Pulmonary and CNS Oxygen Toxicity

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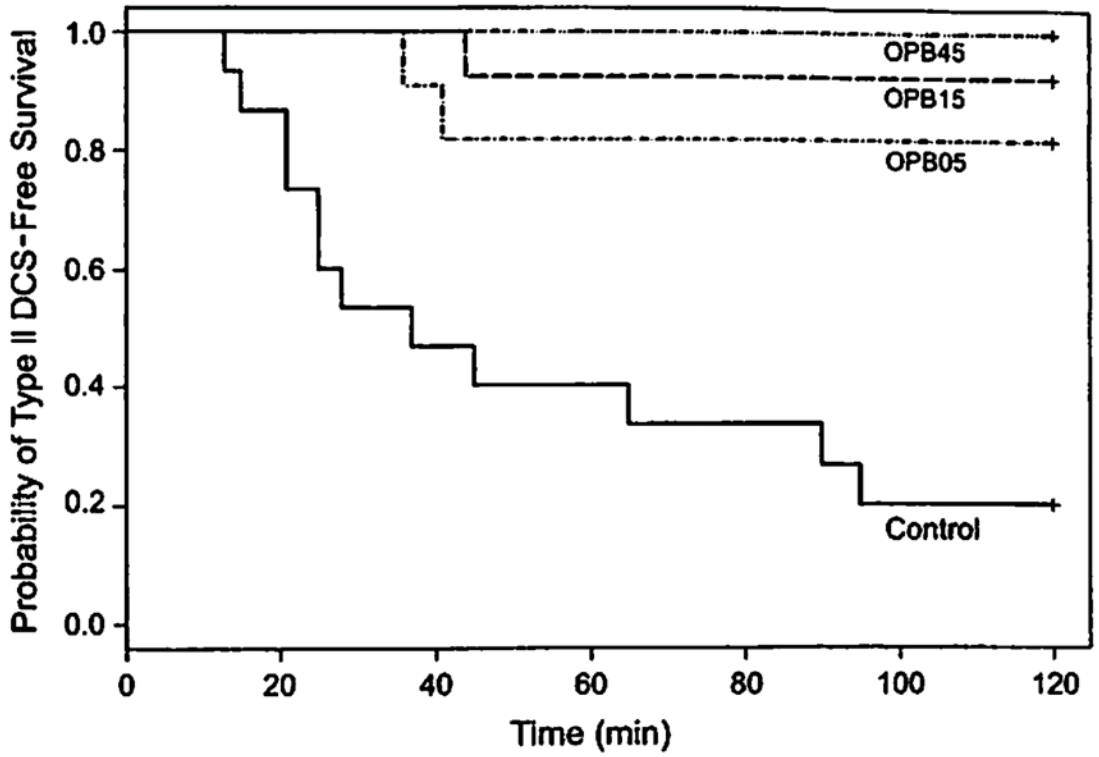
Oxygen and Diving

Oxygen is very useful during diving and recompression

- The only metabolized breathing gas
- Reduces decompression obligation
- Promotes inert gas washout



Mahon et al. *Short oxygen prebreathe periods reduce or prevent severe decompression sickness in a 70-kg swine saturation model.* J Appl Physiol 2009: 106; 1459-1463.

Oxygen Toxicity

Breathing oxygen concentrations beyond a pO_2 of 0.5 ATA puts subjects at risk for oxygen toxicity

