Risks from Breathing Elevated Oxygen

Barbara E. Shykoff; Rees L. Lee

INTRODUCTION: Effects of breathing gas with elevated oxygen partial pressure (P_{O_2}) and/or elevated inspired oxygen fraction ($F_{I}O_2$) at sea level or higher is discussed. High $F_{I}O_2$ is associated with absorption problems in the lungs, middle ear, and paranasal sinuses, particularly if $F_{I}O_2 > 80\%$ and small airways, Eustachian tubes, or sinus passages are blocked. Absorption becomes faster as cabin altitude increases. Pulmonary oxygen toxicity and direct oxidative injuries, related to elevated P_{O_2}, are improbable in flight; no pulmonary oxygen toxicity has been found when $P_{O_2} < 55$ kPa [418 Torr; 100% O_2 higher than 15,000 ft (4570 m)]. Symptoms with P_{O_2} of 75 kPa [520 Torr; 100% O_2 at 10,000 ft (3050 m)] were reported after 24 h and the earliest signs at P_{O_2} of 100 kPa (760 Torr, 100% O_2 at sea level) occurred after 6 h. However, treatment for decompression sickness entails a risk of pulmonary oxygen toxicity. Elevated P_{O_2} also constricts blood vessels, changes blood pressure control, and reduces the response to low blood sugar. With healthy lungs, gas transport and oxygen delivery are not improved by increasing P_{O_2}. Near zero humidity of the breathing gas in which oxygen is delivered may predispose susceptible individuals to bronchoconstriction.

KEYWORDS: aircrew, atelectasis, pulmonary oxygen toxicity, tactical aircraft.

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To prevent hypoxia, military pilots are required to breathe oxygen-enriched gas when they fly at high cabin altitudes; supplemental oxygen is mandated for U.S. pilots at cabin altitudes above 10,000 ft (3050 m). Civilian pilots have a similar requirement; the U.S. Federal Aviation Administration requires oxygen breathing for pilots who are above 12,000 ft (3660 m) for more than 30 min or above 14,000 ft (4270 m) for any duration. Oxygen, delivered through a mask, can be carried on the aircraft as compressed gas or as liquid oxygen, or can be concentrated from the atmospheric air. Onboard oxygen concentrators supply a maximum oxygen fraction of about 94% because argon is also concentrated. While many concentrators always supply the maximum oxygen concentration possible for the operating conditions, others can be set for lower, controlled concentrations. Some aircraft breathing regulators supply the pilot's oxygen mask directly from their oxygen supplies, while others may dilute the supplied gas with cabin air to regulate the concentration. In general, U.S. Navy pilots fly with nominally 94% oxygen from an onboard concentrator or 100% oxygen from a compressed gas supply, but many U.S. Air Force aircraft provide a maximum of 60% oxygen for cabin altitudes up to 15,000 ft (4579 m).

Hypoxia represents a more immediate risk to pilots at altitude than does hyperoxia, but "more" is not necessarily "better" when oxygen is concerned. Hyperoxia is not acutely dangerous, but long-term breathing of hyperoxic gas carries risk. While generations of pilots have flown while breathing close to 100% oxygen, pilots are willing to put up with considerable discomfort to be allowed to fly. This brief literature review addresses the risks of oxygen breathing for pilots.

Adverse effects of breathing gas with elevated oxygen (O_2) can be grouped into physical effects (i.e., atelectasis), toxic effects, and other deleterious effects of oxygen (e.g., otherwise inappropriate vasoconstriction). Further, the low inspired humidity that accompanies oxygen delivery can exacerbate the physical and toxic responses.

The variable of importance for atelectasis is the fraction of oxygen in the inspired gas ($F_{I}O_2$). For all other effects, the oxygen partial pressure (P_{O_2}) is the critical quantity. P_{O_2} is the driving force for oxygen transfer (both into the blood in the lungs and into tissue in the periphery) and is a close approximation of the chemical activity of oxygen.

From the Naval Aerospace Medical Research Laboratory, Naval Medical Research Unit, Wright-Patterson Air Force Base, OH, USA.

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Address correspondence to: Barbara E. Shykoff, Ph.D., Naval Aerospace Medical Research Laboratory, 2624 Q St., Bldg. 851, Area B, Wright-Patterson AFB, OH 45433-7955, USA; shykoff@buffalo.edu.

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In gas, P_{O_2} is the pressure that would prevail if all other gas species were removed. (Dalton's Law states that the total pressure of a gas is the sum of the partial pressures of all components.) It is calculated as the fraction of oxygen present (number of oxygen molecules per total number of molecules in a given volume) multiplied by the ambient pressure. P_{O_2} is thus an index of the amount of oxygen available for any chemical process.

In liquid, P_{O_2} is a measure of dissolved oxygen, again an indicator of the amount of oxygen available for chemical processes. As Henry's Law states, the concentration of a gas species that dissolves in a liquid is proportional to the partial pressure of that species in the gas phase contacting the liquid. When a gas that contains oxygen and a liquid are in contact with each other, oxygen will move between the two until they are equilibrated. At equilibrium, in other words, when there is no net transfer between the phases, the P_{O_2} in the liquid is said to equal that in the gas. Thus, P_{O_2} in a liquid is defined as the P_{O_2} in a hypothetical gas in equilibrium with the liquid. Otherwise put, the P_{O_2} in the liquid is the concentration of dissolved gas divided by the Henry's Law constant for the gas. P_{O_2} differences, for example, blood to tissue or alveolar gas to pulmonary capillary blood, are the driving force for diffusive oxygen transfer.

GAS EXCHANGE

The rate of oxygen delivery to the tissues and brain is a function of local capillary oxygen partial pressure and blood flow, and the local tissue oxygen partial pressure, representing the oxygen dissolved in the blood, is in equilibrium with the hemoglobin oxygen saturation.

Ideal Lungs

Consider first an "ideal" lung in which alveolar gas is homogenous, blood flow to the lungs is well-distributed, and thus arterial oxygen partial pressure (P_aO_2) equals alveolar oxygen partial pressure (P_AO_2). P_AO_2 is related to but always less than the P_{O_2} of inspired gas (P_IO_2).

The alveolar gas equation[30,70] is derived from the premise that at steady state the amount of inert gas inhaled equals the amount of inert gas exhaled. If the gas inhaled is 100% oxygen, no inert gas is inhaled, and

$$P_AO_2 = P_IO_2 - P_ACO_2 \quad \text{Eq. 1.}$$

$$= F_IO_2 \cdot (P_T - P_W) - P_ACO_2 \quad \text{Eq. 2.}$$

$$= P_IO_2 - [\dot{V}CO_2/\dot{V}_A] \cdot (P_T - P_W) \quad \text{Eq. 3.}$$

where P_ACO_2 is alveolar carbon dioxide partial pressure, P_T is ambient (total, cabin) pressure, P_w is the partial pressure of water vapor in air saturated at body temperature, $\dot{V}CO_2$ is the rate of CO_2 release into lung gas from the blood, and $\dot{V}_A$ is the rate of alveolar ventilation, that is, the volumetric flow of fresh gas to the gas exchange zones of the lungs.

