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REVIEW | *Exploiting Environmental Factors to Improve Health and Performance*

Highs and lows of hyperoxia: physiological, performance, and clinical aspects

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Brugniaux JV, Coombs GB, Barak OF, Dujic Z, Sekhon MS, Ainslie PN. Highs and lows of hyperoxia: physiological, performance, and clinical aspects. *Am J Physiol Regul Integr Comp Physiol* 315: R1–R27, 2018. First published February 28, 2018; doi:10.1152/ajpregu.00165.2017.—Molecular oxygen (O_2) is a vital element in human survival and plays a major role in a diverse range of biological and physiological processes. Although normobaric hyperoxia can increase arterial oxygen content (Ca_{O_2}), it also causes vasoconstriction and hence reduces O_2 delivery in various vascular beds, including the heart, skeletal muscle, and brain. Thus, a seemingly paradoxical situation exists in which the administration of oxygen may place tissues at increased risk of hypoxic stress. Nevertheless, with various degrees of effectiveness, and not without consequences, supplemental oxygen is used clinically in an attempt to correct tissue hypoxia (e.g., brain ischemia, traumatic brain injury, carbon monoxide poisoning, etc.) and chronic hypoxemia (e.g., severe COPD, etc.) and to help with wound healing, necrosis, or reperfusion injuries (e.g., compromised grafts). Hyperoxia has also been used liberally by athletes in a belief that it offers performance-enhancing benefits; such benefits also extend to hypoxemic patients both at rest and during rehabilitation. This review aims to provide a comprehensive overview of the effects of hyperoxia in humans from the "bench to bedside." The first section will focus on the basic physiological principles of partial pressure of arterial O_2, Ca_{O_2}, and barometric pressure and how these changes lead to variation in regional O_2 delivery. This review provides an overview of the evidence for and against the use of hyperoxia as an aid to enhance physical performance. The final section addresses pathophysiological concepts, clinical studies, and implications for therapy. The potential of O_2 toxicity and future research directions are also considered.

health; hyperoxia; oxygen; performance

INTRODUCTION

Molecular oxygen (O_2) is one of the most important elements on Earth, particularly for aerobic organisms that depend on it to release energy from carbon-based molecules. The concentration of oxygen in the atmosphere is ~20.93–20.95% (209–460 ppm), depending on the source (196, 310), but this has fluctuated markedly throughout history (Fig. 1) (175). Although Earth is ~4.5 billion years old, its early atmosphere contained virtually no O_2 whatsoever. Over time, however, oxygen became the predominant source for energy to be generated by nonphotosynthesizing cells through oxidative phosphorylation in mitochondria. As billions of years passed by, an equilibrium was established whereby the concentration of oxygen fluctuated within a habitable range, between ~15% and 35%, which has been maintained from the beginning of the Cambrian period 540 million years ago until the present day (Fig. 1). Each surge in the atmosphere's oxygen concentration was accompanied by a new burst of life, whereas the troughs were associated with downscaling and extinction of species.

The discovery of O_2 has a rich history, spanning from the Greeks as early as the 6th century BC to the 17th century AD. In the 17th century, the term "molecular O_2" was clearly, albeit somewhat controversially, described by Antoine Lavoisier (Fig. 2). Many excellent and in-depth reviews exist on the historical accounts of respiratory gas exchange and related aspects and contributions of O_2 discovery (36, 245, 246, 262,

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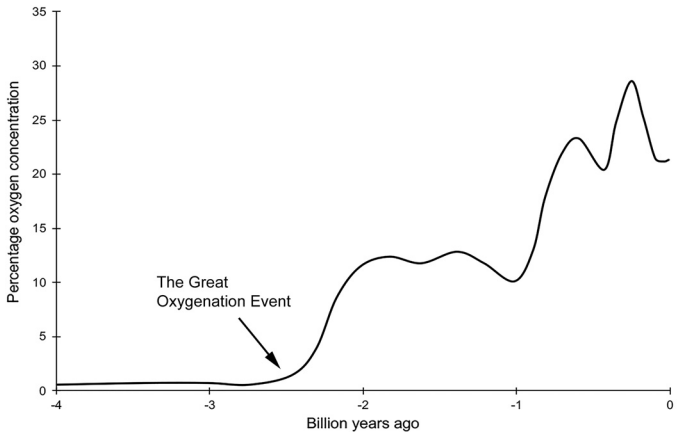
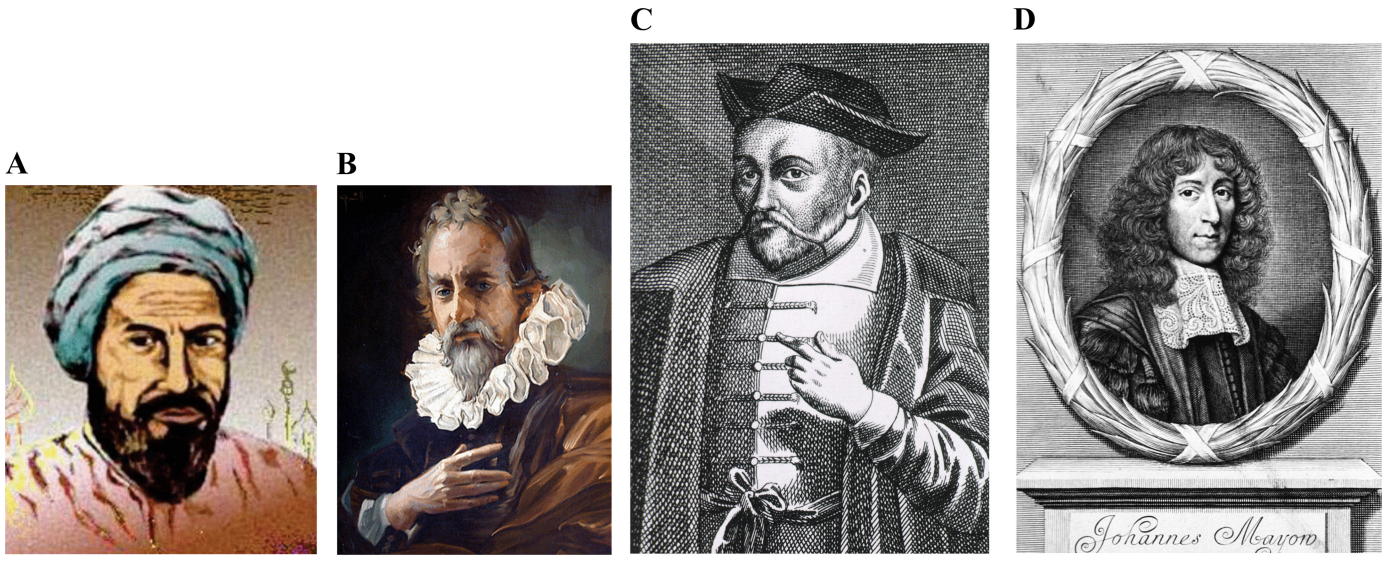


