Oxygen Toxicity

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Oxygen Toxicity

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Oxygen Toxicity

"Are virtue, courage, talent, wit, imagination - are all these qualities or faculties only a question of oxygen?"

- *Jules Verne*

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Oxygen Toxicity

- 1775 - Priestly discovers Oxygen
- 1782 - Scheele notes toxic effect on peas
- 1789 - Sequin and Lavoisier noted toxic effect in animals

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Oxygen Toxicity

"…as a candle burns faster in dephlogisticated air than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air.

- *Joseph Priestly*

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Oxygen Toxicity

Generally Dependent Upon…

- Partial Pressure of Oxygen
- Duration of Exposure
- Inter- and Intra-individual variation in susceptibility

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Oxygen Toxicity

Tissue Specific

- Biochemical characteristics
- Level of metabolic activity
- Antioxidant defense reserves
- Local oxygen supply

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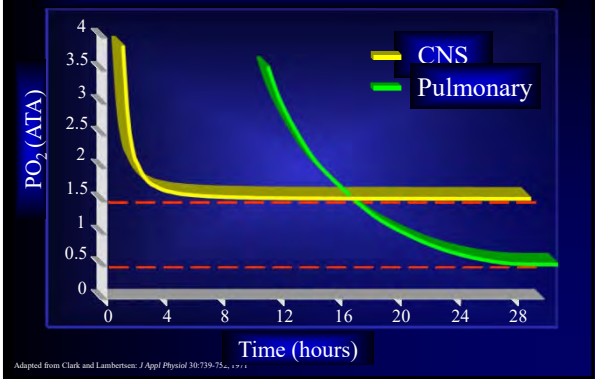
Oxygen Toxicity



Adapted from Clark and Lambertsen: *J Appl Physiol* 30:739-75..

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Oxidative Physiological Stress

- Oxygen must be reduced to produce toxic effects.
- The rate of univalent reduction increases as partial pressures of oxygen are increased.

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Oxygen Toxicity

"In considering oxygen as a therapeutic agent, as with all drugs, the potential for benefits depends on the dose (concentration) and duration of exposure."

- Stephen Thom

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Oxygen Toxicity

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"Nothing yet - how about you, Newton?"

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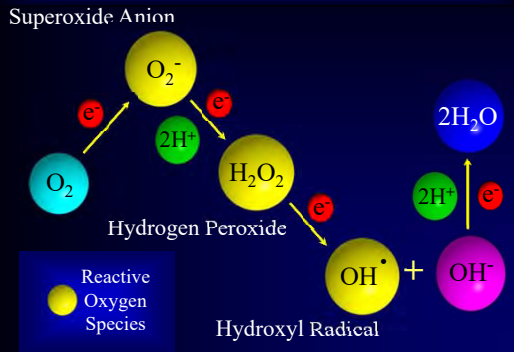
Oxidative Stress



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Host Defenses

- Enzymatic
  - Superoxide Dismutase
  - Catalase
  - Peroxidases

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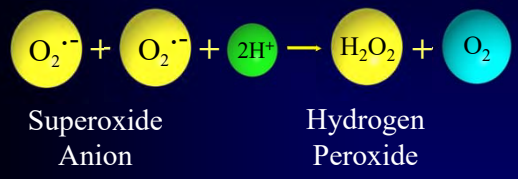
Host Defenses
Superoxide Dismutase



Superoxide Anion

Hydrogen Peroxide

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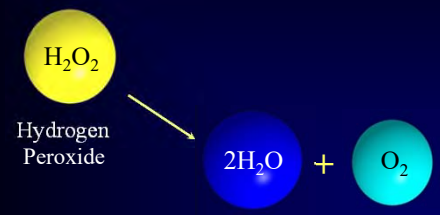
Host Defenses
Catalase



Hydrogen Peroxide

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Host Defenses

- Antioxidants
  - Vitamin E (α-tocopherol)
  - Reduced glutathione
  - Selenium
  - Others

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Oxygen Toxicity

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Oxidative Physiological Stresses

- Damage to
  - Proteins
  - Lipids
  - Nucleic acids
- Alteration of enzyme titers
- Diversion of reducing moieties

