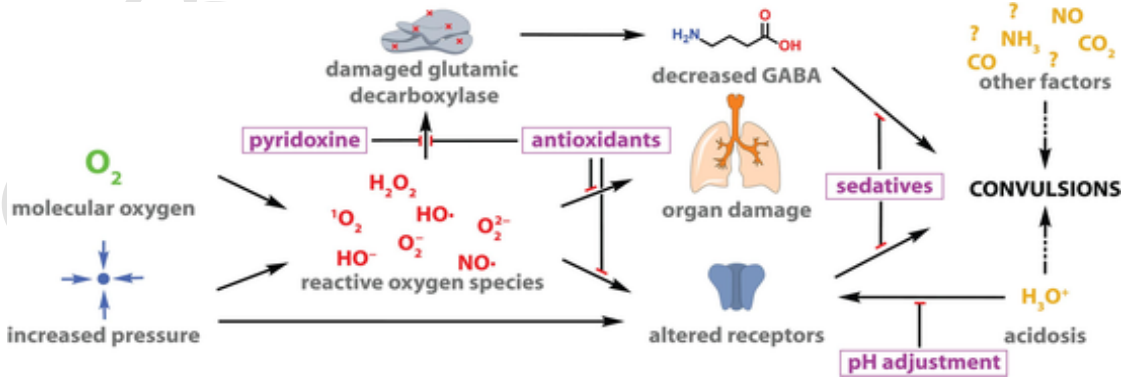


**Fig. 3.** Mechanisms of hyperbaric toxicity. Increased pressure and oxygen concentrations enhance the production of ROS, which damage peripheral organs and alter cell receptors. As these changes of receptors are irreversible, ROS-derived changes cumulatively decrease the threshold to convulsions. Moreover, ROS damages glutamic decarboxylase, thereby decreasing the synthesis of GABA, further predisposing to convulsions. Furthermore, pressure directly alters the functions of receptors, thereby reversibly facilitating convulsions. Finally, acidosis and other factors play a role in hyperbaric toxicity by yet unknown mechanisms. Consequently, CNSOT may be prevented by antioxidants, inhibitory drugs (*e.g.* sedatives or anticonvulsants), pyridoxine, and blood pH adjustments.

## 2. Implications from deep-sea diving

Deep-sea divers face significant risks due to the high pressures they encounter, one of the most serious being CNSOT (and HPNS in high pressures). The CNSOT seizures are especially dangerous because they can cause a diver to lose consciousness, putting their life in immediate danger. The situation is further complicated because divers cannot simply ascend to lower depths to alleviate the pressure, as a rapid decrease in pressure can trigger life-threatening barotrauma, decompression sickness and other health consequences. Therefore, developing preventive strategies to reduce the risk of CNSOT is crucial for the safety of divers. The use of medications to limit the risk of CNSOT prior to diving has been suggested previously [18] but is highly controversial [114,115] because even medications with a low effect on divers' cognition can have unanticipated effects in elevated pressure. Yet, over the last 100 years of experimenting with various breathing and anesthetic gas mixtures, we have gathered enough data to show some important trends.

Divers normally breathe compressed air (78 % N2, 21 % O2). However, nitrogen has anesthetic properties - its minimal alveolar concentration (MAC, *i.e.,* partial pressure of study gas, at which half of the test subjects were anesthetized) is around 35 ATA in rodents. [117–120] Even at nitrogen partial pressures much lower than its MAC (4 to 6 ATA), nitrogen can reduce cognitive ability and attention in humans, [36,121,122] subjectively this state is likened to a "drunk-like state". [123] However, compressed air should not be used for diving below 40 m ($pN_2 > 4$ ATA) to avoid nitrogen narcosis while diving. [36] For deeper dives, nitrogen-oxygen mixtures are replaced by helium-oxygen mixtures, [36] because helium has extremely low anesthetic potency (MAC ≫ 100 ATA in rodents, [117–120,124,125]). While these mixtures successfully prevent nitrogen narcosis, their negligible inhibitory properties cannot entirely avert excitatory HPNS at great depth. Nevertheless, adding nitrogen into helium-oxygen mixtures in a balanced amount does not induce nitrogen narcosis and reduces the onset of HPNS, thereby allowing descent into much greater pressures. [7,8] Similarly, hydrogen has very mild anesthetic properties (MAC ≈ 100 ATA in rodents, [118–120] slight signs of hydrogen narcosis in hydrogen-oxygen breathing mixtures have been reported at ≈ 50 ATA in divers [126], so adding hydrogen into helium-oxygen mixtures (hydreliox) allows descent into even greater depths without narcosis or hyperbaric convulsions. [9]