Fig. 1. Approximate change in the concentration of oxygen in Earth's atmosphere over the last 4 billion years. Modified from https://link.springer.com/article/10.1007/s12576-016-0501-0 (175) and used under Creative Commons Attribution 4.0 https://creativecommons.org/licenses/by/4.0/.

303–309); as such, only a brief overview is provided here. As summarized in Figs. 2 and 3, between the 13th and 18th centuries, there were a number of key scholars that informed the ultimate discovery of molecular O_2. Although not defined as O_2 per se, it should be noted that the early work of the philosophers and physicians Galen (born ca. 130 AD) and Erasistratus (born ca. 304 BC) developed the "pneumatic" theory of respiration. This theory held that inspired air upon arriving at the left ventricle forms the "vital spirit" that is then distributed throughout the body. One of the first opponents of the so-called Galenical school of circulation and gas exchange was promulgated by Ibn al-Nafis (1213–1288) (308). In the context of contributions to O_2 discovery, he provided the first description that arterial blood in the pulmonary circulation mixes with air to form the vital spirit. A few centuries later, Michael Servetus (1511–1553) (36, 305) described the notion that blood flows through the lung tissue, excretes waste products (later to be identified as CO_2 by Joseph Black in the late 1700s), and changes the color of the blood. Around the same time, the contributions of John Mayow (1641–1679) (262) were outlined in a book he wrote that contained important aspects that he named "spiritus nitro-aerus." This latter term referred to the possibility that air consumed fire and that it could be breathed internally to provide both body heat and energy. Unfortunately, however, this posit was discredited due to the false (which was unknown at that time) phlogiston theory; the phlogiston theory was that a fire-like element (called phlogiston) is contained within combustible bodies and released during combustion. The 1700s, however, formed the critical century for O_2 discovery.

Here, during various experiments, Carl Scheele (1742–1786) (303) identified a gas that markedly brightened a candle flame, which also supported life in mice; he called it "fire air." This information was sent to Antoine Lavoisier; however, he apparently did not reply or acknowledge this important finding (246). Lavoisier was later accused of plagiarism and failing to acknowledge discoveries of others. Scheele's discovery of fire



Ibn al-Nafis (1213-1288) Michael Servetus (1511-1553) Michael Sendivogius (1566-1636) John Mayow (1641-1679)

Fig. 2. Key scholars from the 13th to the 17th century involved in the developments and the discovery of oxygen. *A*: Ibn al-Nafis, who made the first description that arterial blood in the pulmonary circulation mixes with air to form the "vital spirit." The term vital spirit was posited by Galen (~200 CE), which referred to red (a.k.a: arterialized) blood. See Ref. 308 for further details. Photo retrieved from https://id.wikipedia.org/wiki/Ibnu_al-Nafis (public domain). *B*: Michael Servetus, who described the notion that blood flows through the lung tissue, excretes waste products (later identified to be CO_2 by Joseph Black in the late 1700s), and changes to the color of the blood. See Refs. 36 and 305 for further details. Photo retrieved from http://www.miguelservet.org/servetus/iconografia/guillermo.htm with permission from the Insituto de Estudios Sijenenses "Miguel Servet." *C*: Michael Sendivogius, whose published work suggested that air contained the "secret food of life." The controversial aspect was the claim that Sendivogius advised on how to make oxygen on board the first manned submarine (while submerged). This, however, was never proven or documented. It was suggested that it was more likely that tubes were used as snorkels to obtain fresh air into the submarine. See Ref. 246 for further details. Photo retrieved from https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101428714-img (public domain). *D*: John Mayow, who wrote a book about an aspect of what he named "spiritus nitro-aerus". The possibility that air consumed fire and that it could be breathed internally to provide both body heat and energy was discredited due to the false phlogiston theory; this was unknown at that time. The phlogiston theory was that a fire-like element (called phlogiston) is contained within combustible bodies and released during combustion. See (262) for further details. Photo retrieved from https://en.wikipedia.org/wiki/John_Mayow (public domain).