The same result (Eq. 1–4) is obtained if the respiratory ratio $R = 1$. By definition $R = \dot{V}CO_2/(\dot{V}O_2)$, where $\dot{V}O_2$ is the rate of oxygen uptake from lung gas into the blood. If the gas inhaled includes nitrogen, argon, or another inert component and steady state $R < 1$, the equation becomes more complicated in form.

$$P_AO_2 = P_IO_2 - P_ACO_2 \cdot [1-R]/R \quad \text{Eq. 4.}$$

$$= P_IO_2 - [\dot{V}CO_2/\dot{V}_A \cdot R] \cdot (P_T - P_W) \cdot [1 - F_IO_2(1-R)] \quad \text{Eq. 5.}$$

$$= P_IO_2 - [\dot{V}O_2/\dot{V}_A] \cdot (P_T - P_W) \cdot [1 - F_IO_2(1-R)] \quad \text{Eq. 6.}$$

The inhaled gas is assumed to be free of CO_2. All volumes here are expressed at standard temperature and pressure, dry (STPD). [STPD indicates that the volume is expressed at 0°C (273 K; 32°F), a pressure of 101.3 kPa (1 standard atmosphere, 760 Torr, 14.7 psia), and with no water vapor.] All gas fractions (F) are expressed on a dry gas basis, i.e., where $F_{O_2} + F_{CO_2} + F_{\text{inert gas}} = 1$, with the fraction of water vapor not included in the summation.

This equation in the several forms given above indicates that: 1) inhaled O_2 is diluted by CO_2 and by water vapor in the lungs; 2) that the amount of dilution with CO_2 depends on the ratio of metabolic rate (rate of oxygen consumption, $\dot{V}O_2$) to the volume and rate of breathing (alveolar ventilation, $\dot{V}_A$); and 3) that ambient pressure and inhaled oxygen fraction have effects individually, not only as the product of $P_IO_2 = F_IO_2 \cdot (P_T - P_w)$. Both P_ACO_2 and P_w are independent of ambient pressure; from Eq. 2 it is clear that they may limit P_AO_2 if P_T is low.

Hemoglobin oxygen saturation S_aO_2 is a nonlinear function of the P_{O_2} in the blood (**Fig. 1**). (The functional relationship is altered by abnormal hemoglobin molecules or by hemoglobin poisoned, for example, by carbon monoxide or cyanide.) The sigmoidal relationship indicates that little more oxygen can be taken up by hemoglobin once P_{O_2} exceeds about 100 Torr. For a person with a normal hemoglobin concentration, approximately 20 mL (STPD) of oxygen is bound to hemoglobin in each 100 mL of arterial blood when $P_AO_2 \geq 100$ Torr. Low hemoglobin concentration causes low oxygen-carrying

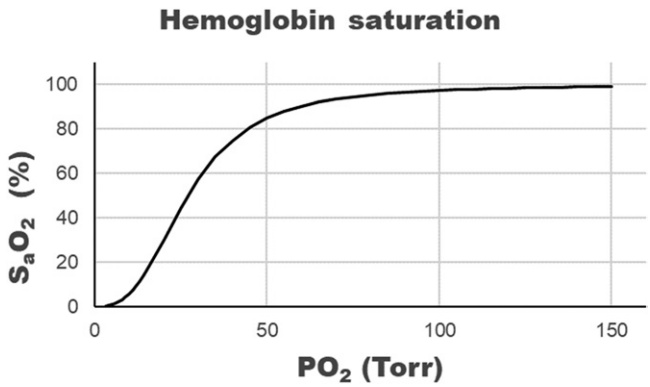

Fig. 1. A representative hemoglobin-oxygen saturation curve as given by the Hill equation (P_{50} = 27 Torr, Hill coefficient = 2.8).

capacity without changing the relationship between P_{O_2} and saturation.

If P_AO_2 is greater than approximately 100 Torr, only the amount of oxygen dissolved in blood can increase. The capacity for oxygen in solution in 100 mL of blood is 0.003 mL (STPD)/Torr. A fivefold increase in inhaled oxygen partial pressure leads to less than a 10% increase in the total volume of oxygen, dissolved and bound, contained in arterial blood. In someone with healthy lungs, the practical effects of hyperoxia on gas exchange are minimal.

Hemoglobin oxygen saturation affects CO_2 transport in the blood (the Haldane effect), with high hemoglobin oxygen saturation decreasing the sequestration of CO_2 in the blood and thus slightly increasing local P_{CO_2}. P_{CO_2} affects the hemoglobin saturation curve (the Bohr effect), with decreased P_{CO_2} increasing the affinity of hemoglobin for oxygen, and thus slightly decreasing the local P_{O_2} for a given oxygen content.

Heterogeneous Ventilation

Not all regions of the lung receive the same fraction of the air flow or of the blood flow. Each small region of the lung has its own P_AO_2 and its own fraction of blood flow which equilibrates with the gas. Regional pulmonary blood flow is sensitive to regional P_{O_2} and P_{CO_2}; particularly when blood vessels delivering blood to a region in which the P_{O_2} is lower constrict, redirecting the blood to better-ventilated zones. (Note that in response to hypoxia, while the systemic vasculature dilates, the pulmonary vasculature constricts.[46]) When P_IO_2 increases, even lung zones with low air flow see an increase in local P_AO_2, and the local "hypoxic pulmonary vasoconstriction" relaxes, causing a more-uniform distribution of blood flow in the lung. This results in better gas exchange in those lung regions, increasing the effective surface area for gas transfer in the lung and reducing the presence of regions in which only a small amount of gas is exchanged. However, in healthy lungs, thus presumably in aviators, the ratios of regional ventilation (air flow) to perfusion (blood flow) are similar throughout the lungs. (The lung bases are an exception, discussed below.) Elevated P_IO_2 has virtually no effect on gas exchange in healthy lungs.

The bases of even healthy lungs are prone to short-term airway closure at low lung volumes in some postures. Lung regions served by intermittently closed airways are at risk of complete collapse (atelectasis) if they contain 100% oxygen. If some regions of the lung receive no ventilation because of airway closure and/or atelectasis, any blood passing through those zones ("shunted") will have the P_{O_2} of venous blood. The P_aO_2 in the arterialized blood entering the left side of the heart is a volume average of the P_{O_2} from all zones of the lung. If the shunt fraction (fraction of total blood flow not undergoing gas exchange in the lungs) is large, systemic arterial P_{O_2} will be depressed and provision of even 100% oxygen in inspired gas will not increase it. S_aO_2 corresponds to systemic P_aCO_2.