Rate of symptom onset and severity is variable

- Depth
- pO_2
- Time
- Environment

Two types of oxygen toxicity

- CNS
- Pulmonary

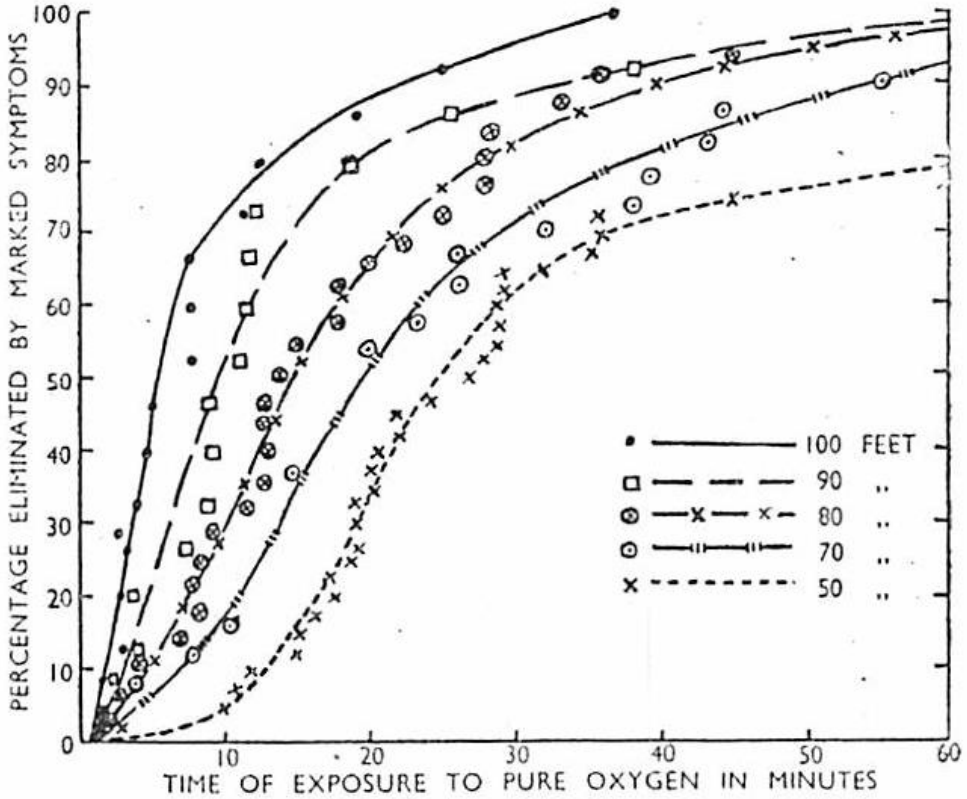
CNS Oxygen Toxicity

Primary Manifestation is Seizure

- Substantial variance in onset both between individuals and from exposure to exposure