Fig. 3. Key scholars of the 18th century involved in the developments and the discovery of oxygen. *A*: Antoine Lavoisier. Lavoisier began studies on Priestley's newly published gas (220). Although he termed this gas "principe oxigene," he still referred to it as "vital air". It was not until he (along with 8 other eminent chemists) tried to prove the later observations of Henry Cavendish (see below) wrong that he named the vital air "oxygen." This work resulted largely in the disbandment of phlogiston. See Ref. 304 for further details. Photo retrieved from https://commons.wikimedia.org/wiki/File:Antoine-Laurent_Lavoisier_(by_Louis_Jean_Desire_Delaistre).jpg (public domain). *B*: Henry Cavendish. By burning inflammable air, Cavendish and Priestley showed that dew formed on the inside of glass; Cavendish analyzed this and established that the dew was pure water. In part of this observation, it has been suggested that Cavendish made the most important experimental observation (related to vital air) since it solved Lavoisier's (and others') belief that water was an element that could not otherwise be made. See Refs. 246 and 306 for further details. Photo retrieved from https://en.wikipedia.org/wiki/Henry_Cavendish (public domain). *C*: Carl Scheele. During various experiments, Scheele identified a gas that markedly brightened a candle flame; it also supported life in mice; he called it "fire air." This information was sent to Lavoisier; however, he apparently did not reply or acknowledge this important finding. Lavoisier was later accused of plagiarism and failing to acknowledge the discoveries of others. Scheele's discovery of fire air was one example of this. See Ref. 303 for further details. Photo retrieved from https://en.wikisource.org/wiki/Popular_Science_Monthly/Volume_31/October_1887/Sketch_of_Karl_Wilhelm_Scheele (public domain). *D*: Joseph Priestley, who stablished the term "dephlogisticated air." Somewhat similar to Scheele, Priestley made a gas (via heating mercuric oxide) that caused a glowing splinter to be set on fire and sustained the life of a mouse in a sealed bottle. Once again, although this information was relayed to Lavoisier, he never acknowledged this help. See Ref. 309) for further details. Photo retrieved from: https://en.wikipedia.org/wiki/Joseph_Priestley (public domain).

air was one example of this. During a similar time, the term "dephlogisticated air" was coined by Joseph Priestley (1733–1804) (309). Somewhat similar to Scheele, Priestley made a gas (via heating mercuric oxide) that caused a glowing splinter to set on fire and sustained the life of a mouse in a sealed bottle. Once again, although this information was relayed to Lavoisier, he never acknowledged this help (246). By burning inflammable air, Henry Cavendish (1731–1810) (306) and Priestley showed that dew formed on the inside of glass; Cavendish analyzed this and established that the dew was pure water. In part of this observation, it has been suggested that Cavendish made the most important experimental observation (related to vital air) since it solved Lavoisier's (and others') belief that water was an element that could not be otherwise made. Antoine Lavoisier (1743–1794) (304) began studies on Priestley's newly published gas. Although he termed this gas "principe oxigene," he still refed to it as "vital air." It was not until he (along with 8 other eminent chemists) tried to disprove the later observations of Henry Cavendish that he named the vital air "oxygen;" this work resulted largely in the disbandment of phlogiston! An elegant review on these so-called eight sages of the discovery of O_2 and the controversial "approaches" of Lavoisier is found elsewhere and makes for excellent reading on this topic and debate (246). Although it is somewhat insidious to single out one or two individuals, and invariably some may have been missed, these key scholars involved in the development and the discovery of O_2 are summarized in Figs. 2 and 3.

From this evolutional and historical development, it is clear that O_2 is essential in human survival and hence plays a pivotal role in key biological and physiological processes. In medical practice, O_2 is the cornerstone for the treatment of critical illness (32), especially in acute shock and emergency medicine (285). To make sure tissue O_2 levels are maintained, O_2 therapy during mechanical ventilation, anesthesia, and resuscitation usually exceeds physiological levels. The Renaissance physician Paracelsus noted that "Nothing is without poison—the poison is in the dose" (96). The contemporary interpretation of this famous statement by Paracelsus is that dose and effect move together in a predictably linear fashion, and therefore, lower exposures to a hazardous compound will always generate lower risks. Although perhaps not the case in every aspect of toxicology (96), this hormetic response may also be applicable to the O_2 molecule (6). The concept of O_2 toxicity was originally described in the late 19th century by James Smith (252) and Paul Bert (28); however, it took a century before the effects of hyperoxia were better understood. Over the last 50 or so years, hyperoxia has not only been employed in a wide range of clinical interventions and pathologies, it has also been used liberally by athletes in a belief that it offers performance-enhancing benefits. The latter is of growing interest since the World Anti-Doping Agency does not regulate the practice of hyperoxia in athletes or related competition. Nevertheless, the performance benefits of hyperoxia are unclear, and several lines of evidence indicate that hyperoxia may be harmful; however, new potential benefits are still being explored, and robust interventional studies are still limited (reviewed in Ref. 117).

The aim of this review, with particular focus on humans, is to provide a comprehensive overview of the effects of hyper-

oxia from "bench to bedside." Although many focused reviews on hyperoxia exist (12, 62, 135, 251, 258, 260, 271, 286, 297), the goal of this review is to provide a balanced up-to-date overview of key physiological, performance, and clinical aspects to the use of hyperoxia in health and disease states. The review is divided into three main sections. The first section will focus on the basic physiological principles of partial pressure of arterial oxygen (Pa_{O_2}), arterial O_2 content (Ca_{O_2}), barometric pressure, and and how these changes, in combination, lead to changes in regional O_2 delivery (DO_2). The next section provides an overview of the evidence for and against the use for hyperoxia as an aid to enhance physical performance, including rehabilitation. The final section addresses pathophysiological concepts, clinical studies, and implications for therapy. Future research directions are also considered.