In healthy aviators, increasing normobaric or hypobaric P_AO_2 above about 100 Torr cannot significantly improve gas exchange or oxygen transport. If airways have closed, for example, because of acceleration stress, increased oxygen partial pressure cannot improve arterial oxygenation.

ADVERSE PHYSICAL EFFECTS OF OXYGEN FRACTION: ATELECTASIS

Oxygen is readily absorbed into tissues because tissue metabolism consumes it. Thus, if a volume of gas that contains oxygen is enclosed in a poorly ventilated gas space in the body, the volume of contained gas will shrink as molecules of oxygen leave the space. If the gas is room air, the volume can shrink only to about 80% of its initial size, leaving nitrogen behind. However, if the gas is 100% oxygen, the entire volume can be absorbed, causing, for example, the beneficial disappearance of an oxygen gas bubble, a reduction of pressure in a rigid space sufficient to draw liquid from the surrounding tissues and to induce pain, or the collapse of a pliant structure to the point where the surrounding tissues touch.

Gas Bubbles

Oxygen prebreathing before decompression provides a degree of protection against decompression sickness by displacing dissolved nitrogen from tissue. Although oxygen bubbles may form in blood and tissues as a result of tissue oxygen supersaturation, particularly in the presence of residual nitrogen,[23] metabolism will clear them fairly rapidly. Bubbles still may begin a cascade of adverse effects[42] caused by short-term capillary obstruction and tissue-bubble interface activity—for example, platelet aggregation and endothelial damage[7,47]—while they last. For a review of the effects of microbubbles in the circulation, see Barak et al.[7]

Rigid Space

When a large fraction of oxygen is trapped in the middle ear, the resulting decrease in pressure as the gas is absorbed causes acute pain, fluid leakage from tissue into the gas space, eardrum deformation, and altered hearing. The oxygen absorption causes delayed otic barotraouma, effectively an ear "squeeze" up to 24 h after the exposure. This phenomenon may be called aural atelectasis, middle ear absorption syndrome, delayed ear block, or oxygen ear. The reduced pressure in the middle ear may be relieved by the same ear-clearing maneuvers used during changes in altitude as long as they are initiated before the pressure difference becomes severe enough to cause fluid leakage. Even with frequent ear-clearing after flight, delayed ear barotraouma does occur.[39]

Pliant Structure

When gas with a large fraction of oxygen is trapped in a region of the lung, that region will collapse as the oxygen is absorbed, causing absorption atelectasis. Symptoms of atelectasis include cough and a sense of chest tightness or the inability to inhale deeply,[68] a feeling that is similar to that of lying on one's chest on a hard surface. This is a common side effect of surgery[26] when patients are ventilated with high oxygen-fraction gas.[34,53,54] The common factors between the surgical and the aviation setting are healthy lungs, the closure of small airways serving lung regions filled with gas with a high oxygen fraction,

and limited tidal volume that does not reopen the closed airways until the gas has had time to be absorbed. Although reduction in vital capacity from closed airways alone is easy to clear immediately after its onset,[68] after total collapse of alveoli or after atelectasis has persisted for several hours, considerable pressure is needed to separate the liquid-liquid interface between the membranes.[24]

Absorption atelectasis occurs only if parts of the lungs are poorly ventilated or not ventilated at all because of closure of small airways. Airway closure is common when lung gas volume is reduced, for example, by a restrictive vest;[14] when blood is translocated into the chest, for example, during head-out water immersion;[6] or on inflation of an antigravity ensemble.[31] For some individuals, airway closure is normal in a supine posture,[40,72] or at the base of the lungs even when seated,[40] because of movement of blood into the chest or compression of the lowest parts of the lungs by the abdomen.

Occasional deep breaths can reopen closed airways before the regions behind them have collapsed completely. Alveolar stretch also renews the film of lung surfactant, the detergent-like substance that helps to stabilize alveoli by reducing surface tension, on alveolar membranes.[26] Thus, the inability to take deep breaths promotes atelectasis.

Altitude increases the need for anticlosure maneuvers like deep breaths. As total pressure decreases, a volume of oxygen represents fewer molecules than it does at ground level, and the rate of volumetric absorption of oxygen behind closed airways increases.[24,52]

Acceleration atelectasis[68] is an exacerbation of absorption atelectasis by compression of the bases of the lungs by the extra weight of blood and tissue during acceleration and anti-G straining that pushes the diaphragm up into the chest to close airways. The weight of flight equipment, flow limitations of the life support system, and repeated G maneuvers prevent deep breaths that can open the closed airways. When the aviator has been breathing nearly 100% oxygen, absorption atelectasis begins. High cabin altitude means rapid loss of trapped gas volume.

Even in healthy people, atelectasis can remove significant fractions of the lungs from gas exchange. For example, Balldin et al.[6] found that 2 h of water immersion to the chin reduced vital capacity (the volume of gas between maximum inspiration and maximum expiration, that is, the changeable lung gas volume) by about 8% when subjects breathed air, but by 22% when the subjects breathed 100% oxygen, a difference the authors attributed to absorption atelectasis.

Atelectic regions of the lung cannot contribute to gas exchange because they do not contain alveolar gas. Any blood flow to them is part of the shunt fraction, the fraction of the cardiac output (blood flow from the heart) that bypasses the gas exchange regions of the lungs. A shunt fraction of 10% means that 90% of the blood is oxygenated, probably to 100% saturation, but 10% is not. The arterial blood leaving the heart is a mixture of the two. For example, if the content of oxygen in the blood leaving the lungs is 20 mL (STPD)/100 mL and that in the mixed venous blood reaching the lungs is 15 mL/100 mL, with a 10% shunt the arterial content will be $(0.9 \times 20) + (0.1 \times 15) = 19.5$ mL/100 mL. Paradoxically, high oxygen fraction in the breathing gas sometimes can reduce the amount of oxygen available to the brain and tissues by promoting atelectasis and, hence, shunt.

Only small fractions of inert gas need to be present in breathing gas to prevent total alveolar collapse, though the necessary inert gas fractions are better established in the clinical setting than for aviation. During or after surgery, gas with 80% or less oxygen has been suggested as sufficient to significantly reduce atelectasis,[2,28] with the incidence and severity of atelectasis after anesthesia similar for 80% or 30% oxygen.[2] Rothen et al.[53] documented an effective average shunt fraction of 9.8% of cardiac output in six patents ventilated with 100% oxygen, but an average shunt fraction of only 3.2% in six people ventilated with 30% oxygen. Those authors also showed that atelectasis can be cleared in the long term by lung reinflation with 40% oxygen, while it rapidly reappears after similar reinflation with 100% oxygen. At altitude in one individual, 5% nitrogen (95% oxygen) was shown to prevent atelectasis,[25] but a case study of one individual cannot be generalized very far.

