Hyperbaric Physiology:
Mechanisms of Action

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I. Introduction

In order to safely and confidently use hyperbaric oxygen as a therapeutic modality, a basic understanding of the behavior of gases and the physiology of gas exchange is essential. In addition, an understanding of the mechanisms of hyperbaric oxygen is needed to make therapeutic applications.

II. Physiology

A. Oxygenation

1. alveolar oxygenation - the alveolar oxygen tension is dependent upon the inspired oxygen concentration and the degree of oxygen utilization, and may be quantitated by the modified alveolar gas equation:

Eq. 2.1

$$P_AO_2 = \{(P_{BTPS} \times F_iO_2) - (P_aCO_2 \div R)\}$$

Where F_iO_2 is the inspired oxygen concentration, P_{BTPS} is the barometric pressure at body temperature saturated with water vapor, and R is the respiratory quotient.

Example 1: Given the following conditions; F_iO_2 = 21%, barometric pressure = 760 mm Hg, P_aCO_2 = 40 mm Hg, R = 0.8, and water vapor pressure = 47 mm Hg.

$$P_AO_2 = \{((760 - 47) \times 0.21) - (40 \div 0.8)\}$$

$$= \{(713 \times 0.21) - 50\}$$

$$\cong 100mmHg$$

Example 2: Given the following conditions; F_iO_2 = 100%, barometric pressure = 2280 mmHg, P_aCO_2 = 40 mmHg, R = 0.8, and water vapor pressure = 47 mmHg.

$$P_AO_2 = \{((2280 - 47) \times 1.0) - (40 \div 0.8)\}$$

$$= \{(2233 \times 1.0) - 50\}$$

$$\cong 2183mmHg$$

Arterial oxygen partial pressure (PaO_2) will be somewhat less than the ideal alveolar oxygen partial pressure. This is due to some mixing of venous blood from the bronchial veins and the Thebesian veins in the heart and due to ventilation /perfusion mismatch in the lung.

Arterial oxygen partial pressures may be closely estimated using the arterial /alveolar oxygen ratio which is a constant at ambient pressures up to approximately 3000 mmHg. This is accomplished by calculating the alveolar partial pressure of oxygen at baseline and then calculating the a/A ratio utilizing the arterial partial pressure of oxygen obtained on blood gas analysis.[1, 2]

2. Oxygen Content of Blood

a. Normobaric Conditions

In a normoxic environment essentially all of the oxygen carried by the blood is bound to hemoglobin (97.5%). The remaining 2.5% is carried by the plasma in the dissolved state.

The content of oxygen bound to hemoglobin may be quantitated using the following equation:

Eq.2.2 $$O_2\ Content = 1.34\ ml O_2 / gm\ Hgb \times gms\ Hgb / 100\ ml \times \%\ Saturation$$

Under normal sea level conditions, the arterial and venous hemoglobin saturations are 97% and 70% respectively. Using equation 2.2 and assuming an average hemoglobin concentration of 15gms/100cc blood, the oxygen content of arterial and venous blood are calculated to be 20 vol% and 14 vol% respectively.

From the above relationship it can be seen that at rest the average arterial to venous oxygen difference (a-v O_2) is **6 vol%.**

b. Hyperbaric Conditions

The above relationship holds true for partial pressures of oxygen up to approximately 200 mm Hg; however, at higher levels of oxygen partial pressures, the fraction of oxygen dissolved in the plasma becomes significant. Under hyperbaric conditions the quantity of oxygen physically dissolved in plasma must be considered.

According to Henry's Law the content of oxygen dissolved in plasma may be calculated using the following equation:

Eq. 2.3

$$Dissolved\ Oxygen\ (vol\%) = 0.0031\,(ml O_2 / 100ml / mmHg) \times P_a O_2\,(mmHg)$$

Therefore the total oxygen content of the blood under hyperbaric conditions is the sum of Eqs. 2.2 and 2.3.