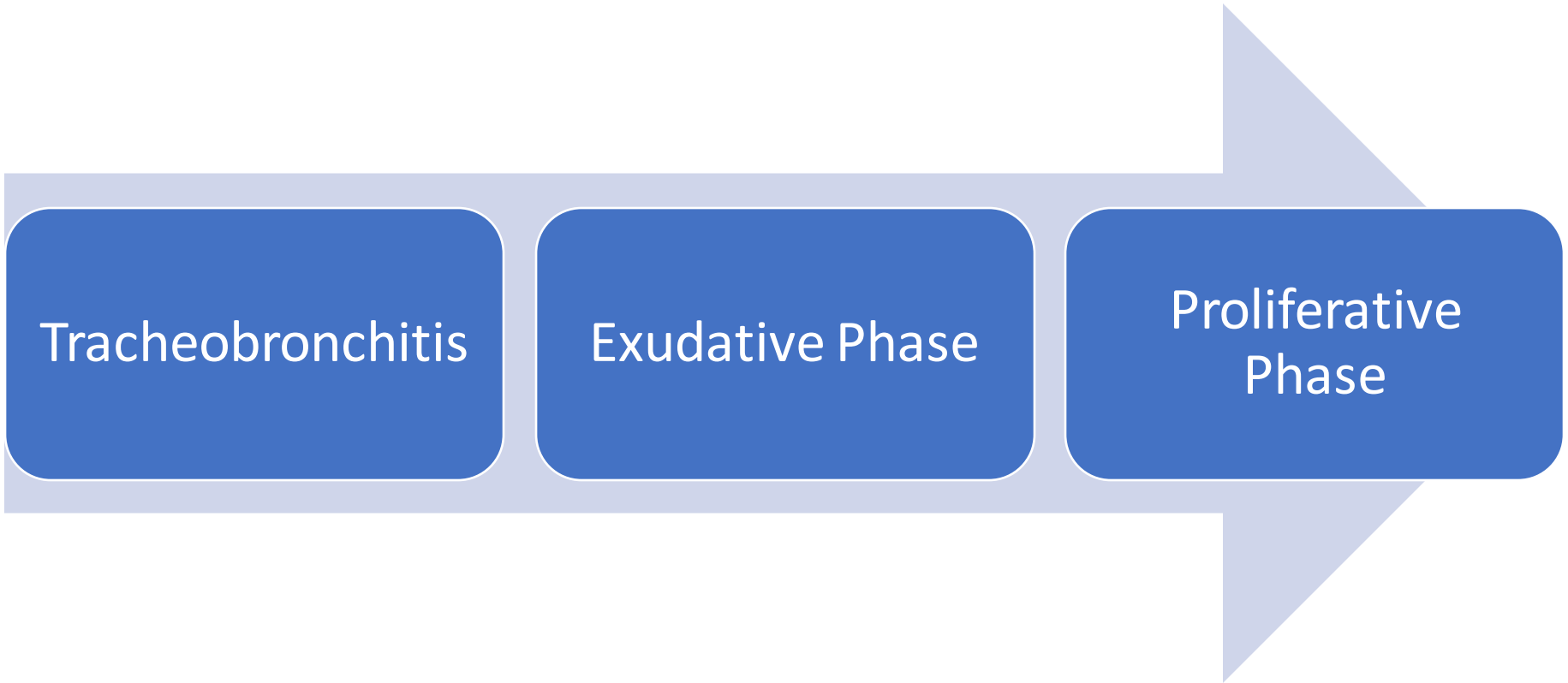
Prodromal symptoms are variable

- **V**ision
- **E**ars
- **N**ausea
- **T**witching
- **I**rritability
- **D**izziness
- **C**onvulsions



DONALD KW. Oxygen poisoning in man. Br Med J. 1947 May 17;1(4506):667 Use license obtained by journal.

Pulmonary Oxygen Toxicity



Tracheobrochitis

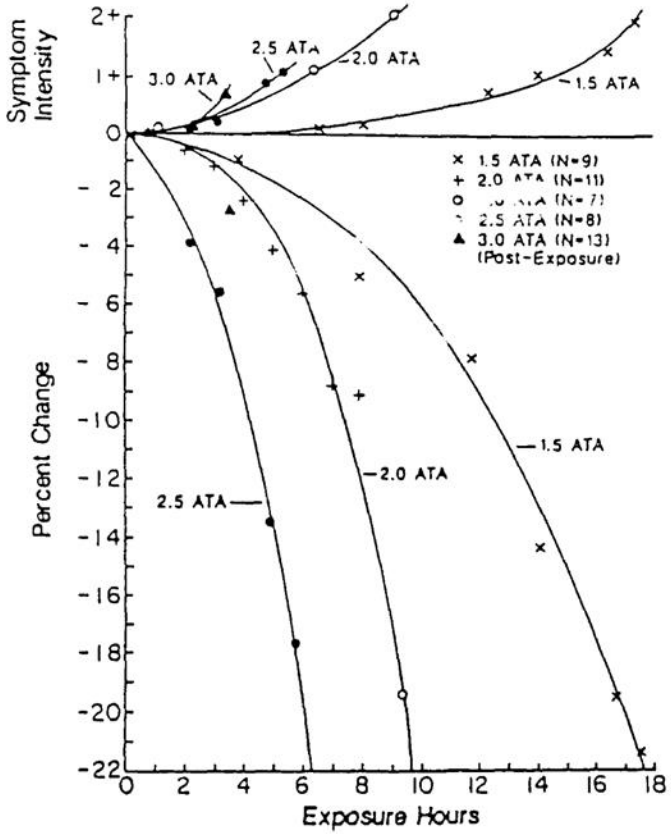
Most commonly encountered during diving and recompression.

Diagnosis is based on symptoms.

- Cough
- Dyspnea
- Inspiratory burning

Symptom severity is intolerable prior to progression to exudative phase.

Reductions in pulmonary function observed.



Lambertsen CJ. Final Report Definition of Oxygen Tolerance in Man (Predictive Studies V) . 31DEC1987 Accession number: ADA239247

Prevention

Centered around limiting O_2 exposure.

- Oxygen exposure limits
- Unit Pulmonary Toxic Dose (UPTD)
  - 1 UPTD unit corresponds to the pulmonary toxicity produced by breathing a pO_2 of 1 ATA for 1 minute.
  - Vital Capacity sole index of pulmonary toxicity
  - Early model
    - Newer models have been developed

Table 16-2. *Single-Depth Oxygen Exposure Limits.*

Depth	Maximum Oxygen Time
25 fsw	240 minutes
30 fsw	80 minutes
35 fsw	25 minutes
40 fsw	15 minutes
50 fsw	10 minutes

$$UPTD = \frac{PO2 - 0.5}{1.0 - 0.5} * t$$

U.S. Navy Dive Manual Rev 7 CHANGE A

Research –So What's new?