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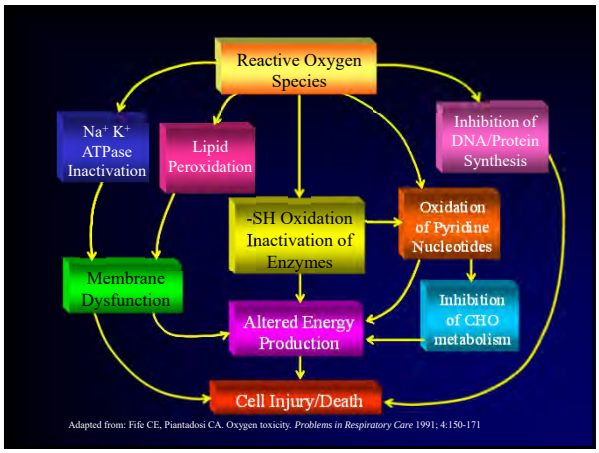

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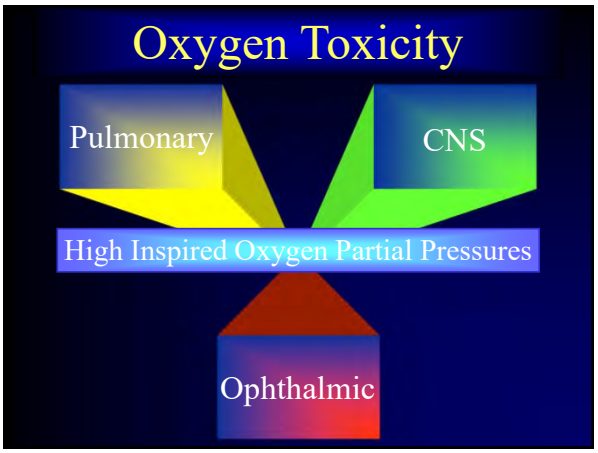

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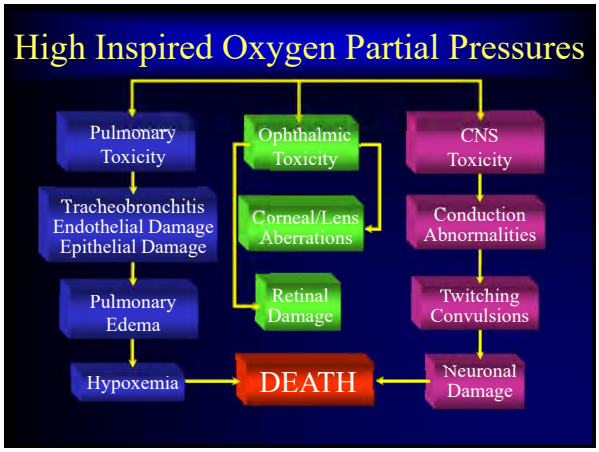

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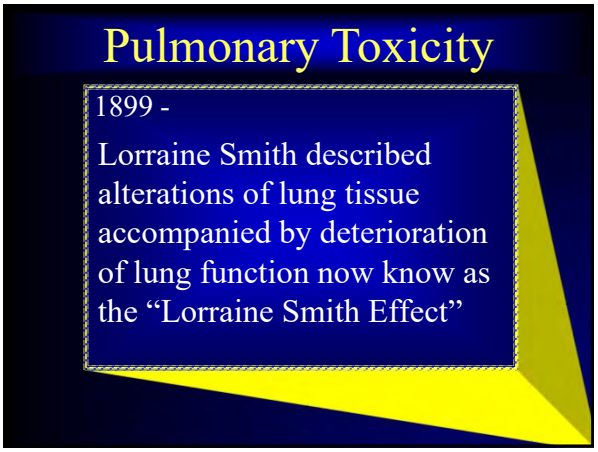

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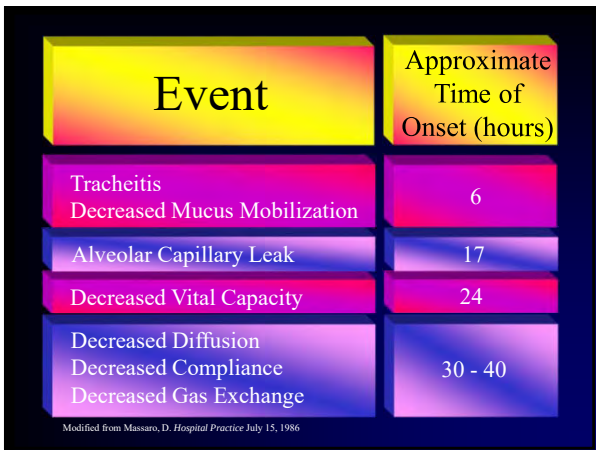