In an environment of 100% oxygen at 3 ATA the PaO_2 is approximately 2000 mmHg. At this level of oxygen pressure hemoglobin remains 100% saturated. Using equations 2.1 and 2.2 the total oxygen content of the blood under the given conditions is roughly calculated to be 27vol% (i.e. an additional 7 vol% above the normal sea level, room-air value). **Thus oxygen delivered under high pressure is capable of supplying an adequate oxygen content in the absence of hemoglobin**[3] (figure 1).

B. Carbon dioxide transport

Carbon dioxide is carried in the blood in three ways:

- 75% is carried as bicarbonate
- 20% is carried as carbaminohemoglobin
- 5% is carried physically dissolved in the plasma

Carbon dioxide carried in combination with hemoglobin largely depends on deoxygenation of the hemoglobin molecule (i.e. the Haldane effect). Therefore, under hyperoxic conditions where hemoglobin remains saturated with oxygen, the PaCO2 may rise. Typically, this is not clinically observed except in cases of underlying pulmonary disease or in conditions where the work of breathing is increased.

C. Pulmonary effects

1. Work of breathing

The work of breathing may be quantitated using the following relationship:

Eq. 2.4

$$Work\ of\ Breathing = Pressure \times Volume$$

Increased ambient pressure results in increased gas density. With increasing gas density, the change in pressure required to move a given volume of gas into the lungs is increased.

This elevation in the work of breathing is usually of no clinical significance; however, patients with compromised lung mechanics (e.g. COPD) or with artificial airways may experience difficulty while at pressure[1, 4,5] (Figure 2).

2. Ventilation - alveolar ventilation is increased due to central nervous system stimulation by increased central partial pressures of carbon dioxide.[6]

D. Cardiovascular effects

1. Cardiac effects

a. blood pressure - systolic and diastolic blood pressures remain relatively unchanged during exposure to oxygen at high pressures. Occasionally a minimal increase can be observed.[5, 7,8,9,10,11]

b. stroke volume - stroke volume is largely unaffected but may vary depending on the loading conditions of the heart.

c. inotropism- the inotropic state of the heart remains unchanged.[29]

d. chronotropism - heart rate is generally decreased during exposure to oxygen at high pressures. Typically a decrease in rate of 10 - 20 % may be observed.

e. cardiac output - cardiac output may be decreased by as much as 20% during hyperbaric oxygen therapy. Cardiac output may be expressed by the following relationship:

Eq 2.5

$$Cardiac\ Output = Stroke\ Volume \times Heart\ Rate$$

Since stroke volume remains relatively constant and heart rate is decreased it follows that the reduction in cardiac output is a direct result of bradycardia.

2. Peripheral vascular resistance

Peripheral vascular resistance is increase due to generalized peripheral arterial vaso-constriction.[5, 7,8,9,10,11] This may be seen through the following relationship:

Eq 2.6

$$MAP - CVP = Cardiac\ Output \times TPR$$

Where *MAP* is mean arterial pressure, *CVP* is central venous pressure, and *TPR* is the total peripheral resistance.

With vascular pressures remaining constant with a concomitant decrease in cardiac output it follows from Eq. 2.6 that systemic vascular resistance is necessarily increased.

E. Effects on Oxygen Delivery

Oxygen delivery may be quantitated by the following:

Eq. 2.7 $$Oxygen\ Delivery\ (DO_2) = O_2\ Content \times Cardiac\ Output$$

Oxygen delivery during hyperbaric oxygen exposure is maintained at normal or supranormal levels due to the large increase in the oxygen content of the arterial blood! [12]

F. Central Nervous System (CNS) effects

1. Vascular Resistance

CNS vascular tone is increased during exposure to oxygen under high pressure. This increased tone is due to the indirect effects of hyperbaric oxygen on the arterial partial pressure of carbon dioxide ($PaCO_2$). CNS vascular tone is indirectly proportional to the arterial partial pressure of carbon dioxide (Figure 3). [6]

At the end-capillary level, the venous partial pressure of carbon dioxide increases due to the inability of oxyhemoglobin to transport CO_2. This in turn stimulates the CNS respiratory centers resulting in hyperventilation. The augmented alveolar ventilation results in peripheral arterial hypocapnia and thus CNS vaso-constriction.[6]