CNS Oxygen Toxicity

- Major developments:
  - Nitric oxide is a key player in the pathophysiology of CNS oxygen toxicity[5].
  - Human CNS oxygen toxicity studies are being conducted at Duke University (Dr. Bruce Derrick).

CNS Oxygen Toxicity

- Prevention: Probabilistic modeling significantly hampered by intra-subject variance (known since Donald WW2).
  - A source of persistent worry for divers breathing enriched oxygen gas mixtures.
  - Ki Chon at University of Connecticut in conjunction with manned studies at Duke investigating electrodermal Activity (EDA) as a potential signal for an impending seizure (1-5 min prior notice)[6].
  - Xavier Vrijdag at the University of Aukland using quantitative EEG to determine whether EEG can predict seizure.

Can biomarkers predict CNS oxygen toxicity risk for a **given dive** on a **given day**?

Treatment/Prophylaxis

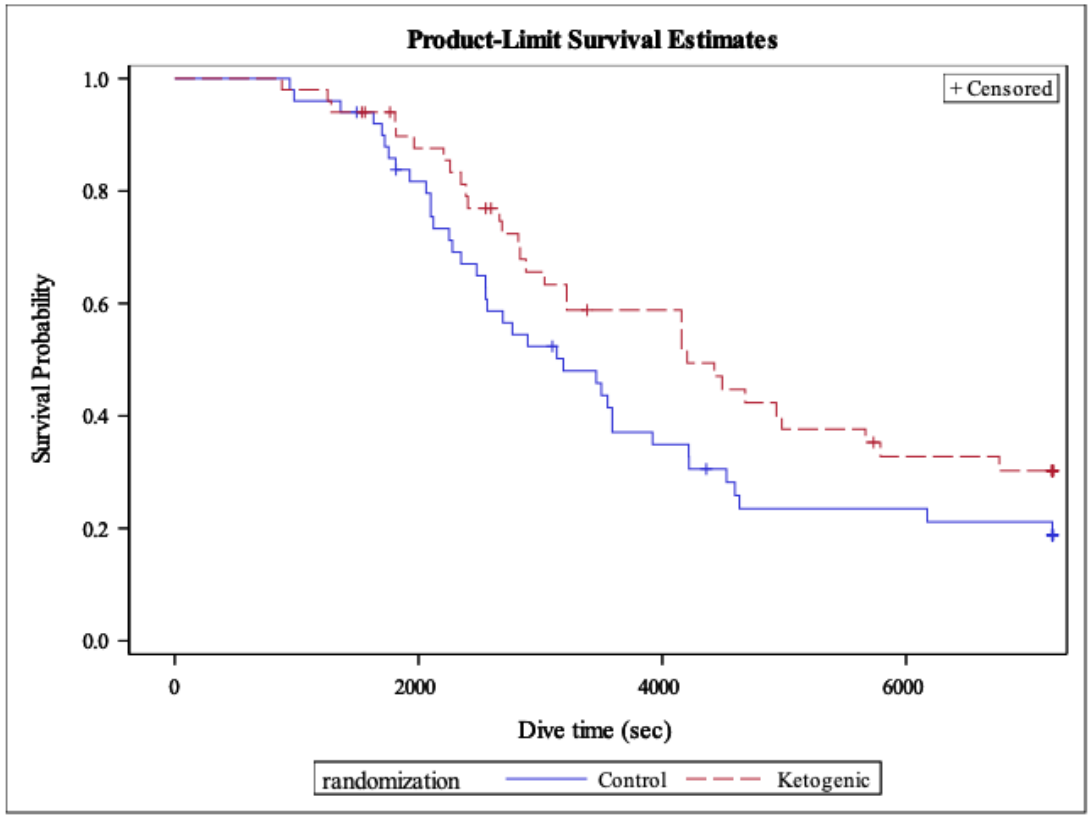
Animal Research

- Traditional anti-epileptics can prevent seizure
  - GABA enhancers[7], ion channel blockers[8], magnesium supplementation[9] all effective.
  - Testing in conjunction with relevant inert gas (i.e., Nitrogen) warranted.
  - Exercise performance impacts unknown.
  - Ketones show significant efficacy in extending seizure latency[10]

Treatment/Prophylaxis

Human Research

- Nutritional ketosis showed modest efficacy.
- Planned study using exogenous ketone esters to reduce variance.



Dr. Bruce Derrick "Ketogenic diet for CNS oxygen toxicity" Control Diet vs Ketogenic Diet Kaplan Meier Survival, ITT analysis: Log-rank p-value 0.09. Used with permission.

