The occurrence of paroxysmal narcotic episodes including psychotic-like symptoms in divers participating to experimental deep diving programs with various gas mixtures has constituted, beyond the classical symptoms of the high-pressure neurological syndrome, the major limitation for deep diving. With the development of new saturation deep diving programs and experiments by the eastern nations, such as India and China, we believed that it is of interest to examine what could be the ultimate depth that could be reached by saturation human divers. Based on previous data and the critical volume model of inert gas narcosis, we propose that the ultimate depth for saturation diving could be around 1,000 m.

Key words: deep diving; ultimate depth; psychotic-like disorders; inert gas narcosis; high-pressure neurological syndrome

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Table 1: Environmental conditions of absolute pressure and partial pressure of each inert gas during the experimental dives in which paroxysmal narcotic episodes occurred

| Paroxysmal narcotic episodes | Pressure (ATA) | Partial pressure (ATA) |
|-----------------------------|---------------|------------------------|
| Case 1 (Adolfson and Muren, 1965) | 13.2 | He: 10.44; H₂: 2.76; N₂: 0.4; O₂: 0.4 |
| Cases 2 and 3 (Douchet et al., 1990; Raoul et al., 1991) | 31 | He: 30.6; H₂: 0.4 |
| Case 3 (Douchet et al., 1990; Raoul et al., 1991) | 51 | He: 25.8; H₂: 2.40; N₂: 0.8; O₂: 0.4 |
| Case 4 (Stoudemire et al., 1984) | 66 | He: 62.3; H₂: 3.3; N₂: 3.3; O₂: 0.4 |

Note: 1 Atmosphere absolute (ATA) = 0.1 MPa. He: helium; H₂: hydrogen; N₂: nitrogen; O₂: oxygen.

Table 2: Partial molar volume and mole fraction solubility of the gases used during the experimental dives in which paroxysmal narcotic episodes occurred using benzene as a model of the gases' hydrophobic site of action

| Inert gas | Vᵢ (mL) | Xᵢ(× 10⁻⁴) at 25°C |
|-----------|---------|-------------------|
| He        | 36      | 0.77              |
| H₂        | 35      | 2.58              |
| N₂        | 53      | 4.46              |
| O₂        | 28      | 7.04              |

Note: Vᵢ: Partial molar volume of the gas in the solvent; Xᵢ: the mole fraction solubility of the gas in that solvent when its partial pressure is 1 ATA.

Diving gases at raised pressure have narcotic effects which relative potencies are highly correlated with lipid solubility (Smith and Paton, 1976; Dodson et al., 1985; Bennett, 1993; Abraini, 1995a, b). Although their structural mechanisms of action-thought to be similar to that of the noble and general anesthetic gases xenon and nitrous oxide (Colloc’h et al., 2001; Abraini et al., 2014; Sauguet et al., 2016)—are still under discussion (Dodson et al., 1985; Abraini et al., 1998; David et al., 2001; Abraini et al., 2003), the critical volume model (or some extension of it) (Miller et al., 1973; Halsey et al., 1978; Abraini, 1995a, b) has allowed predictive studies in both humans (Abraini, 1995a, b, 1997) and experimental animals (Dodson et al., 1985). This model states that, for a similar pharmacological effect, narcosis occurs when the volume of a hydrophobic cell region is caused to expand beyond a certain critical volume by the absorption of an inert substance. The fractional expansion E that occurs when a gas at a partial pressure Pᵢ dissolves in the hydrophobic site is given by:

E = Vᵢ . Xᵢ . Pᵢ / Vₘ

Where Vᵢ is the partial molar volume of the gas in the solvent (or some model of it such as olive oil or benzene) of molar volume Vₘ and Xᵢ is the mole fraction solubility of the gas in that solvent when its partial pressure is 1 ATA. For a mixture of gases, the net effect is given by the sum of the individual terms if each gas. Table 2 indicates the values for Vᵢ and Xᵢ for the range of gases that have been used for deep diving; the value of Vₘ is estimated to be 640 mL (Dodson et al., 1985).

Given that the psychotic-like episodes occurring at raised pressure have been shown to result from the sum of the narcotic potency of each gas used to compose the breathing mixture, the advantage of adding the narcotic gases nitrogen or hydrogen to the basic helium-oxygen breathing mixture does not appear readily apparent inasmuch the physical strategies used to reduce HPNS, such as slow compression rates with stages and adaptation with time at depth, have allowed divers breathing helium-oxygen mixtures to reach depths up to 610 (62 ATA) as early as the 1970s (Bennett and Rostain, 1993). As shown in Figure 1, calculations with the critical volume model have allowed establishing that the mean expansion of the diving gas hydrophobic site of action necessary for the expression of psychotic-like narcotic episodes is about 0.0453 ± 0.0032% (Abraini, 1995a, b). As also illustrated in Figure 1, taking into account this expansion value, the onset depth for the occurrence of psychotic-like disorders with the basic helium-oxygen mixture may be estimated between 930 m and 1,080 m (94–109 ATA) (mean depth: 1,005 m, i.e., 101.5 ATA).

Support for an onset depth between 930 m and 1,080 m for the occurrence of psychotic-like disorders with the basic helium-oxygen mixture is the fact that no electroencephalographic epileptic patterns have been recorded in human divers at depths up to 701 m (71.1 ATA) and that convulsions in primates, while using much faster compression rates than those used in human divers, only occurred at around 1,000 m (101 ATA) (Bennett and Rostain, 1993). From this onset depth, if one considers (1) approximately 50% of the divers participating to the dives in which psychotic-like narcotic

Note: Vi: Partial molar volume of the gas in the solvent; Xᵢ: the mole fraction solubility of the gas in that solvent when its partial pressure is 1 ATA.
Figure 1: Full squares represent the net theoretical expansion of the gases’ hypothetical site of action, using benzene as a model solvent, at the time paroxysmal narcotic episodes occurred using air, and hydrogen (H₂)-oxygen (O₂), helium (He)-H₂-nitrogen (N₂)-O₂, or H₂-N₂-O₂ breathing mixtures.

Note: Data show that whatever the gas mixture used the fractional expansion was remarkably similar (mean value: 0.0453 ± 0.0032%) at the time the dives have had to be stopped because of the occurrence of paroxysmal narcotic episodes including psychotic-like symptoms. Taking into account this expansion value, the onset depth for the occurrence of paroxysmal narcotic episodes in helium-oxygen mixture may be thus estimated between 930 m and 1,080 m (94–109 ATA). 1 ATA = 0.1 MPa. ATA: Atmosphere absolute.

 episodes occurred were concerned by such symptoms, (2) it is only necessary to increase the minimal anesthetic concentration of common inhalational anesthetics (that is the concentration that produces anesthesia in 50% of subjects) by 10–15% to narcotize the vast majority of subjects (de Jong and Eger, 1975), it can be estimated that no human dives would be possible beyond 1,030–1,200 m (104–121 ATA) even in divers showing a low sensitivity to helium-oxygen narcosis.

In conclusion, we suggest that improvement of the physical strategies used to reduce HPNS, such as slow compression rates with stages and adaptation with time at depth, may be the key for successfully going deeper, beyond the current world record human dives of 534 m (54.4 ATA) in the open sea and of 701 m (71.1 ATA) in hyperbaric chambers.

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**Author contributions**

All authors contributed equally to the manuscript, read and approved the final version of the paper for publication.

**Conflicts of interest**

The authors declared no competing interest.