2. Intracranial Pressure

Intracranial pressure (ICP) is initially reduced at the onset of hyperbaric oxygen exposure. Thereafter, ICP gradually rises throughout the time of hyperbaric oxygen exposure. In addition, a rebound effect is also seen following discontinuation of oxygen under high pressure. Elevation in ICP can be anticipated in those individuals who are unable to increase minute ventilation i.e. ventilator dependent patients.[13]

G. Metabolic effects

Hyperbaric oxygen exposure has been known to result in the development of hypoglycemia in patients with diabetes mellitus. This phenomenon is likely the result of increased glucose uptake and utilization by skeletal muscle. HBO is felt to have an affect at the cellular level and is independent of insulin or other hormonal mediation. In the study by Martindale, muscle cell uptake of glucose was 57% higher at 2.4 ATA, 100% O_2, than under control conditions.[30]

III. Mechanisms of action

Hyperbaric oxygen is beneficial in a variety of clinical problems. The mechanisms by which HBO is therapeutic fall into two broad categories. Primary mechanisms are those due directly to the physical effects of oxygen under high pressures. Secondary mechanisms include those which are due to physiologic and biochemical effects and are thus delayed in action.

A. Primary effects

1. Hyperoxygenation - as previously mentioned, oxygen carrying capacity of the blood is significantly increased resulting in hyperoxygenation. Alveolar and arterial oxygen pressures change rapidly with exposure to hyperbaric oxygen. Tissue levels equilibrate slower and to a lesser degree. Studies have shown that muscle and subcutaneous tissues begin to plateau in 60-90 minutes and reach partial pressures as high as 300 mmHg with exposure to oxygen at 2 ATA (Figures 4 and 5).[14] Diffusion is also an important factor in hyperoxygenation. Diffusion of oxygen in tissue fluid has been shown to be proportional to the square root of the dissolved oxygen in the capillary. If there is a 10 fold increase in dissolved capillary oxygen under hyperbaric conditions, this would allow a three fold increase in diffusion distances.[15,16]

   Diffusion may be quantitated by the following equation:

Eq. 2.8

$$Diffusion = \frac{\Delta p \cdot A \cdot Cs}{d \cdot \sqrt{MW}}$$

Where Δp is the pressure differential, A is the cross-sectional area of the diffusing surface, Cs is the solubility coefficient, d is the thickness of the diffusing membrane, and MW is the molecular weight of the gas of interest. Thus it follows from Eq. 2.7 that diffusion will increase with an increase in the driving pressure (Δp).

Examples of clinical applications of hyperoxygenation include (1) conditions characterized by a decreased ability to carry oxygen such as severe blood loss anemia and carbon monoxide poisoning, (2) conditions characterized by a relative decrease in perfusion such as crush injury and graft salvage, (3) conditions where barriers to diffusion may exist such as edematous states.

2. Bubble size reduction - this effect initially is a direct result of the increased pressure as predicted by Boyle's Law.

   In addition, bubble size reduction is also accomplished via diffusion. Due to the hyperoxic environment outside the bubble, a favorable diffusion gradient is established. This gradient allows for oxygen to diffuse into the bubble while nitrogen is displaced. Oxygen inside the bubble is then metabolized. Finally, the bubbles become less stable with decreasing volume according to Laplace's Law:

Eq. 2.9

$$p = \frac{4T}{r}$$

where p is the pressure, T is the surface tension, and r is the radius. Clinical applications of bubble size reduction are (1) air/gas embolism, (2) decompression sickness.

B. Secondary effects

1. Vasoconstriction - hyperbaric oxygen exposure results in generalized vasoconstriction; however, as previously mentioned, tissue oxygenation is adequately maintained. Studies have demonstrated up to a 20% reduction in arterial inflow in regional vascular beds with no relative change in venous outflow. [17,18] This allows for tissue fluid resorption and therefore aids in reducing edema. Clinical applications for vasoconstriction include (1) crush injury with compartment syndrome, (2) acute burns.