Absent clear evidence of the amount of inert gas needed to prevent absorption atelectasis in flight, the fraction of oxygen in the breathing gas should be as low as possible commensurate with maintaining P_AO_2. Ernsting[29] recommended that the target should be a P_AO_2 of 103 Torr, the P_AO_2 of normal breathing at sea level (approximately 100 Torr, as listed above), which requires that P_IO_2 is approximately 150 Torr. An exception is that a higher oxygen fraction may be necessary to keep P_aO_2 greater than or equal to 30 Torr in the event of rapid decompression of the cabin at high altitude;[29] the oxygen fraction thus should be at least $[30/P_{altitude}]$, where $P_{altitude}$ is the pressure outside the aircraft, measured in Torr. Most tactical aircraft maintain a maximum 5 psi (approximately 260 Torr) pressure differential across the hull, but keep the cabin pressurized to an equivalent 8000-ft (2440-m) altitude (about 564 Torr) until the aircraft is high enough to exceed that differential.

Pilots who must breathe high oxygen fractions should be encouraged (and able) to take very deep breaths periodically, particularly at high altitude and after landing. Deliberate coughing may also help to open closed airways. Pilots should also be encouraged to "clear" their ears frequently during and after flight

ADVERSE EFFECTS OF ELEVATED Po_2

Oxygen Toxicity

Oxygen toxicity is not a serious issue in aviation. Pilots at cabin altitude below 18,000 ft (5490 m) who breathe nearly 100% oxygen are exposed to Po_2s that could provoke pulmonary oxygen toxicity, but toxic effects at those Po_2s require exposures longer than a typical sortie. Central nervous system oxygen toxicity does not occur under normo- or hypobaric conditions. The greatest risk of pulmonary oxygen toxicity for pilots comes from potential postflight treatments at ground level, whether with normobaric oxygen for a prolonged period[17,19,55] or with

hyperbaric oxygen.[61,66] Nonetheless, pulmonary oxygen toxicity caused by oxygen treatment is self-limiting and self-correcting.

Central nervous system oxygen toxicity produces neurological symptoms the most severe of which is convulsion. The threshold for any concern in diving (submerged) is an inspired Po_2 of 1.3 atm[48] (approximately 130 kPa; 990 Torr), with a somewhat higher threshold before seizures have been recorded.[43] In dry exposures (hyperbaric treatment chambers), seizures are rare; the seizure rate with inspired Po_2s of 2 to 2.5 atm (approximately 200 to 250 kPa, 1580 to 1980 Torr) for 60 to 120 min is only 0.03%.[33]

Pulmonary oxygen toxicity begins with airway symptoms and some degradation of pulmonary function. If left unchecked, it can progress over the course of hours or days of continuous exposure, depending on the Po_2, to serious lung injury and even death. Data indicate that Po_2 of 0.55 atm (420 Torr) is safe for at least 24 h of continuous exposure;[16,17] there is no oxygen toxicity risk from flying while breathing 100% oxygen at cabin altitudes of 18,000 ft (5490 m) or higher. Po_2 of 0.75 atm [570 Torr, 100% O_2 below 8000 ft (2440 m)] for 24 h will provoke symptoms in about half of those who breathe it.[17] There have been no measurements between those values.

Symptoms of pulmonary oxygen toxicity are initially those of a tracheo-bronchitis: a burning or aching sensation in the central chest that is made worse by rapid or deep inhalation; cough; chest tightness, breathlessness, or shortness of breath; and sometimes hoarseness.[16,43] Those with even low levels of pulmonary oxygen toxicity also often report unreasonable fatigue and exercise intolerance for up to days after the oxygen exposure.[27,59,60] The fatigue is probably not related to pulmonary injury—there is no correlation with any indices of pulmonary function[59,60]—but rather a separate manifestation of oxygen toxicity.

Pulmonary oxygen toxicity with Po_2 from about 75 kPa (0.75 atm; 570 Torr) to about 160 kPa (1.6 atm) begins in the lungs, with an inflammatory process following the initial oxygen insult, while the nervous system is implicated in pulmonary oxygen toxicity after exposure to high, hyperbaric Po_2s ($>$ 200 kPa; 2 atm; 1520 Torr).[21] For the lower Po_2s, pulmonary oxygen toxicity is somewhat analogous to sunburn; an inflammatory injury follows the initial damage, and the injury exists before the symptoms and signs are apparent. The first attack, presumably by reactive oxygen species, damages the pulmonary capillary endothelium, that is, the lining of the small gas-transfer blood vessels in the lung. The resulting immune response causes further damage, leading to leaks from the blood into the interstitial spaces (the spaces between the cells) with resultant reduction in gas exchange efficiency. Lung volume changes caused by interstitial edema are within the error of measurement of vital capacity measurements,[59] though the fluid cuffing of airways may decrease forced expired volume in 1 s (FEV_1). If the injury progresses, liquid will leak into the alveoli themselves, where alveolar edema can be measured as a decrease of vital capacity, and severe edema causes appreciable shunt. Continued oxygen insult will lead to what amounts to scarring and permanent thickening of the alveolo-capillary membrane as fibrous material is laid down. Continued oxygen exposure can lead to death, an endpoint reached in many animal studies.

Early animal studies had suggested that pulmonary oxygen toxicity developed faster with 100% oxygen than with the equivalent oxygen partial pressure in the presence of inert gas,[27] perhaps because decreases in vital capacity are used both to indicate the presence of pulmonary oxygen toxicity and to indicate the presence of atelectasis. Researchers who find deleterious effects of 100% oxygen at ground level unfortunately often suggest that they have found a danger for pilots. However, three sets of studies provide evidence that pulmonary oxygen toxicity is related to oxygen partial pressure (Po_2) and not to oxygen fraction (Fo_2). 1) Comroe et al.[17] compared 34 subjects who breathed 100% oxygen at normal atmospheric pressure to 10 who breathed 50% oxygen at normal pressure and 6 who breathed 100% oxygen in an altitude chamber at 18,000 ft (5490 m, total pressure 50 kPa, 0.5 atm, 380 Torr). Those for whom inspired Po_2 was 50 kPa had no symptoms regardless of whether the gas was 50% or 100% oxygen, while 30 of 34 for whom Po_2 was 1 atm complained of substernal pain. 2) A hyperbaric chamber exposure to air at 5 atm[27] (Po_2 approximately 1 atm) produced results indistinguishable from those after several studies conducted at atmospheric pressure with 100% oxygen. 3) A series of three underwater exposures to $Po_2 = 130$ kPa (1.3 atm, 1088 Torr),[62–64] one at a total pressure of 130 kPa with 100% oxygen, one at a total pressure of 160 kPa (1.6 atm) with 80% oxygen, and one at a depth of 50 ft (15 m) with a rebreather UBA that controls to $Po_2 = 1.3$ atm, produced indistinguishable signs and symptoms of pulmonary oxygen toxicity.

Pulmonary oxygen toxicity was not evident in any of 13 reports of exposures to Po_2 less than or equal to 0.55 atm.[16] Note, though, that although exposure to Po_2 of 50 kPa (0.5 atm; 380 Torr)[17] for 24 h caused no symptoms in 16 subjects, it may have reduced vital capacity by a meaningful amount in one person, as read and interpreted from the figure in the paper.