PHYSIOLOGICAL EFFECTS OF HYPEROXIA

Partial Pressure and Oxygen Content

At sea level, where the barometric pressure is ~760 mmHg, the inspired partial pressure of oxygen ($P_{I_{O_2}}$) is roughly 150 mmHg when estimated using a fraction of inspired oxygen ($F_{I_{O_2}}$) in ambient air of 0.21 and accounting for saturated water vapor pressure of air in the lungs (i.e., 47 mmHg). However, Pa_{O_2} is closer to 97 mmHg based on an estimate of alveolar partial pressure of O_2 (PA_{O_2}), using the alveolar gas equation (assumptions: Pa_{CO_2} = 40 mmHg; RER = 0.85) and assuming an alveolar-arterial difference ($A-aP_{O_2}$) of 5 mmHg at rest in a young healthy male. The vast majority of the inspired O_2 is present in arterial blood bound to the protein hemoglobin (Hb), where 1 g of Hb can be combined with 1.36 ml of O_2. In addition, O_2 is dissolved in plasma, where for each mmHg of P_{O_2} there is 0.003 ml O_2/100 ml blood. Thus, Ca_{O_2} can be calculated as follows: Ca_{O_2} (ml O_2/100 ml blood) = (1.36 × Hb × Sa_{O_2}/100)+ 0.003 × Pa_{O_2}, where Hb concentration in normal blood for a male is 15 g/100 ml (14 g/100 ml for females) and Sa_{O_2} refers to the arterial O_2-Hb saturation (%). For example, the blood of a resting healthy individual at sea level with a Sa_{O_2} of 98% will contain roughly 20.3 ml O_2/100 ml blood: 20.3 (ml O_2/100 ml blood) = (1.36 × 15 g/100 ml × 98/100)+ 0.003 × 97 mmHg.

If the same individual then breathes a hyperoxic gas mixture (e.g., $F_{I_{O_2}}$ = 0.60), the Pa_{O_2} will be increased to ~360 mmHg, assuming an $A-aP_{O_2}$ of 20 mmHg based on data from Asmussen and Nielsen (13), which will result in a small increase of Ca_{O_2} by ~4%: 21.1 (ml O_2/100 ml blood) = (1.36 × 15 g/100 ml × 98/100) + 0.003 × 360 mmHg.

Increases in Pa_{O_2} (or the end-tidal partial pressure in O_2) when breathing supplemental oxygen are proportional to $F_{I_{O_2}}$ (3, 146); however, increases in Ca_{O_2} are limited to <10% at sea level with an $F_{I_{O_2}}$ of 1.0. In contrast, hyperbaric oxygen can be a much more potent stimulus by which one can achieve levels of Pa_{O_2} well in excess of normal values, in turn increasing the proportion of dissolved O_2 within plasma. For instance, in a diving scenario at 3 atm (ambient $F_{I_{O_2}}$), Pa_{O_2} would be ~405 mmHg [3 × (760 − 47) × 0.21], assuming an $A-aP_{O_2}$ of 35 mmHg based on data from Clark and Lambertsen (61). Therefore, Ca_{O_2} will also be increased by ~4% due to a greater concentration of O_2 dissolved in plasma: 21.1 (ml O_2/100 ml blood) = (1.36 × 15 g/100 ml × 98/100) + 0.003 × 367 mmHg.

Clinically, hyperbaric and hyperoxic oxygen (e.g., 3 atm; $F_{I_{O_2}}$ = 1.0) are commonly used as treatments for various traumas or conditions (296, 297). In this scenario, Pa_{O_2} is increased to ≥2,000 mmHg [~2,000 mmHg based on an $A-aP_{O_2}$ of 100 mmHg, using data from Clark and Lambertsen (61)], and consequently, Ca_{O_2} is increased by ~28%: 26.0 (ml O_2/100 ml blood) = (1.36 × 15 g/100 ml × 98/100) + 0.003 × 2,000 mmHg.

This elevated Ca_{O_2} should in turn improve DO_2 to the tissues by creating a steeper intracellular O_2 gradient, as illustrated in Fig. 4, leading to more diffusion from the capillaries to tissues. Yet in studies with healthy participants where hyperoxia is

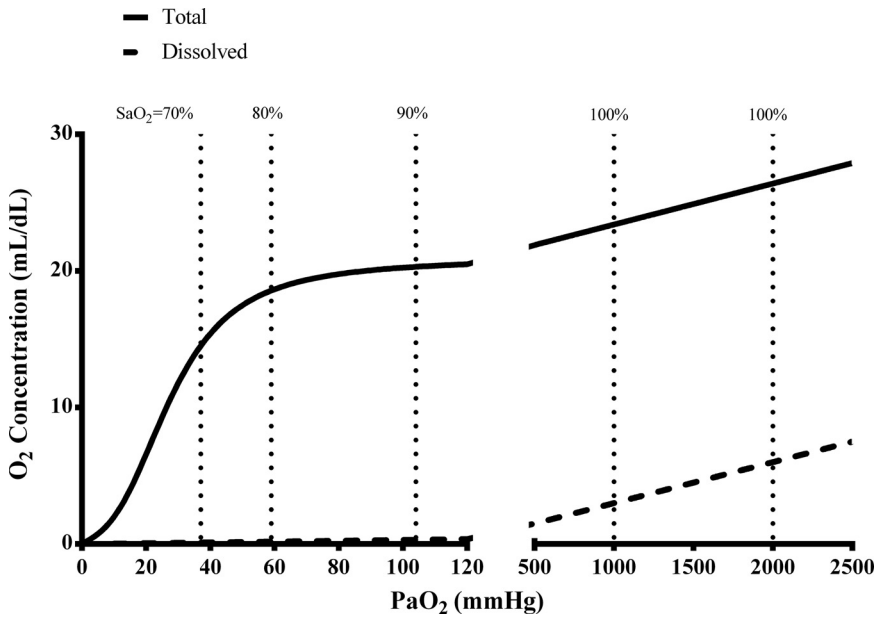


Fig. 4. Relationship between arterial oxygen content (Ca_{O_2}) and arterial O_2-hemoglobin (Hb) saturation (Sa_{O_2}) for a range of arterial partial pressure of O_2 (Pa_{O_2}) from 0 to 2,500 mmHg (achievable via hyperbaric hyperoxia). Note that values were calculated for a given Pa_{O_2} using the Severinghaus equation (247) and a Hb value of 15 g/100 ml (i.e., normal for males).