2. Fibroblast proliferation - fibroblast proliferation as well as collagen synthesis are oxygen dependent processes. Healing markedly decreases when tissue oxygen partial pressures drop to less than 30 mmHg.[20]

3. Neovascularization - angiogenesis is stimulated by a hypoxic environment and may be inhibited by hyperoxia. Hyperbaric oxygen therapy (HBO), however, increases the oxygen gradient found in the wound environment which serves to further stimulate fibroblastic activity. This augmentation of fibroblastic activity promotes capillary growth by providing a collagenous scaffolding to support early capillary buds.[20,21,22,23]

   Clinical applications related to fibroblastic activity and to neovascularization include (1) graft salvage, (2) soft tissue radionecrosis, (3) osteoradionecrosis.

4. Leukocyte oxidative killing - leukocytes generate oxygen dependent radicals (superoxides and peroxides) for intracellular killing. Hypoxic environments with partial pressures of oxygen less than 30 mmHg significantly inhibit the formation of these Radicals.[19]

Clinical applications for the use of HBO in this area include (1) necrotizing soft tissue infections, (2) chronic refractory osteomyelitis.

5. Toxin production inhibition / inactivation - HBO has been shown to halt production of clostridial alpha toxin. It is also effective in inactivating existing toxins such as clostridial cardiotoxin and likely the toxin of the brown recluse spider.[24, 25]

6. Antibiotic synergism - aminoglycosides and amphotericin B require oxygen for transport across cell membranes. HBO, therefore, may facilitate transport of these antimicrobials.[26]

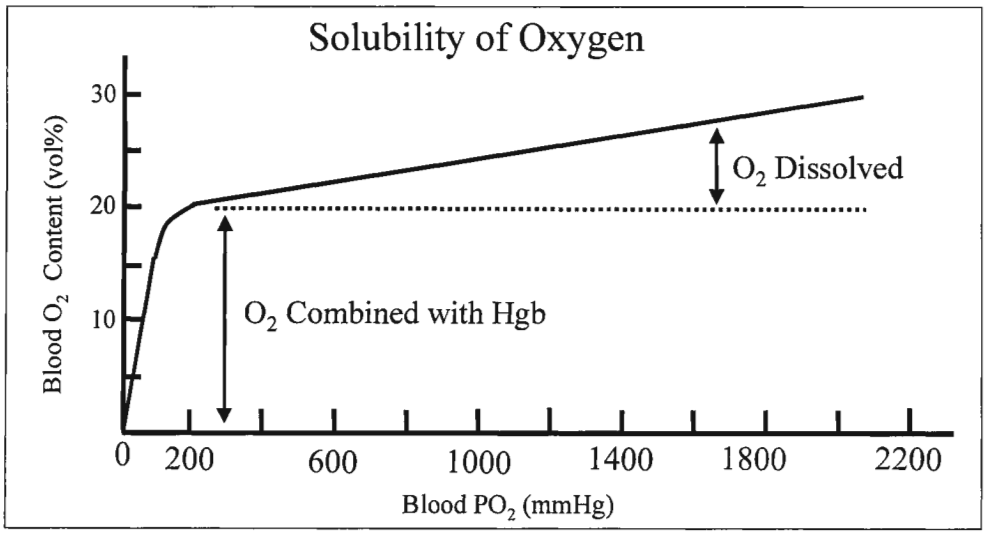

Figure 1. Extension of oxygen-hemoglobin curve.

Blood oxygen content (vol%) available at high levels of blood oxygen pressure (PO_2), assuming a normal hemoglobin level of 15 g/100 ml blood. (from B. E. Bassett & P. B. Bennett [27].)