Inspired Po_2 does not need to be much higher than 55 kPa (0.55 atm; 418 Torr; 8.1 psi) to be toxic to the lungs after prolonged exposures. After 24 h, Po_2 of 75 kPa provoked symptoms in five of nine subjects.[17] That exposure also caused a meaningful decrease in vital capacity in one or perhaps two individuals, again as read and interpreted from the figure in the paper. Pulmonary oxygen toxicity with Po_2 from 83 to 89 kPa (0.83 to 0.98 atm) has been reported by five other groups after exposures of 24 h or more, as reviewed by Clark and Lambertsen.[16] Since that review, Davis et al.[19] reported evidence of alveolo-capillary leaks after 17 h exposure to Po_2 of 95 kPa (0.95 atm). Additionally, Sachner et al.[55] showed tracheitis and impaired mucociliary transport in 10 subjects after only 6 h exposure to Po_2 of 95 kPa (720 Torr).

Exposures to high oxygen fraction with Po_2 less than 55 kPa (0.55 atm, 473 Torr), that is, to 100% oxygen at altitudes greater than 18,000 ft (5490 m), appear to be free of pulmonary oxygen toxicity,[24] though not of ear and nasal passage effects.[17,35,45] Multiday exposures to 100% oxygen at low total pressure may cause other problems; at a total pressure of 190 Torr

(34,000 ft/10,360 m), 17 d exposure to 100% O_2 provoked symptoms—perhaps from the altitude—in some of the eight subjects participating.[45]

Increased Oxidative Stress

Oxidative stress, usually from the action of reactive oxygen species in the body, has been associated with many disease states and with the process of aging. The concern that exposure to elevated oxygen levels could increase overall disease risk is valid. However, most, if not all, studies of increased oxidative stress after exposure to oxygen are conducted with 100% oxygen at the laboratory altitude, that is, with P_IO_2 close to 100 kPa (760 Torr). They therefore represent a much higher Po_2 than that encountered by pilots at altitude. The risk of increased oxidative stress for pilots breathing oxygen at altitude is minimal. For those breathing 100% oxygen at low altitude, duration of exposure is probably important, but data are hard to find.

OTHER EFFECTS OF ALTERED Po_2

Carotid Body

Ventilatory control. Elevated Po_2 progressively depresses some of the functions of the carotid bodies. In cats, arterial Po_2 greater than 200 Torr (100% oxygen below 32,000 ft/9750 m cabin altitude) eliminates carotid body chemoreceptor output.[38] The partial pressure for this effect in humans is similar but less clearly defined. Elevated Po_2 causes a time lag between changes in arterial blood and the respiratory responses[18] that can occur only after the change communicates across the blood-brain barrier to the central chemoreceptors.

Blood sugar control. The response to hypoglycemia, particularly the release of adrenalin and glucagon that counteract it, has been shown to be depressed in people breathing 100% oxygen at atmospheric pressure.[73] Although no hypoglycemic incidents have been documented in flight, pilots flying at relatively low cabin altitudes for extended periods while breathing high fractions of oxygen should be encouraged to eat a balance of protein, fat, and complex carbohydrate before and during flight to maintain glycemic control.

Cardiovascular variables. Relative to breathing air at atmospheric pressure, because of hyperoxic vasoconstriction, breathing 100% O_2 at atmospheric pressure causes the baroreflex to decrease heart rate further in response to an elevation in blood pressure.[65] It also increases the blood pressure response to isometric exercise and to the presence of metabolites in local tissue beds (e.g., blood flow in a limb reduced by a restriction after exercise) even though lactate production decreases.[36] However, the carotid body chemoreceptors influence arterial resistance when they are active,[32] and elevated Po_2 progressively decreases muscle sympathetic nervous activity,[58] relaxing the blood vessels within muscle.

Hyperoxic Vasoconstriction

Elevated arterial Po_2 with constant arterial Pco_2 stimulates systemic vasoconstriction, that is, narrowing of the resistance arteries. Simultaneously, blood vessels within muscles relax as chemoreceptor activity decreases. The overall vasoconstriction increases blood pressure until reflex systems reduce heart rate to normalize blood pressure. A progressive increase in oxygenation from normal to mildly hyperoxic (transcutaneous Po_2 from 20 to 60 kPa; approx.150 to 460 Torr) causes a progressive increase in vascular resistance and decrease in stroke volume of approximately 13% in supine subjects.[5]

Blood flow to the brain stays constant for a wide range of blood pressures, a phenomenon known as cerebral autoregulation. However, the magnitude of that constant flow is modified by Pco_2 and by hypoxia[10,75,76] and, according to many[1,13,37] but not all[76] investigators, by hyperoxia.[41,71] At any blood pressure within the range where flow is controlled, hypercapnia or hypoxia increase brain blood flow, while hypocapnia or hyperoxia decrease it. Some reports indicate that oxygen delivery to the brain is unaffected by 100% oxygen at sea level because the vasoconstriction is balanced by the small increase in blood oxygen content.[13,37] Other experiments indicate that the constriction is great enough that oxygen delivery decreases.[71] Some variability in results is probably a result of differing changes in P_aCO_2 across experiments, and some because the signals that are obtained may vary with P_aO_2.[13]

Dynamic autoregulation (i.e., rapid response to control blood flow after a sudden change in blood pressure) is impaired by elevated Pco_2,[22] but not by elevated Po_2.[49] Laboratory results with 100% oxygen do not necessarily translate to higher altitude where Po_2 is considerably less than 760 Torr; Po_2 less than about 70 kPa (532 Torr) may not significantly lower brain blood flow.[1,41]

In mucosal tissues which are accessible for viewing,[44] and presumably in other tissues as well, both the number of open capillaries and the diameter of those that are open decreases with hyperoxia relative to normoxia. Consequently, the diffusion distance increases for oxygen, CO_2, and all other chemicals transported in the blood, and hyperoxia can paradoxically reduce oxygen availability within tissue.

Hyperoxic Hyperventilation

At rest, hyperventilation (lowered P_aCO_2) is often reported during hyperoxia, though 8 h with P_aO_2 held at 300 Torr showed minute ventilation not significantly different from control and P_aCO_2 only 2.2 Torr lower.[51] One possible mechanism is that the graded reduction brain blood flow caused by hyperoxia slows the removal of carbon dioxide (CO_2) from the central chemoreceptors. An elevated Pco_2 at the central chemoreceptors would increase respiratory minute ventilation until the effects on P_aCO_2 balanced the effects of vascular restriction.

Additional mechanisms have been proposed for hyperoxic hyperventilation.[11,20] Independent of the mechanism that increases ventilation, though, chemoreceptor response to the lowered arterial Pco_2 limits the increase in ventilation. Resting minute ventilation increases and P_aCO_2 decreases only slightly.[11] The hypocapnia is not sufficient to be expected to cause cognitive changes[50] or any significant shifts in hemoglobin oxygen affinity in either arterial or venous blood.