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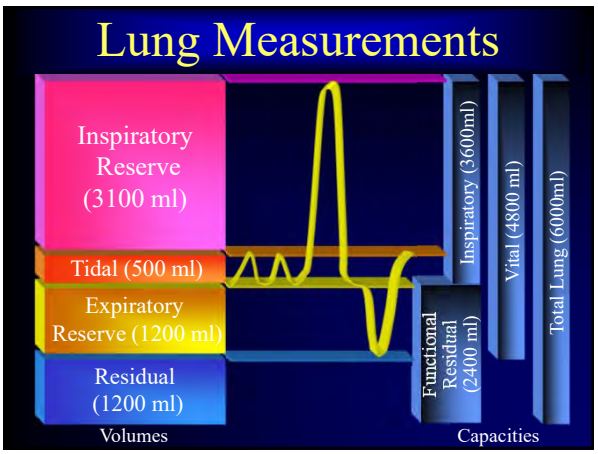

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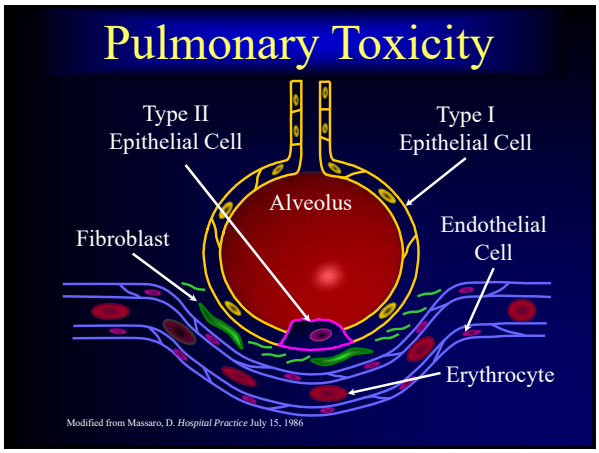

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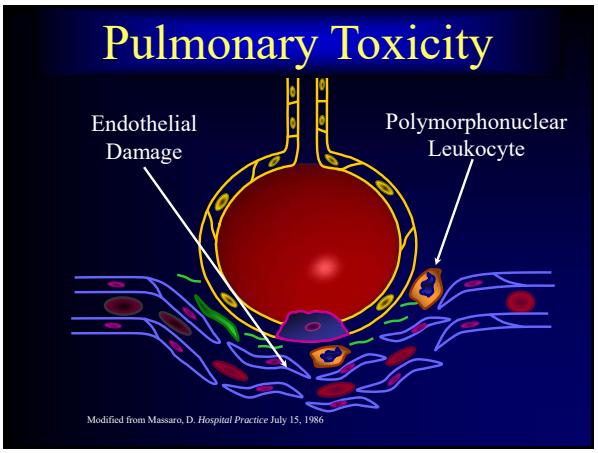

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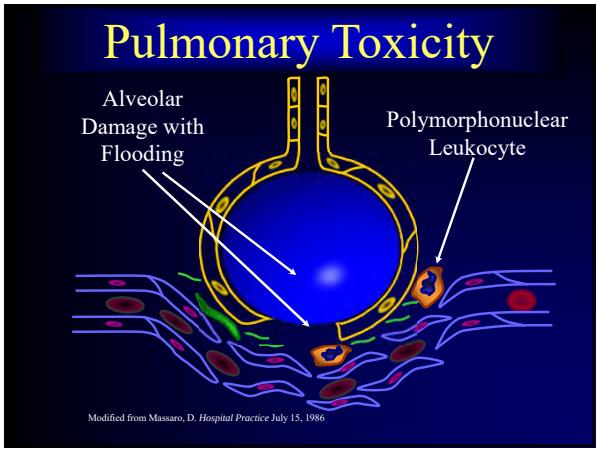