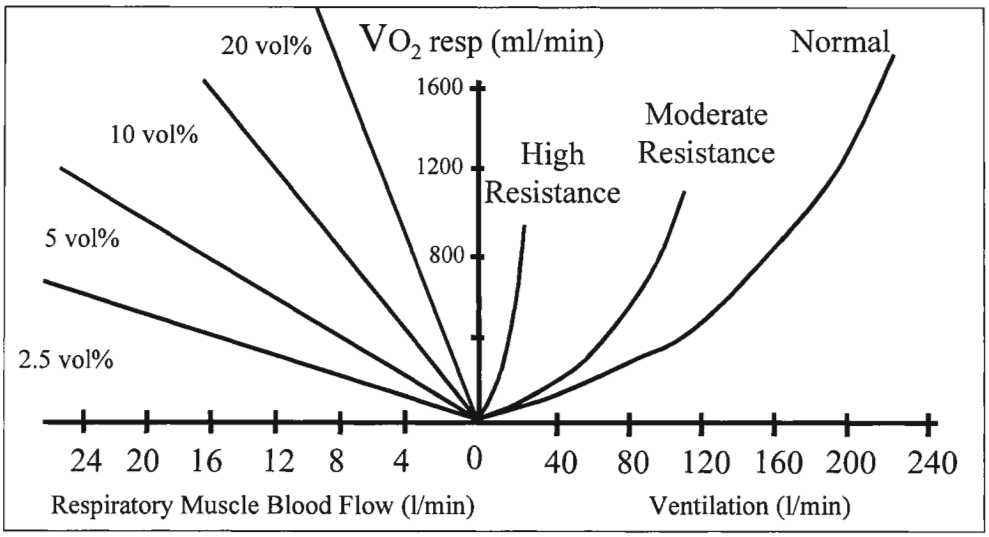

Figure 2. Respiratory -Muscle Oxygen Consumption in Relation to Ventilation and Respiratory-Muscle Blood Flow.

The left-hand panel plats the oxygen cost of breathing against respiratory-muscle blood flow for various values of CaO_2 -CvO_2, and is the graphic solution of the Fick equation. The right-hand panel shows experimental data relating respiratory-muscle oxygen consumption and minute ventilation for various degrees of airway obstruction. (Modified from C. Roussos & P. T. Macklem [28].)

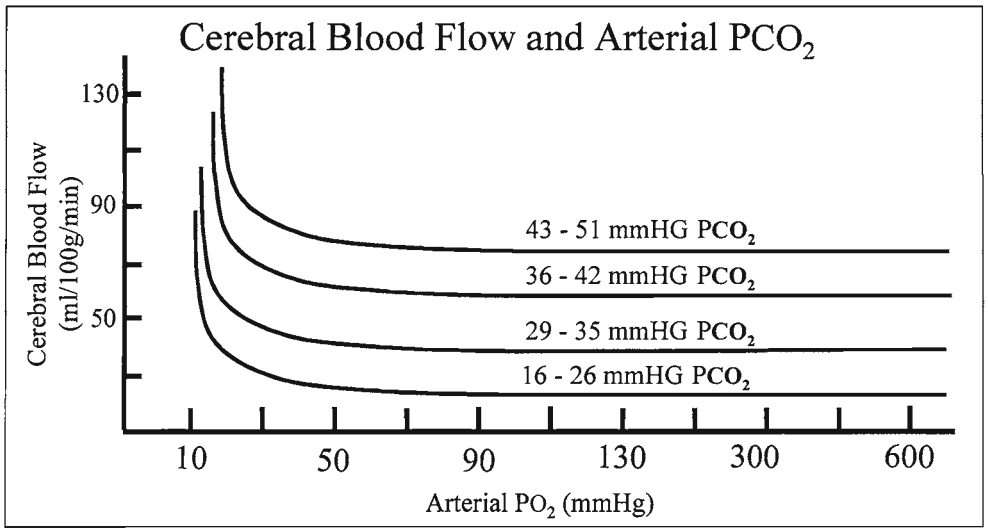

Figure 3. Relationship among arterial PO_2 , PCO_2 , and cerebral blood flow. (Modified from Lambertsen [6].)