Nonphysiological Causes of Hyperventilation

Hyperventilation, by definition, causes hypocapnia. Although hyperventilation for any reason other than hyperoxia is not an effect of oxygen, symptoms of hypocapnia can be mistaken for symptoms of hypoxia. Hyperventilation could result from any phenomenon that induces people to breathe deeper and/or faster because they feel short of breath. Physiologically significant hyperventilation can be stimulated by an expiratory threshold load of 15 cm H_2O or more[9] or by positive pressure breathing of similar magnitude.[12] Like hyperoxia, hypocapnia reduces brain blood flow. This could lead to a local accumulation of CO_2 in the brain despite abnormally low P_aCO_2 and, thus, to a paradoxical increase in the drive to breathe until chemoreceptor response overcomes it. Spontaneous breathing remains high for several breaths after active hyperventilation ostensibly ends[69] and, although other mechanisms are certainly also involved, the interactions of brain blood flow and chemoreception may play a role. Elevated inspired PO_2 which suppresses carotid body chemoreception and damps central chemoreception may prolong the elevated respiratory drive; no studies of this "afterdischarge"[69] during sustained hyperoxia were found.

Hypoxic hyperventilation. Note that the healthy ventilatory response to hypoxia is hyperventilation.[70] Eqs. 1, 4, and 5 indicate that a decrease in P_ACO_2 yields an increase in P_AO_2. An additional advantage is that decreased P_aCO_2 increases hemoglobin affinity for oxygen, permitting higher S_aO_2 for a given P_AO_2. Since the hyperventilatory response begins when arterial saturation drops, the increased affinity favors loading of oxygen onto arterial blood in the lungs. At the tissue, local CO_2 will still lower the affinity relative to that in arterial blood to improve oxygen delivery to tissues, though perhaps not to normoxic baseline.

During hypoxic exposures as ventilation increases, respiratory CO_2 washout greatly exceeds metabolic CO_2 production, and the respiratory ratio R increases above 1.[30] Once the P_ACO_2 stabilizes at the value corresponding to the new ventilatory rate, the ratio will once again match that of the metabolism.

Although hyperventilation can cause symptoms and loss of function, at least some measures of brain performance are normal at a P_ACO_2 of 30 Torr.[50] Mentally functional climbers breathing air on Mt. Everest had P_ACO_2 from 11 Torr at 19,850 ft (6050 m) down to 7.5 Torr at the summit.[74] At high altitude, exercise performance is greatest in those with high hypoxic ventilatory responses.[56] It can be argued that adequate brain and tissue PO_2 takes precedence over concerns for low P_aCO_2.

Oxygen Delivery at Low Humidity Predisposes to Increased Airway Reactivity

All current tactical aircraft deliver breathing gas at near-zero relative humidity. Very dry gas is a known airway irritant which can induce bronchoconstriction (that is, narrowing of the large to medium airways as a result of smooth muscle contraction) in susceptible individuals.[4,67] While personnel with diagnosed asthma are excluded from flight training, objective screening is not standard in the U.S. Navy or U.S. Air Force as it is in other air forces.[57] As a result, personnel with asymptomatic reactive airway disease may become pilots. Approximately 7–8% of the U.S. population has some form of asthma or reactive airways disease.[15] This percentage is not significantly different among the young adults of the active duty population.[3,8] When exposed to the low humidity environment of tactical aviation, susceptible individuals may develop obstructive pulmonary function changes. Bronchoconstriction may manifest as shortness of breath, chest tightness, and/or cough. Although this is not an oxygen effect, it may be confused with one, and it potentially contributes to gas trapping in the lung, the first step toward absorption atelectasis when F_IO_2 is high. Additionally, the drying of mucous membranes predisposes to sinus and middle ear gas entrapment.

IN SUMMARY

- The composition of alveolar gas at steady state can be estimated using the alveolar gas equation. The variables involved are P_ACO_2 and respiratory ratio R. These are related directly to metabolic rate and alveolar minute ventilation.
- Absorption atelectasis is a risk for anyone breathing gas with an oxygen fraction in excess of about 80%. Acceleration atelectasis is an absorption phenomenon started when acceleration causes airway closure. Trapped volume decreases faster at altitude than at sea level. Frequent, very deep breaths could be protective of the lungs, and "ear clearing" maneuvers can reduce middle ear problems. These maneuvers should be recommended both at altitude to maintain gas volume and on resumption of air breathing to add nitrogen to the spaces.
- In healthy lungs, no gas exchange advantage is obtained by increasing P_AO_2 above about 150 Torr, and 103 Torr remains a valid minimum. As a first approximation, this suggests that the supplied FO_2 should target the higher of 150 P_{cabin} or 30 $P_{altitiude}$, where both pressures are measured in Torr. Lower inspired oxygen fractions are associated with lower risks of atelectasis manifested as postflight cough and lower risk of delayed otic barotrauma.
- Toxic chemical effects of oxygen are unexpected if $P_IO_2 <$ 380 Torr (0.5 atm, 50 kPa, 100% O_2 at and above 18,000 ft/5490 m). (Note point 2: absorption atelectasis is a risk with 100% O_2 at any altitude.) Toxic effects of oxygen at lower altitudes are not expected unless exposure duration is long, but early, self-correcting problems have been noted after 6 h with 100% oxygen on the ground. Oxygen toxicity is not a serious concern for aviators.
- Carotid body chemoreceptor function is decreased by high P_aO_2 and is probably absent when $P_aO_2 > 200$ Torr (100% O_2 below about 28,000 ft/8530 m). Pilots breathing oxygen at these altitudes may show altered control of CO_2 levels and may also compensate poorly for hypoglycemia. Heart rate and blood pressure control may be altered. This is another reason that inspired oxygen fraction in excess of the values necessary for gas exchange increases risk.
- Low humidity of breathing gases may provoke bronchoconstriction in susceptible individuals.

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Authors and affiliations: Barbara E. Shykoff, M.Sc.E., Ph.D., Naval Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH, USA, and Rees L. Lee, B.S., M.D., Force Surgeon, Commander Naval Surface Force Atlantic, Norfolk, VA, USA.