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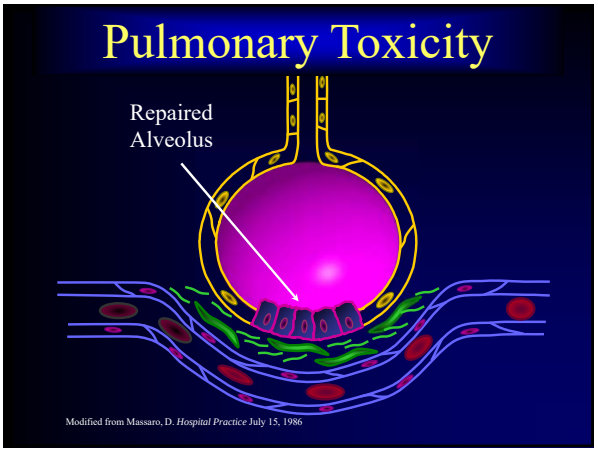

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Pulmonary Toxicity
Unit Pulmonary Toxic Dose (UPTD)

- The UPTD can be calculated for any pulmonary dose in terms of an equivalent lung exposure at 1.0 ATA.
- The calculations are based on the average decrease in vital capacity in 50% of subjects breathing oxygen at varying pressures.

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Pulmonary Toxicity
Unit Pulmonary Toxic Dose (UPTD)

- UPTD Defined as:

$$U = \sqrt[m]{0.5/(P-0.5)} \cdot t$$

Where: P = the inspired PO_2 (ATA)
t = exposure time (min)
m = -1.2 (slope constant)

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Pulmonary Toxicity
Unit Pulmonary Toxic Dose (UPTD)

- Estimation of effect on Vital Capacity (VC)

$$\%VC = -0.009 \cdot (P - 0.38) \cdot t$$

Where: P = the inspired PO_2 (ATA)
t = exposure time (min)

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Pulmonary Toxicity
Unit Pulmonary Toxic Dose (UPTD)

- The UPTD is limited by significant individual variability.
- The calculations are based on continuous exposures in normal volunteers.
- Will lead to overestimation of pulmonary toxicity in intermittent exposure.

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CNS Toxicity

1878 -

Paul Bert described a variety of neurological symptoms related to oxygen exposure at high pressure now known as the "Paul Bert Effect".

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CNS Toxicity
Common Symptoms

- Visual disturbances
  - Tunnel vision
  - Loss of acuity
  - Decreased intensity

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CNS Toxicity
Common Signs

- Nausea and vomiting
- Hiccoughs
- Irritability and behavioral changes
- Twitching of lips, cheeks, nose

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CNS Toxicity
Common Signs

- Acoustic
  - tinnitus
  - vertigo
- Gustatory and olfactory

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CNS Toxicity
Common Signs

- Gross, sudden changes in heart rate (tachy- or bradycardia)
- Syncope
- Convulsions

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CNS Toxicity
Convulsions

- Hart (1966) reported a general incidence of 1 in 4690 treatments (0.02%).
- Incidence in patients who were febrile, toxic, or treated at > 2.8 ATA 0.21%.

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CNS Toxicity
Convulsions

- Hart (1987) reported 44 seizures in 32 out of 3160 patients.
- Fifty percent of all seizures occurred in 313 patients (10%) treated with HBO at > 2.5 ATA.

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CNS Toxicity
Convulsions

- Davis et al. (1988) reported an incidence of 5 cases in 52,758 treatments (0.009%)

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CNS Toxicity
Convulsions

- Kindwall and Goldman (1995) overall seizure incidence 1 in 7500 treatments (0.013%).

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CNS Toxicity
Convulsions

- Hampson and Atik (2003) overall seizure incidence 1 in 3388 treatments (0.03%).

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CNS Toxicity
Convulsions

- Incidence is variable.
- In selected patients treated at typical oxygen pressure the overall incidence is ~ 0.01%.
- Dependent upon patient acuity and predisposing factors.

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CNS Toxicity
Convulsions

- Predisposing factors
  - Fever (T ≥ 100° F)
  - Hypermetabolic states e.g. hyperthyroidism, sepsis, burns, stress
  - Hypoglycemia

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CNS Toxicity
Convulsions

- No satisfactory consistent warning of impending convulsions.
- ANY unusual symptom should be considered as a premonitory sign.

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CNS Toxicity
Convulsions

- Characteristics
  - Occur abruptly with minimal to no aura.
  - Retrograde amnesia is common.
  - Postictal state is characteristically one of somnolence.
  - No permanent neurological sequelae described in humans.