used (as opposed to hyperbaric O_2), unless the $F_{I_{O_2}}$ is significantly different from normoxia, the effects on Ca_{O_2} will indeed be marginal. Conversely, in hypoxemic patients, where the Pa_{O_2} can lie on the steep part of the oxyhemoglobin dissociation curve, any improvement toward normoxic levels will have drastic consequences on Ca_{O_2} and, therefore, the patient's health. Nonetheless, hyperoxia tends to increase Pa_{O_2} more so than Sa_{O_2}, and Pa_{O_2} makes only a small contribution to the overall Ca_{O_2} (compared with Hb or Sa_{O_2}). Thus, in disease states, increased Ca_{O_2} may have a pivotal yet controversial (128) role in ensuring adequate hemoglobin saturation for DO_2 (where DO_2 = blood flow × Ca_{O_2}) and overcoming diffusion barriers to restore normal cellular metabolism (see *Medical Uses of Oxygen*).

Ventilation

In response to marked reductions in Pa_{O_2} (i.e., hypoxemia), the peripheral chemoreceptors located in the carotid bodies stimulate hyperventilation to offset the hypoxemia and hence improve Sa_{O_2} (81, 123). Intuitively, one might expect that when breathing high levels of O_2 (i.e., >21% O_2 at sea level), minute ventilation will fall due to inhibition of the peripheral chemoreceptors. However, after an apparently transient decrease in ventilation within the first 1–2 min of hyperoxic (at least when $F_{I_{O_2}} = 1.0$) breathing (77, 173), a paradoxical increase in the respiratory response increases minute ventilation, rising beyond preexposure levels within 5 min in a dose-dependent manner (21). Increases in ventilation in response to hyperoxia have been attributed to rising tidal volume rather than greater frequency of breathing (21, 146, 226). Hyperoxic hyperventilation also occurs in animals even after carotid body denervation, which indicates a central mechanism to stimulate breathing (181), whereas the initial hypoventilation (1–2 min) is dependent on inhibition of the peripheral chemoreceptor (294). This notion is supported in humans by the fact that some degree of sensitivity to reductions in O_2 remained intact in patients following carotid body resection (193). At extremely high levels of P_{O_2} [e.g., >3 atm (60)], short-term O_2 toxicity is well documented in the central nervous system (CNS) and can result in abnormal breathing patterns and eventually death (249). At less toxic levels, the accumulation of O_2 free radicals and other oxidative enzymes, collectively termed reactive oxygen species (ROS; see *Oxygen toxicity and safety*), can still directly stimulate respiratory control centers of the brainstem (187). For instance, neurons in the solitary complex of rat brain slices were observed to be sensitive to hyperoxia, which suggests a central component to the ventilatory response to O_2 independent of the central chemoreceptors (187). In contrast, from a mechanistic point of view, it has also been reported that the hyperoxia-induced production of superoxide and nitric oxide, notably from the mitochondria, is responsible for the stimulation of the central CO_2 chemoreceptors in the caudal solitary complex (59, 69). However, the level of antioxidant defense should also be considered, as the cell's ability to remove damaged lipids and proteins to avoid apoptosis may limit the increase in oxidative and nitrosative stress (58).

The arterial partial pressure of carbon dioxide (Pa_{CO_2}) also plays a central role in the hyperventilatory response. For example, when breathing a hyperoxic gas mixture under poikilocapnic conditions, elevations in ventilation are attenuated compared with isocapnic hyperoxia via hypocapnic inhibition of the central chemoreceptors (226, 238). Currently, the best explanation of this phenomenon points to the Haldane effect, which weakens the affinity of CO_2 for hemoglobin when high levels of oxygen completely saturate hemoglobin, thereby acidifying the cerebral spinal fluid and necessitating CO_2 removal via hyperventilation (55, 128). Indeed, Lambertsen et al. (145) observed that breathing hyperbaric O_2 (3 atm) for ≤30 min increased internal jugular P_{CO_2} and H^+ by 2–3 mmHg, which was apparently sufficient to increase ventilation by ~25%. However, the majority of evidence demonstrates that increases in ventilation in hyperoxia occur proportionally to increases in Pa_{O_2} and in a time-dependent fashion (Fig. 5) (20, 21, 77, 146, 173). When the exposure is prolonged for 8 h (226) to 5 days (75), ventilation progressively decreases over the duration of the exposure. It has been suggested that the mechanisms responsible for this decline are opposite of those observed during ventilatory acclimatization to hypoxia (226). It was also suggested that the stimulus that triggers the initial hyperventilatory response is not sustained due to a decrease in cerebral blood flow and/or a reduction in the efficiency of the CO_2 carriage by the blood (146). Finally, oxygen toxicity could have a negative impact on the physiological response; however, this would depend on the level of hyperoxia used (see *Oxygen toxicity and safety*) (226).

Hyperoxia also appears to exert a lasting effect upon a return to normal Pa_{O_2} values, whereby ventilation remains elevated in a graded manner following 30 min of exposure to hyperoxia with or without controlling for Pa_{CO_2} levels (20, 21). Because of the decline in ventilation with longer exposures, ventilation does not appear to be significantly different from baseline, at least when normoxic breathing is measured within the first hour after an 8-h exposure to isocapnic hyperoxia (55).