Pulmonary Oxygen Toxicity

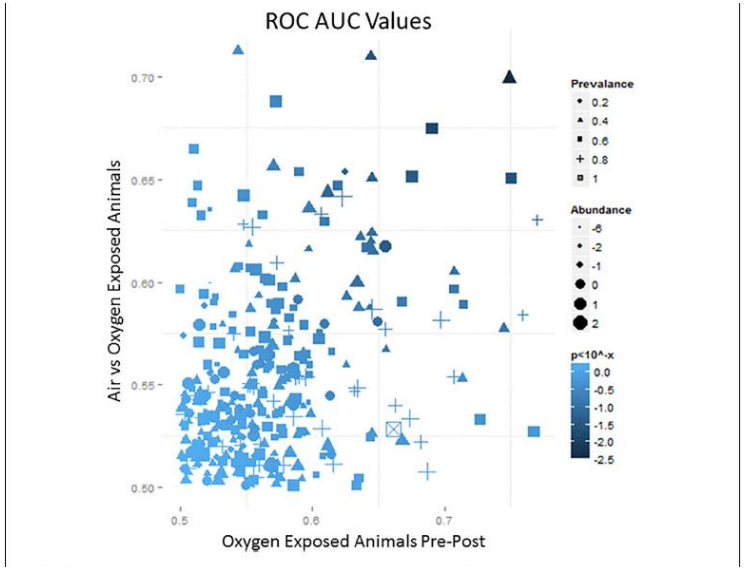
- Major developments:
  - Nitric oxide is a key player in the pathophysiology of pulmonary oxygen toxicity[11].
  - Creation of **operational** risk models for pulmonary oxygen toxicity **symptoms**[12].

Pulmonary Oxygen Toxicity

- Prevention:
  - Exhaled breath condensate and volatile organic compounds[13,14]
    - Naval Medical Research Command/Naval Submarine Medical Research Laboratory/Navy Experimental Diving Unit
    - NATO allies - Royal Netherlands Navy
  - Exhaled NO[15]
    - Predictive but difficult to measure in an operational setting.

Exhaled Volatile Organic Compounds Precedes Pulmonary Injury in a Swine Pulmonary Oxygen Toxicity Model

William A. Cronin[1,2†], Angela S. Forbes[1†], Kari L. Wagner[1], Peter Kaplan[3], Renee Cataneo[3], Michael Phillips[3], Richard Mahon[2,4] and Aaron Hall[2]*



Cronin WA, Forbes AS, Wagner KL, Kaplan P, Cataneo R, Phillips M, Mahon R, Hall A. Exhaled Volatile Organic Compounds Precedes Pulmonary Injury in a Swine Pulmonary Oxygen Toxicity Model. Front Physiol. 2019 Dec 3;10:1297.

Treatment/Prophylaxis

Animal Research

- Parasympathetic nervous system involved in pulmonary oxygen toxicity.
  - Long-Acting Muscarinic Antagonists (LAMAs) reduce pulmonary function decrements in swine exposed to hyperbaric oxygen.
    - Spiriva (Tiotropium Bromide)
    - Concern about transition to humans due to symptom masking and increased of exudative phase
  - Exudative phase countermeasures exist
    - Focus on modulating the immune system
    - IL-11[16], GM-CSF[17], IL-6[18], IL-10[19], Endotoxin[20]

Human Research

- None transitioned

References

1.) Mahon RT, Dainer HM, Gibellato MG, Soutiere SE. Short oxygen prebreathe periods reduce or prevent severe decompression sickness in a 70-kg swine saturation model. J Appl Physiol (1985). 2009 Apr;106(4):1459-63.

2.) DONALD KW. Oxygen poisoning in man. Br Med J. 1947 May 17;1(4506):667

3.) Lambertsen CJ. Final Report Definition of Oxygen Tolerance in Man (Predictive Studies V) . 31DEC1987 Accession number: ADA239247

4.) Commander, Naval Sea Systems Command, U.S, Navy Diving Manual (Revision 7 change A). Washington DC: Naval Sea Systems Command, 2018, Publication No. SS521-AG-PRO-010

5.) Demchenko IT, Piantadosi CA. Nitric oxide amplifies the excitatory to inhibitory neurotransmitter imbalance accelerating oxygen seizures. Undersea Hyperb Med. 2006 May-Jun;33(3):169-74.