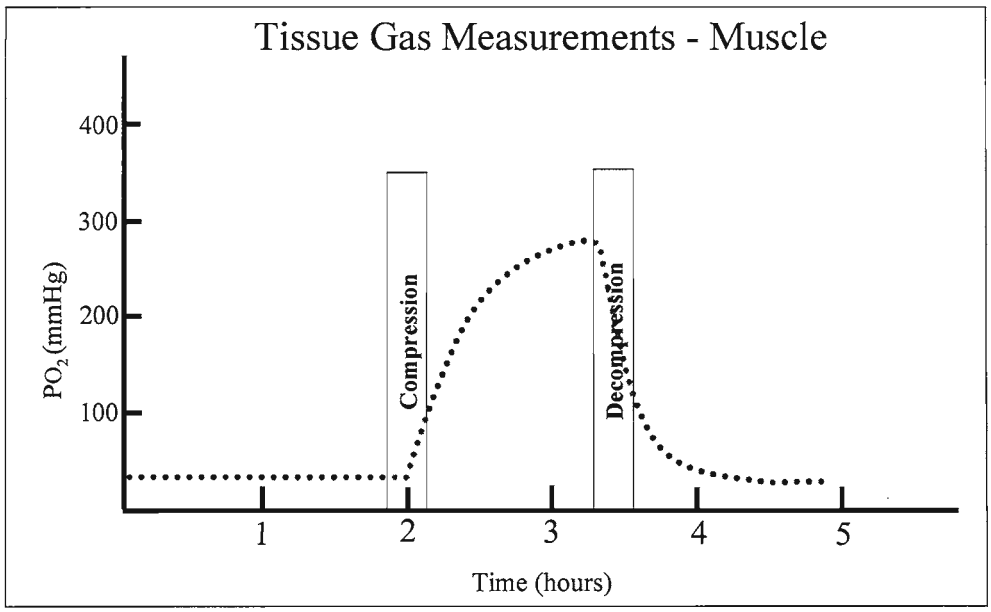

Figure 4. Muscle tissue oxygen and carbon dioxide, means and standard deviations, eight male volunteers. (Modified from C. H. Wells, J. E. Goodpasture, D. J. Horrigan & G. B. Hart [14].)

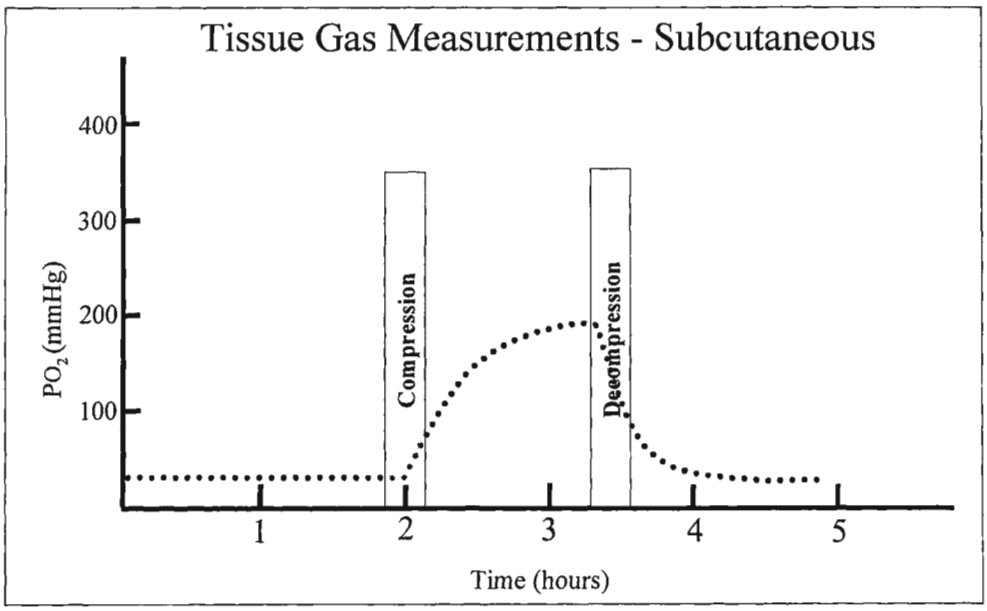

Figure 5. subcutaneous tissue oxygen, and carbon dioxide, means and standard deviations, eight male volunteers. (Modified from C. H. Wells, J. E. Goodpasture, D. J. Horrigan & G. B. Hart [14].)

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