In addition to its narcotic properties, nitrogen has another negative effect on diving. It dissolves in body tissues, its dissolved amount is proportional to the depth (pressure) and the length of the dive. The ascent to the surface then requires a slow ascent so that nitrogen can diffuse back into the exhaled air and prevent decompression sickness. [36] Therefore, divers sometimes use oxygen-enriched air (nitrox) to reduce the partial pressure of nitrogen in the breathing medium. With each breathing mixture (air, nitrox, trimix, hydreliox) it is possible to dive only to a depth where the partial pressure of oxygen does not exceed 1.6 ATA, otherwise CNSOT may occur. [116]

Herein, we argue that nitrogen (and hydrogen) in breathing mixtures acts as a low-potency anesthetic whose potency increases with their partial pressure. Consequently, very mild nitrogen (hydrogen) anesthesia can effectively reverse high-pressure-induced excitations of HPNS (including convulsions).[4] Therefore, future studies should consider nitrogen (hydrogen) in these breathing mixtures as a low-potency anesthetic that helps the body's own protective inhibitory (adaptive) mechanisms to alleviate HPNS. Advantageously, increasing the ambient pressure increases the solubility of nitrogen and hydrogen (according to Henry's law), thereby increasing its inhibitory potency in higher pressures, where it is most needed. Noteworthily, all anesthetic gases take some time to reach their equilibrium distribution in the body (usually ≥10 min, depending on their biodistribution properties), [127,128] which explains why nitrogen protects against HPNS and possibly hyperbaric convulsions only when the increase of ambient pressure is slow. [129] In line with this slow kinetics of anesthetic gas distribution - HNPS is most pronounced when anesthetic is absent or the submersion rate is too fast for the anesthetic gases to distribute into CNS.

In that sense, future studies should investigate breathing mixtures containing multiple inert gases with various MACs, whose content and anesthetic profiles would enable the safest deep diving without risk of anesthesia or convulsions. Such mixtures could contain oxygen, carrier gases with negligible anesthetic potency[5] (such as helium [117–120,124,125],[g] or certain perfluorocarbons [131–133]) and low-potent anesthetic gases with various MACs, *e.g.* neon, [119,120] hydrogen, [118–120], tetrafluoromethane, [119,120,131] methane, [119,134] nitrogen, [117–119] argon, [117,119,120] sulphur hexafluoride, [117,119] ethane [119,120,134] *etc.*

As such, developing new breathing mixtures could balance their narcotic effect at elevated pressures and the convulsive effect of hyperbaric exposure. Future studies should also ascertain if low doses of non-volatile inhibitory drugs with only minor effects on divers' attention and cognition may improve their safety. Noteworthily, the knowledge of these medications and new breathing mixtures under high pressure is limited, and their efficacy and safety should be tested in a well-controlled setting.

## 3. Future perspectives

The lack of prevention strategies for CNSOT hinders attempts to broaden the clinical applications of HBOT. [1,2] Therefore, future studies should determine whether the combination of antioxidants, pyridoxine, and sedatives may prevent hyperbaric oxygen toxicity, as suggested in *Section 2.2*. Moreover, future studies should ascertain whether "pressure-resistant" drugs (whose effect is not antagonized by high pressure, *e.g.*, neurosteroids, [37] zoxazolamine [67] or gaboxadol [68][f]) are more effective than "pressure-sensitive" drugs (whose effect is antagonized under high pressures, *e.g.*, phenobarbital or diazepam[6]) and compare those with the effects of direct $GABA_A$ agonists (*e.g.*, progabide or $\gamma$-amino-$\beta$-hydroxybutyric acid) and indirect $GABA_A$ agonists (*e.g.*, vigabatrin or valproate [112]). Moreover, the efficacy of other inhibitory compounds that do not directly affect ionotropic $GABA_A$ and glycine receptors (*e.g.* baclofen, melatonin, zoxazolamine, [67] chlorzoxazone, [111] mephensin, [91] ketamine, haloperidol, levomepromazine, fentanyl, or suvorexant) should be investigated because their inhibitory effect may be (in some cases is known to be) pressure-independent and

[4] Helium is generally considered a biologically inert gas. Nevertheless, *in silico* simulations suggested that hyperbaric helium at 25 ATA may contribute to excitations in NMDA receptors [64], but these findings have yet to be verified *in vitro* and *in vivo*.The reversal may be incomplete, some residual signs and symptoms of HPNS may remain

[5] Helium likely has a MAC as well, yet it is very high (≫ 100 ATA [117–120,124,125]) and, therefore, can be regarded as non-existent for most purposes. Some authors describe tremors in test animals in helium [117,125,130] or neon [117,130] atmosphere around 75 to 95 ATA that occurred with fast pressurization (1.25 to 2 ATA / min). These tremors diminished on their own within 60 min and may be ascribed to HPNS rather than excitatory properties of helium or neon. [125] Some gases (perfluoropropane, perfluorobutane, perfluoropentane, perfluorohexane and perfluoroneopentane) have been suggested to lack MAC altogether. [131–133] Note that determining the MAC of a gas mixture involves increased pressure, which may antagonize the effect of the anesthesia. Consequently, a compound's "true" MAC (if no external pressure were applied) may be much lower than the MAC measured. It is also possible that the MAC of a gas would be so low that the high pressure would antagonize any signs of anesthesia altogether.