6.) Posada-Quintero HF, Derrick BJ, Winstead-Derlega C, Gonzalez SI, Claire Ellis M, Freiberger JJ, Chon KH. Time-varying Spectral Index of Electrodermal Activity to Predict Central Nervous System Oxygen Toxicity Symptoms in Divers: Preliminary results. Annu Int Conf IEEE Eng Med Biol Soc. 2021 Nov;2021:1242-1245.

7.) Hall AA, Young C, Bodo M, Mahon RT. Vigabatrin prevents seizure in swine subjected to hyperbaric hyperoxia. J Appl Physiol (1985). 2013 Sep;115(6):861-7.

8.) Demchenko IT, Zhilyaev SY, Moskvin AN, Krivchenko AI, Piantadosi CA, Allen BW. Antiepileptic drugs prevent seizures in hyperbaric oxygen: A novel model of epileptiform activity. Brain Res. 2017 Feb 15;1657:347-354.

9.) Katz A, Kerem D, Sherman D. Magnesium sulfate suppresses electroencephalographic manifestations of CNS oxygen toxicity. Undersea Biomed Res. 1990 Jan;17(1):45-9. PMID: 2316059.

10.) Stavitzski NM, Landon CS, Hinojo CM, Poff AM, Rogers CQ, D'Agostino DP, Dean JB. Exogenous ketone ester delays CNS oxygen toxicity without impairing cognitive and motor performance in male Sprague-Dawley rats. Am J Physiol Regul Integr Comp Physiol. 2021 Aug 1;321(2):R100-R111

11.) Demchenko IT, Welty-Wolf KE, Allen BW, Piantadosi CA. Similar but not the same: normobaric and hyperbaric pulmonary oxygen toxicity, the role of nitric oxide. Am J Physiol Lung Cell Mol Physiol. 2007 Jul;293(1):L229-38

12.) Shykoff BE. Residual oxygen time model for oxygen partial pressure near 130 kPa (1.3 atm). Undersea Hyperb Med. 2015 Nov-Dec;42(6):547-64.

13.) Cronin WA, Forbes AS, Wagner KL, Kaplan P, Cataneo R, Phillips M, Mahon R, Hall A. Exhaled Volatile Organic Compounds Precedes Pulmonary Injury in a Swine Pulmonary Oxygen Toxicity Model. Front Physiol. 2019 Dec 3;10:1297.

14.) Wingelaar TT, Brinkman P, Hoencamp R, van Ooij PA, Maitland-van der Zee AH, Hollmann MW, van Hulst RA. Assessment of pulmonary oxygen toxicity in special operations forces divers under operational circumstances using exhaled breath analysis. Diving Hyperb Med. 2020 Mar 31;50(1):2-7.

15.) Fothergill DM, Gertner JW. Exhaled Nitric Oxide and Pulmonary Oxygen Toxicity Susceptibility. Metabolites. 2023 Aug 8;13(8):930.

16.) Waxman AB, Einarsson O, Seres T, et al. Targeted lung expression of interleukin-11 enhances murine tolerance of 100% oxygen and diminishes hyperoxia-induced DNA fragmentation. J Clin Invest. 1998;101(9):1970-1982. doi:10.1172/JCI1337

17.) Paine R 3rd, Wilcoxen SE, Morris SB, et al. Transgenic overexpression of granulocyte macrophage-colony stimulating factor in the lung prevents hyperoxic lung injury. Am J Pathol. 2003;163(6):2397-2406. doi:10.1016/S0002-9440(10)63594-8

18.) Ward NS, Waxman AB, Homer RJ, et al. Interleukin-6-induced protection in hyperoxic acute lung injury. Am J Respir Cell Mol Biol. 2000;22(5):535-542. doi:10.1165/ajrcmb.22.5.3808

19.) Li, H.-D., Zhang, Q.-X., Mao, Z., Xu, X.-J., Li, N.-Y. and Zhang, H. (2015), Exogenous interleukin-10 attenuates hyperoxia-induced acute lung injury in mice. Exp Physiol, 100: 331-340. doi:10.1113/expphysiol.2014.083337.

20.) Berg JT, Allison RC, Prasad VR, Taylor AE. Endotoxin protection of rats from pulmonary oxygen toxicity: possible cytokine involvement. J Appl Physiol (1985). 1990;68(2):549-553. doi:10.1152/jappl.1990.68.2.549