REFERENCES

1. Ainslie PN, Ogoh S, Burgess K, Celi L, McGrattan K, et al. Differential effects of acute hypoxia and high altitude on cerebral blood flow velocity and dynamic cerebral autoregulation: alterations with hyperoxia. J Appl Physiol. 2008; 104(2):490–498.
2. Akça O, Podolsky A, Eisenhuber E, Panzer O, Hetz H, et al. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. Anesthesiology. 1999; 91(4):991–998.
3. Al-Hazmi M, Wooldrage K, Anthonisen NR, Becklake MR, Bowie D, et al. Airflow obstruction in young adults in Canada. Can Respir J. 2007; 14(4):221–227.
4. Anderson SD, Davidskas E. The mechanism of exercise-induced asthma is…. J Allergy Clin Immunol. 2000; 106(3):453–459.
5. Bak Z, Sjöberg F, Rousseau A, Steinvall I, Janerot-Sjöberg B. Human cardiovascular dose–response to supplemental oxygen. Acta Physiol (Oxf). 2007; 191(1):15–24.
6. Balldin UI, Dahlbäck GO, Lundgren CE. Changes in vital capacity produced by oxygen breathing during immersion with the head above water. Aerosp Med. 1971; 42(4):384–387.
7. Barak M, Nakhoul F, Katz Y. Pathophysiology and clinical implications of microbubbles during hemodialysis. Semin Dial. 2008; 21(3):232–238.
8. Bar Dayan Y, Elishkevits K, Goldstein L, Goldberg A, Fichler M, et al. Screening for common respiratory diseases among Israeli adolescents. Can Respir J. 2004; 11(4):298–300.
9. Barrett J, Cerny F, Hirsch JA, Bishop B. Control of breathing patterns and abdominal muscles during graded loads and tilt. J Appl Physiol. 1994; 76(6):2473–2480.
10. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. J Physiol. 2011; 589(Pt. 12):3039–3048.
11. Becker HF, Polo O, McNamara SG, Berthon-Jones M, Sullivan CE. Effect of different levels of hyperoxia on breathing in healthy subjects. J Appl Physiol. 1996; 81(4):1683–1690.
12. Bishop B, Hirsch J, Thursby M. Volume, flow, and timing of each breath during positive pressure breathing in man. J Appl Physiol. 1978; 45(4):495–501.
13. Bulte DP, Chiarelli PA, Wise RG, Jezzard P. Cerebral perfusion response to hyperoxia. J Cereb Blood Flow Metab. 2007; 27(1):69–75.
14. Caro CG, Butler J, DuBois AB. Some effects of restriction of chest cage expansion on pulmonary function in man: an experimental study. J Clin Invest. 1960; 39(4):573–583.
15. Centers for Disease Control and Prevention. Asthma in the U.S. CDC Vital Signs. 2011; [Accessed March 2018]. Available from https://www.cdc.gov/vitalsigns/asthma/index.html.
16. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. Pharmacol Rev. 1971; 23(2):37–133.
17. Comroe JH, Dripps RD, Dumke PR, Deming M. Oxygen toxicity: the effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. JAMA. 1945; 128(10):710–717.
18. Dahan A, DeGoede J, Berkenbosch A, Olievier IC. The influence of oxygen on the ventilatory response to carbon dioxide in man. J Physiol. 1990; 428(1):485–499.
19. Davis WB, Rennard SI, Bitterman PB, Crystal RG. Pulmonary oxygen toxicity — early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med. 1983; 309(15):878–883.
20. Dean JB, Mulkey DK, Henderson RA, Potter SJ, Putnam RW. Hyperoxia, reactive oxygen species, and hyperventilation: oxygen sensitivity of brain stem neurons. J Appl Physiol. 2004; 96(2):784–791.
21. 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; 293(1):L229–L238.
22. Dineen NE, Brodie FG, Robinson TG, Panerai RB. Continuous estimates of dynamic cerebral autoregulation during transient hypocapnia and hypercapnia. J Appl Physiol. 2010; 108(3):604–613.
23. Donald KW. Oxygen bends. J Appl Physiol. 1955; 7(6):639–644.
24. DuBois AB, Hyde RW, Hendler E. Pulmonary mechanics and diffusing capacity following simulated space flight of 2 weeks duration. J Appl Physiol. 1963; 18(4):696–698.
25. DuBois AB, Turaids T, Mammen RE, Nobrega FT. Pulmonary atelectasis in subjects breathing oxygen at sea level or at simulated altitude. J Appl Physiol. 1966; 21(3):828–836.
26. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005; 102(4):838–854.
27. Eckenhoff RG, Dougherty JH Jr, Messier AA, Osborne SF, Parker JW. Progression of and recovery from pulmonary oxygen toxicity in humans exposed to 5 ATA air. Aviat Space Environ Med. 1987; 58(7):658–667.
28. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration Induction of general anesthesia. Anesthesiology. 2003; 98(1):28–33.
29. Ernsting J. Physiological requirements for advanced oxygen systems. In: Ernsting J, Miller RL, editors. Advanced oxygen systems for aircraft, chapter 5. Neuilly-Sur-Seine (France): AGARD; 1996. AGARD-AG-286.
30. Fenn WO, Rahn H, Otis A. A theoretical study of the composition of alveolar air at altitude. Am J Physiol. 1946; 146(5):637–653.
31. Grönkvist M, Bergsten E, Eiken O, Gustafsson PM. Inter- and intraregional ventilation inhomogeneity in hypergravity and after pressurization of an anti-G suit. J Appl Physiol. 2003; 94(4):1353–1364.
32. Guyenet PG. Neural structures that mediate sympathoexcitation during hypoxia. Respir Physiol. 2000; 121(2–3):147–162.
33. Hampson N, Atik D. Central nervous system toxicity during routine hyperbaric oxygen therapy. Undersea Hyperb Med. 2003; 30(2):147–153.
34. Hedenstierna G, Edmark L. Mechanisms of atelectasis in the perioperative period. Best Pract Res Clin Anaesthesiol. 2010; 24(2):157–169.
35. Herlocher JE, Quigley DG, Behar VS, Shaw EG, Welch BE. Physiologic response to increased oxygen partial pressure 1: clinical observations. Aerosp Med. 1964; 35(7):613–618.
36. Houssière A, Najem B, Cuylits N, Cuypers S, Naeije R, van de Borne P. Hyperoxia enhances metaboreflex sensitivity during static exercise in humans. Am J Physiol Heart Circ Physiol. 2006; 291(1):H210–H215.
37. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest. 1948; 27(4):484–492.
38. Lahiri S, DeLaney RG. Relationship between carotid chemoreceptor activity and ventilation in the cat. Respir Physiol. 1975; 24(3):267–286.
39. Landolfi A, Autore A, Torchia F, Ciniglio Appiani M, Morgagni F, Ciniglio Appiani G. Ear pain after breathing oxygen at altitude: prevalence and prevention of delayed barotrauma. Aviat Space Environ Med. 2010; 81(2):130–132.
40. Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on "airway closure" in man. J Appl Physiol. 1970; 28(4):448–451.
41. MacDonald ME, Berman AJL, Mazerolle EL, Williams RJ, Pike GB. Modeling hyperoxia-induced BOLD signal dynamics to estimate cerebral blood flow, volume and mean transit time. Neuroimage. 2018; 178:461–474.