[6] The effect of phenobarbital and diazepam was fully reversed at 12 ATA of pressure *in vitro*, but lower pressures (closer to those used in HBOT, 2 to 3 ATA) may not fully reverse their effects.

thus effective regardless of ambient pressure. Because even closely related compounds have shown vastly different properties in anesthesia reversal and convulsion prevention (Fig. 2),[7] future studies must identify the best compounds (or their combinations) and their dosing[8] for clinical applications.

The nitrogen content in HBOT breathing mixtures is often overlooked, but as we discussed in *Section 3*, its narcotic properties can have a substantial protective effect. Similarly, carbon dioxide concentrations should be monitored to avoid respiratory acidosis in patients, which can trigger convulsions. Moreover, future research should also aim to understand how increased pressure and pH affect receptors to highlight the underlying mechanism of HBOT toxicity and avoid its adverse effects. Finally, future studies should elucidate why some factors (ammonia, nitrogen monoxide, *etc.*) increase the chances of convulsions. Only by gaining deeper insights into the underlying causes of CNSOT convulsions can we develop appropriate prevention strategies.

## 4. Conclusion

Hyperbaric oxygen convulsions (CNS toxicity of oxygen) originate from several intertwined mechanisms. First, increased $pO_2$ increases the concentrations of ROS in tissues and thus may cumulatively and irreversibly alter the function of CNS, causing a long-term predisposition for convulsions (*section 1.1*). Second, increased ROS in the brain reversibly decreases concentrations of GABA, further predisposing patients to convulsions (*section 1.2*). Third, increased ambient pressure (≥ 2 ATA) reversibly alters the function of GABA, glycine and other receptors (a phenomenon closely related to pressure-reversal of anesthesia and HPNS), which may cause sudden and quickly reversible convulsions (*section 1.3*). Fourth, acidosis increases patients' sensitivity to CNSOT (*section 1.4*). Only a combination of these mechanisms explains why prolonged and repeated HBOT increases the chances of convulsions that can occur quickly with an increase of $pO_2$ and/or ambient pressure but cease quickly upon reducing $pO_2$ and/or ambient pressure (*section 1.5*). Other mechanisms and molecules (*e.g.*, ammonia and nitrogen monoxide) may also play a role, but the mechanism is unclear (*section 1.6*).

Based on our proposed mechanism, we highlight possible preventive strategies that may reduce the risk of CNSOT towards increasing the efficacy of HBOT (*section 2.2*). These preventive strategies include preemptive administration of antioxidants (ROS-scavengers), pyridoxine, inhibitory drugs (such as sedatives or anesthetics[7]) and adjusting blood pH. These preventive strategies have shown promising results in animal studies (and a few human studies, too) and, therefore, should be considered for future human trials. Additionally, we highlight that the breathing mixtures in deep-sea divers that contain mildly anesthetic gases successfully prevent the onset of hyperbaric convulsions (*section 3*). Therefore, the development of new breathing mixtures for deep-sea diving and hyperbaric medicine may improve their safety and efficacy.

[7] Even structurally similar inhibitory drugs can vary greatly in their predominant clinical effect and side effects [135]. At this point, we need more data to determine which of these drug categories is best at mitigating HBOT-associated convulsions.

[8] Even subclinical dosing of inhibitory drugs may sufficiently lower the risk of HBOT-induced convulsions with negligible side effects. Nevertheless, patients undergo HBOT sessions repeatedly only a few times and would not have to take the medications in long term. Consequently, potential common side-effects associated with clinical bolus dosing of inhibitory drugs (such as drowsiness) are acceptable, considering these drugs may increase the safety and efficacy of the HBOT. Some authors argue that some inhibitory drugs can hypothetically have unpredictable side-effects, which do not occur under atmospheric pressure. Therefore, before broad clinical use, all drugs should be thoroughly tested for side-effects in high-pressure environments. Currently, some data for safety of some inhibitory drugs in divers is available, [114,136,137] which may help identify potentially dangerous drugs before further studies.

## CRediT authorship contribution statement

**Ondrej Groborz:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Petr Marsalek:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Ludek Sefc:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

## Declaration of competing interest

All authors declare no conflict of interest.

## Acknowledgement

We want to thank prof. Kai Simmons, Dr. Tomáš Slanina, MSc. David Dunlop, and MSc. Jan Kadlec, for their critical comments and helpful suggestions. The authors also thank Dr. Carlos V. Melo for editing the manuscript.

The paper has been supported by Charles University grants GAUK 199124 and SVV 260635/2023, and by MEYS CR grant LM2023050 Czech-BioImaging.

## Data availability

The data used for calculations are available in Supplementory file.

## Appendix A. Supplementary data

The supplement includes raw data adapted from a previous article and recalculated data used to prepare Figs. 1 and 2. The recalculation and its rationale are explained in the supplement. Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2024.123169.

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