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Ophthalmic Toxicity

1936 -

Behnke first described the effects of prolonged HBO exposures on the retina.

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Ophthalmic Toxicity

Corneal Aberrations → Myopia

Lens Aberrations → Cataracts

Retinal Damage → Blindness

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Ophthalmic Toxicity
Refractive Changes

- Repetitive HBO therapy results in refractive changes.
- Myopia is common and is the result of changes in the lenticular refractive index.

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Ophthalmic Toxicity
Refractive Changes

- Refractive changes are slowly reversible.
- Complete resolution may take as long as a year.

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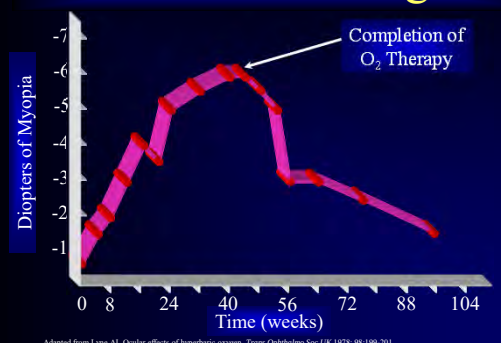
Refractive Changes



Adapted from Lyne AI. Ocular effects of hyperbaric oxygen. *Trans Ophthalmo Soc UK* 1978; 98:199-201.

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Ophthalmic Toxicity
Nuclear Cataracts

- Palmquist (1984) reported the development of nuclear cataracts in patients with an excessive cumulative exposure to HBO compared to controls.

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Ophthalmic Toxicity
Nuclear Cataracts

- Seven out of 15 patients (47%) in this study developed nuclear cataracts that resulted in decreased visual acuity.
- Cataracts developed 6-12 months into treatment.

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Ophthalmic Toxicity
Nuclear Cataracts

- Eight of 10 patients who had cataracts initially experienced progression during the treatment period.

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Ophthalmic Toxicity
Retinal Damage

- Nichols (1969) reported one case of protracted vision loss in a patient with retrobulbar neuritis after a single HBO exposure.

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Ophthalmic Toxicity
Retinal Damage

- Herbstein (1984) reported a permanent visual field defect 2 weeks after a single 1 hour HBO exposure at 2 ATA.

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Oxygen Toxicity

"When meditating over a disease, I never think of finding a remedy for it, but, instead, a means of preventing it."

- Louis Pasteur

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"We should write that spot down."

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Pulmonary Toxicity
Prevention

- Pulmonary toxicity is rare except in the case of patients on continuous supplemental oxygen.
- Patients requiring high F_iO_2 should be closely scrutinized for acceptability for HBO.

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CNS Toxicity
Prevention

- Screen the patient closely for predisposing factors prior to HBO.
- Observe closely for premonitory signs of impending CNS toxicity.
- When in doubt, treat for oxygen toxicity.

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CNS Toxicity
Prevention

- Avoid medications which may directly increase or lead to an increased PCO_2 e.g. Narcotics, carbonic anhydrase inhibitors.
- Closely monitor patients with antecedent hypercapnea.

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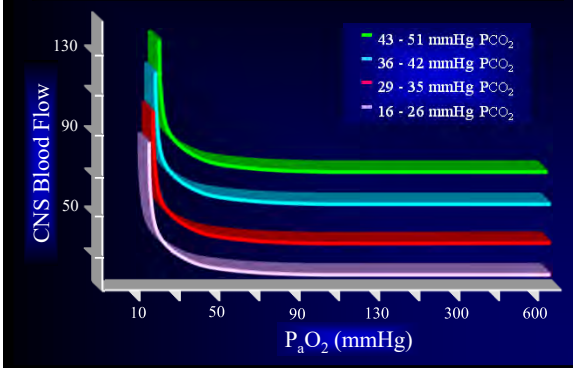
Cerebral Blood Flow



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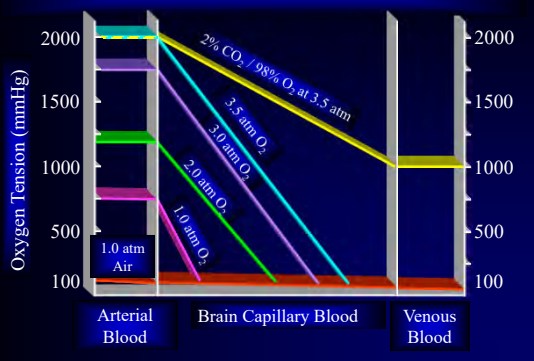
CNS Tolerance



Adapted from Lambertsen CJ. Effects of hyperoxia on organs and their tissues. In Robin ED, ed. Extrapulmonary manifestations of respiratory disease. New York: Marcel Dekker, 1978:239-303.