Vasculature

Hyperoxia also influences DO_2 via its effects on vascular regulation. Generally, hyperoxia induces a reduction in blood flow, thereby counteracting the benefits of increased Ca_{O_2}. This hyperoxia-induced vasoconstriction has been observed in various vascular beds, including the heart (97, 158), skeletal muscle (64, 209), and brain (293), and can reach levels ~30% lower at a Pa_{O_2} of 420 mmHg (237). However, the lungs (158) and kidneys (248) do not exhibit the same reduction in blood flow. The mechanisms by which hyperoxia leads to systemic vasoconstriction are not fully elucidated, but the elevated Ca_{O_2} itself may contribute given the pivotal role of the erythrocyte in O_2 transport (108). It has been demonstrated that hemoglobin acts as an O_2 sensor and can release ATP and nitric oxide (NO) in response to a fall in Hb-O_2 saturation; plasma ATP concentrations were also lower in hyperoxia, suggesting reduced vasodilator signaling (109). The elevated Pa_{O_2} may also reduce the availability of other vasodilators such as prostaglandin PG2 (251). Paradoxically, hyperoxia also increases L-arginine and NO synthase, suggesting a potential effect of the duration of the exposure (251). It is also well established that hyperoxia causes an increase in ROS, notably the superoxide anion, which in turn inhibits a range of vasodilators, including NO (251).

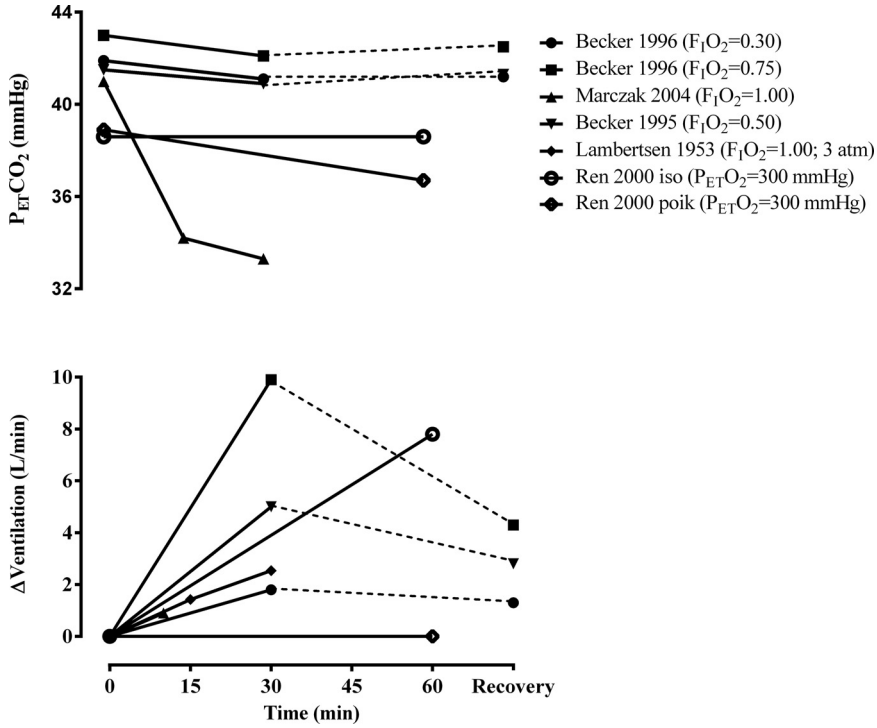


Fig. 5. Relationship between the fraction of inspired O_2 (FI_{O_2}) and the changes in ventilation over time. Data represent a compilation of studies reviewed in Refs. 20, 21, 146, 173, and 226. Values for end-tidal CO_2 ($P_{ET_{CO_2}}$) are displayed for each study using open symbols connected by a dashed line. Note that Marczak and Pokorski (173) did not report $P_{ET_{CO_2}}$, and Becker et al. (21) used 2 different levels of FI_{O_2} (0.3 and 0.75). Hyperoxic values for $P_{ET_{CO_2}}$ and minute ventilation ($\dot{V}E$) from the isocapnic and poikilocapnic trials, respectively, were assumed equivalent to baseline because no significant changes were reported in the absence of measured values in Ren et al. (226).

It is noteworthy that potentially negative effects of hyperoxia have been demonstrated in some vascular beds, including the myocardium and brain (101, 159), and O_2 breathing also contributes to vascular dysfunction (i.e., higher arterial stiffness) in individuals with diabetes (110). Given that cerebral perfusion is highly influenced by changes in arterial blood gases (316) and tissue ischemia is a major concern following myocardial infarct/cardiac arrest (48), blood flow to the brain and coronary circulation is of particular importance in hyperoxia. Moreover, there is evidence that hyperoxia might reduce cardiac output (CO) and increase systemic vascular resistance (SVR) (115, 292), which will be further explained below (see *Cardiac*). The following sections summarize the primary effects of hyperoxia on blood flow and DO_2 to key organs relating to performance and clinical outcomes.