42. Malkevich N, McCarron RM, Mahon RT. Decompression from saturation using oxygen: its effect on DCS and RNA in large swine. Aviat Space Environ Med. 2010; 81(1):15–21.
43. Manning EP. Central nervous system oxygen toxicity and hyperbaric oxygen seizures. Aerosp Med Hum Perform; 2016; 87(5):477–486.
44. Milstein DMJ, Helmers R, Hackmann S, Belterman CNW, van Hulst RA, de Lange J. Sublingual microvascular perfusion is altered during normobaric and hyperbaric hyperoxia. Microvasc Res. 2016; 105:93–102.
45. Morgan TE Jr, Ulvedal F, Cutler RG, Welch BE. Effects on man of prolonged exposure to oxygen at a total pressure of 190 mmHg. Brooks Air Force Base (TX): USAF School of Aerospace Medicine, Aerospace Medical Division; 1963.
46. Moudgil R, Michelakis ED, Archer SL. Hypoxic pulmonary vasoconstriction. J Appl Physiol. 2005; 98(1):390–403.
47. Naval Aerospace Medical Institute. U.S. Naval Flight Surgeon's Manual, 3rd ed. Washington (DC): Bureau of Medicine and Surgery, Department of the Navy; 1991:1–59.
48. Naval Sea Systems Command. U.S. Navy Dive Manual, Rev. 7, 2016. Chapter 3, paragraph 3-9.2.2; and Chapter 15, paragraph 15-12.1 Washington (DC): U.S. Navy; 2016:3-42; 15-24.
49. Ogoh S, Nakahara H, Ainslie PN, Miyamoto T. The effect of oxygen on dynamic cerebral autoregulation: critical role of hypocapnia. J Appl Physiol. 2010; 108(3):538–543.
50. Otis AB, Rahn H, Epstein MA, Fenn WO. Performance as related to composition of alveolar air. Am J Physiol. 1946; 146(2):207–221.
51. Ren X, Fatemian M, Robbins PA. Changes in respiratory control in humans induced by 8 h of hyperoxia. J Appl Physiol. 2000; 89(2):655–662.
52. Robertson WG, Farhii LE. Rate of lung collapse after airway occlusion on 100% O_2 at various ambient pressures. J Appl Physiol. 1965; 20(2):228–232.
53. Rothen HU, Sporre B, Engberg G, Wegenius G, Högman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. Anesthesiology. 1995; 82(4):832–842.
54. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. Lancet. 1995; 345(8962):1387–1391.
55. Sackner MA, Landa J, Hirsch J, Zapata A. Pulmonary effects of oxygen breathing: a 6-hour study in normal men. Ann Intern Med. 1975; 82(1):40–43.
56. Schoene RB, Lahiri S, Hackett PH, Peters RM Jr, Milledge JS, et al. Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. J Appl Physiol. 1984; 56(6):1478–1483.
57. Schwarz YA, Erel J, Davidson B, Caine Y, Baum GL. An algorithm for pulmonary screening of military pilots in Israel. Chest. 1997; 111(4):916–921.
58. Seals DR, Johnson DG, Fregosi RF. Hyperoxia lowers sympathetic activity at rest but not during exercise in humans. Am J Physiol. 1991; 260(5, Pt. 2):R873–R878.
59. Shykoff BE. Pulmonary effects of submerged oxygen breathing: 4-, 6-, and 8-hour dives at 140 KPa. Undersea Hyperb Med. 2005; 32(5):351–361.
60. Shykoff BE. Pulmonary effects of submerged exercise while breathing 140 kPa oxygen. Undersea Hyperb Med. 2008; 35(6):417–426.
61. Shykoff BE. Pulmonary effects of U.S. Navy Treatment Table 6 hyperbaric exposure. Panama City (FL): Navy Experimental Diving Unit TR 08-04; 2008.
62. Shykoff B. Pulmonary oxygen toxicity: PO_2, not FIO_2. Abstract of the Undersea & Hyperbaric Medical Society 2008 Annual Scientific Meeting; June 26-28, 2008; Salt Lake City, UT. North Palm Beach (FL): UHMS; 2007.
63. Shykoff B. Pulmonary effects of eight hours underwater breathing 1.35 ATM oxygen: 100% oxygen or 16% nitrogen, 84% O2. Panama City (FL): Navy Experimental Diving Unit TR 05-18; 2005. [Accessed June 2015]. Available from http://archive.rubicon-foundation.org/3474.
64. Shykoff B. Pulmonary effects of eight-hour MK 16 MOD 1 dives. Panama City (FL): Navy Experimental Diving Unit TR 06-15; 2007. [Accessed June 2015]. Available from http://archive.rubicon-foundation.org/6869.
65. Sinski M, Lewandowski J, Przybylski J, Zalewski P, Symonides B, et al. Deactivation of carotid body chemoreceptors by hyperoxia decreases blood pressure in hypertensive patients. Hypertens Res. 2014; 37(9):858–862.
66. Smerz RW. Incidence of oxygen toxicity events during the treatment of dysbarism. Undersea Hyperb Med. 2004; 31(2):199–202.
67. Stensrud T, Berntsen S, Carlsen KH. Humidity influences exercise capacity in subjects with exercise-induced bronchoconstriction (EIB). Respir Med. 2006; 100(9):1633–1641.
68. Tacker WA, Balldin UI, Burton RR, Glaister DH, Gillingham KK, Mercer JR. Induction and prevention of acceleration atelectasis. Aviat Space Environ Med. 1987; 58(1):69–75.
69. Tawadrous FD, Eldridge FL. Posthyperventilation breathing patterns after active hyperventilation in man. J Appl Physiol. 1974; 37(3):353–356.
70. Taylor A, Rehder K, Hyatt RE, Parker JC. Clinical respiratory physiology. Philadelphia (PA): Saunders; 1989:273–274.
71. Watson NA, Beards SC, Altaf N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. Eur J Anaesthesiol. 2000; 17(3):152–159.
72. Webb WR, Stern EJ, Kanth N, Gamsu G. Dynamic pulmonary CT: findings in healthy adult men. Radiology. 1993; 186(1):117–124.
73. Wehrwein EA, Basu R, Basu A, Curry TB, Rizza RA, Joyner MJ. Hyperoxia blunts counter regulation during hypoglycaemia in humans: possible role for the carotid bodies? J Physiol. 2010; 588(22):4593–4601.
74. West JB, Hackett PH, Maret KH, Milledge JS, Peters RM, et al. Pulmonary gas exchange on the summit of Mount Everest. J Appl Physiol. 1983; 55(3):678–687.
75. Willie CK, MacLeod DB, Smith KJ, Lewis NC, Foster GE, et al. The contribution of arterial blood gases in cerebral bloodflow regulation and fuel utilization in man at high altitude. J Cereb Blood Flow Metab. 2015; 35(5):873–881.
76. Xu F, Liu P, Pascual JM, Xiao G, Lu H. Effect of hypoxia and hyperoxia on cerebral blood flow, blood oxygenation, and oxidative metabolism. J Cereb Blood Flow Metab. 2012; 32(10):1909–1918.