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CNS Toxicity
Prevention

- Avoid medications which may lower seizure threshold
  - Systemic sympathomimetic drugs
  - Corticosteroids
  - ASA
  - Opiates
  - Ascorbic Acid (high doses)

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Oxygen Toxicity

- Bean and Johnson (1955) studied rats and adrenalectomized rats under hyperoxia at 80 psig.
- Rats receiving epinephrine prior to HBO developed CNS oxygen toxicity and pulmonary edema with significantly shorter exposure times.
- Adrenalectomized rats showed a "protective" effect with regard to CNS and pulmonary toxic effects.

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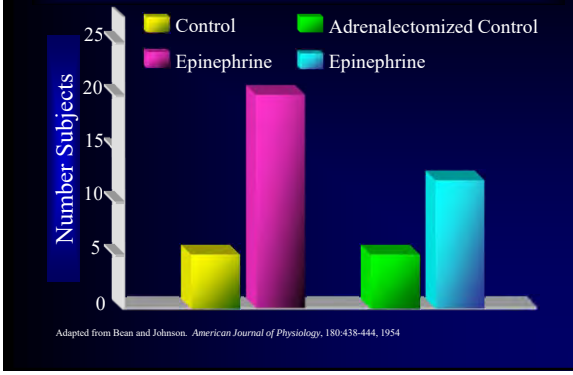
Pulmonary Toxicity



Adapted from Bean and Johnson. *American Journal of Physiology*, 180:438-444, 1954

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CNS Toxicity
Prevention

- Consider prophylactic anticonvulsants for patients with a seizure disorder history.
- Benzodiazepines are the drugs of choice.
- Anticonvulsants don't prevent CNS toxicity but may decrease seizure activity.

67

CNS Toxicity
Prevention

- Intermittent exposure to high oxygen pressure delays onset of both neurological and pulmonary oxygen toxicity.

Diving and Subaquatic Medicine. Third Edition 1992. Eds. C. Edmonds, C. Lowery, and J. Pennefather. Butterworth-Heinemann, Ltd. Oxford, England.

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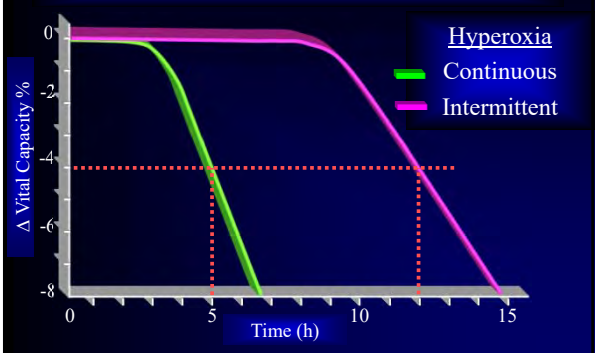
Pulmonary Tolerance



Modified from Hendricks PL, Hall DA et al. Extension of pulmonary O_2 tolerance in man at 2 ATA by intermittent O_2 exposure. *J Appl Physiol:Respir Environ Exercise Physiol* 42:593-599, 1977.

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CNS Toxicity
Prevention

- Air breaks should be implemented for those patients who are at risk or have predisposing factors.

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CNS Toxicity
Prevention

- Never lower chamber pressures during the tonic/clonic phase of a seizure to prevent barotrauma.

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Ophthalmic Toxicity
Prevention

- Ophthalmic abnormality are typically reversible.
- Patients should be informed of possible refractive changes.
- Cataracts are less of a concern with typical treatment regimens < 150 exposures.

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Oxygen Toxicity

Prevention – Antioxidant Therapy

- Vitamin E (α-tocopherol)
  - Deficiencies result in increases in susceptibility to oxidative injury
  - Daily administration of Vitamin E (400 IU bid)

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Oxygen Toxicity

"A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve"

- *Joseph Priestley*

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