Cardiac. Increases in SVR during hyperoxic breathing, as described above, have been demonstrated to result in reductions in heart rate, cardiac output, and cardiac index (115, 237, 292, 299, 312), but some studies have also reported no effect of hyperoxia on markers of cardiac function [e.g., heart rate, cardiac output (55, 282)]. Similarly, MRI data corroborate the reductions in cardiac output and additionally demonstrate decreases in left ventricle perfusion resulting in lower systemic and coronary O_2 delivery (34). Many studies that measure coronary blood flow use cardiac catheterization. For this reason, the individuals participating in such studies often present with cardiac diseases, such as coronary artery disease (CAD) and congestive heart failure (CHF), to combine research data collection with routine clincical diagnostic tests. The evidence from such tests overwhelmingly demonstrates that while breathing hyperoxic gas mixtures, coronary blood flow, measured via catheterization, is reduced compared with normal air (105, 171, 178, 179). It is noteworthy that, although all of these studies include cardiac patients, Ganz et al. (105) also compared coronary blood flow responses to hyperoxia in healthy individuals, and the results followed a similar trend. More recently, studies that have employed echocardiography during hyperoxia also reported reductions in coronary blood velocity compared with normoxia (106, 159). Despite increases in Ca_{O_2} with supplemental oxygen therapy, Fig. 6 demonstrates that coronary DO_2 is reduced in most cases under hyperoxic conditions.

Lungs. Despite pulmonary vasoconstriction during hypoxemia (268), cardiac output and consequently pulmonary blood flow rises. Hyperoxia, however, likely has little impact or may decrease pulmonary artery pressure (55, 282, 299). Therefore, the lungs appear to respond oppositely to hypoxia/hyperoxia compared with the systemic circulation. Moreover, hyperoxia is often used experimentally or clinically to reduce or close intrapulmonary arteriovenous anastomoses (IPAVA), even during exercise (164). In hypoxia, flow through IPAVA increases (148, 163), which is dependent on Pa_{O_2} but not Ca_{O_2} (79); however, in hyperoxia, IPAVAs close or are prevented altogether. The mechanisms behind this response remain unknown (161), but flow through IPAVA is likely also dependent on Pa_{O_2} since breathing 40% O_2 vs. normoxia did not elicit any changes in IPAVA compared with 100% O_2 (90). Likewise, the 100% O_2 method is still commonly used to detect and quantify right-to-left shunt by eliminating end-capillary diffusion limitation and V_A/Q inequality as possible mechanisms of impaired gas exchange (80). Unlike in otherwise healthy humans, however, the use of hyperoxia in clinical conditions of hypoxemia causes a myriad of negative effects, including depression of respiratory drive and the collapse of metastable alveoli, thus increasing the ventilation/perfusion unevenness and ultimately worsening gas exchange. This puts patients with lung disease at special risk of further respiratory function

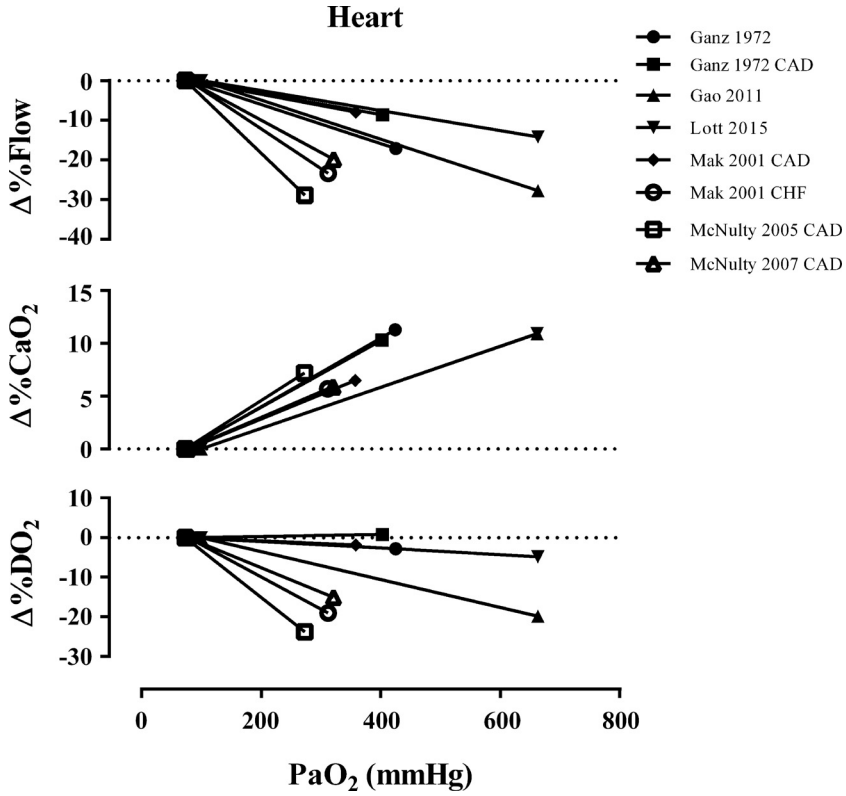


Fig. 6. Relationship between the changes in coronary blood flow, arterial O_2 content (Ca_{O_2}), coronary oxygen delivery (DO_2), and the arterial partial pressure of O_2 (Pa_{O_2}). Data represent a compilation of studies reviewed in Refs. 105, 106, 159, 171, 178, and 179. Note that when not reported, Pa_{O_2} was estimated using the alveolar gas equation with assumed values for alveolar-arterial gradient (10 mmHg), Pa_{CO_2} (40 mmHg if not reported via blood gases or end-tidal CO_2), and respiratory exchange ratio (RER; 0.8 if not reported). If Ca_{O_2} was not reported, then it was estimated as $1.36 \times Hb \times Sa_{O_2} + 0.003 \times Pa_{O_2}$, where Hb was assumed to be 15 g/100 ml for men and 14 g/100 ml for women if unreported, and Sa_{O_2} was assumed to be 98% in normoxia and 100% in hyperoxia if unreported. When not reported, DO_2 was estimated as the product of blood flow and Ca_{O_2}. CAD indicates patients with coronary artery disease, and CHF indicates patients with congestive heart failure.

impairment secondary to hyperoxia. See *Medical Uses of Oxygen* for further details.

Kidneys. The few available studies indicate that kidney perfusion is largely unchanged with hyperoxia in both healthy humans (248) and animals (54, 100). The reasons for the differential sensitivity of the kidneys to hyperoxia compared with other organs (e.g., heart, brain, musle) are unclear. However, in patients with heart failure or severe respiratory failure, where renal plasma flow, and, therefore, glomerular filtration rate, were aleady low, increases in Pa_{O_2} resulted in further impairments of the renal circulation and function (99, 139). However, it was previously demonstrated that Ca_{O_2} per se may not have been the primary mediator of changes in the renal circulation (27). Given the lack of available evidence, the kidneys will not be focused on in further detail in this review, but it is important to note the potential complications to renal function during oxygen supplementation commonly used for many diseases, which will be further discussed in *Medical Uses of Oxygen*.

Skeletal muscle. The peripheral vasculature is also heavily influenced by O_2 availability, and fluctuations of blood flow occur to meet the metabolic demand of tissues. This is particularly evident in skeletal muscle, which experiences large variations in O_2 demand from rest to maximal exercise. For instance, compensatory vasodilation occurs to facilitate blood flow to exercising skeletal muscle when arterial Hb-O_2 saturation is reduced (50). However, the blood flow response of skeletal muscle to hyperoxia is more variable than other vascular beds. Casey et al. (51, 52) observed that breathing 100% O_2 at 2.82 atm increased Ca_{O_2} by ~25–30%, which was associated with a concomitant decrease in forearm blood flow; however, DO_2 was increased due to large increases in Ca_{O_2} from the hyperbaric/hyperoxic environment. Likewise, blood flow to the resting leg was reduced by up to ~30% in other studies (167, 209, 237), with accompanying reductions in DO_2, in a dose-dependent manner with varying levels of normobaric hyperoxic breathing (237).

During lower body exercise, leg blood flow was also attenuated (i.e., it did not increase as much as during normoxic exercise) in some studies (209, 302), whereas in others blood flow was maintained at normoxic levels in both single-leg entension (186) and cycling exercise (143). Without changes in leg blood flow, Knight et al. (143) found that DO_2 and peak leg O_2 uptake ($\dot{V}O_{2peak}$) were improved by 8 and 10%, respectively, during hyperoxia. However, not all studies reported improvements in $\dot{V}O_{2max}$ with maintained blood flow and DO_2 in hyperoxia (167, 209), even with small increases in blood flow in an untrained leg (186). Compared with the brain and heart, DO_2 to the limbs is relatively better maintained despite reductions in blood flow (Fig. 7) (302); however, whether the increase in Ca_{O_2} improves $\dot{V}O_{2max}$ is quite variable (Fig. 9). See *Hyperoxia and Performance* below for a more detailed overview of the effects of hyperoxia on $\dot{V}O_{2max}$ and power output.

Brain. Classic studies by Kety and Schmidt (138) and Lambertsen et al. (146) demonstrated acute reductions in cerebral blood flow in response to elevations in Ca_{O_2} content using the nitrous oxide technique (138). More modern technology has corroborated this evidence using MRI, which has detected decreases in cerebral perfusion with hyperoxia by a range of ~10–30% (35, 44, 101, 293). Transcranial Doppler ultrasound has also been used to demonstrate reductions in middle cerebral artery velocity (MCAv) during hyperoxic breathing (206). However, even within a vascular bed, some

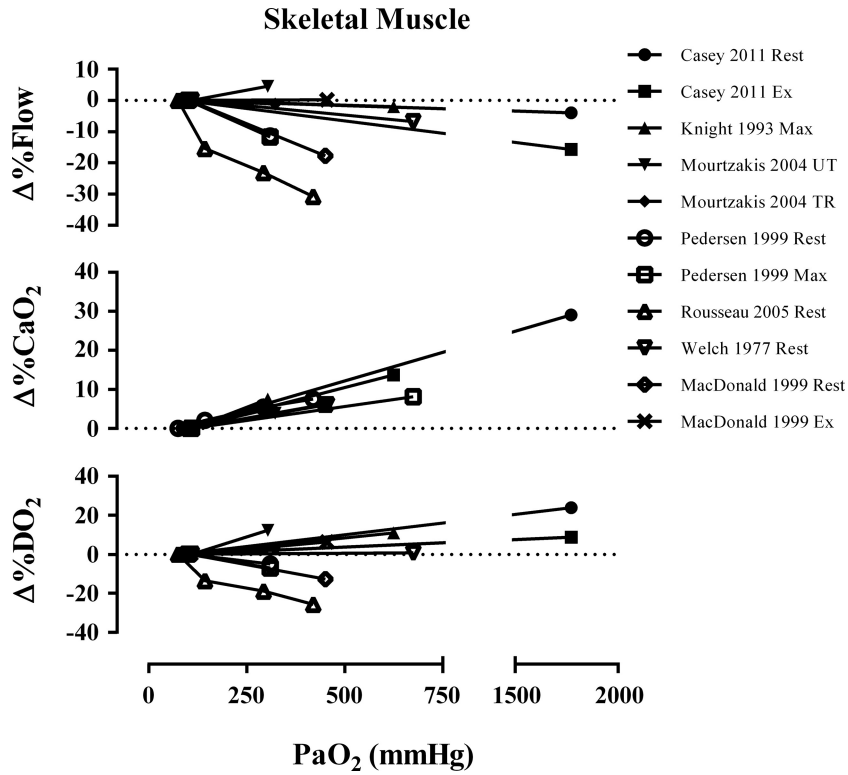


Fig. 7. Relationship between the changes in skeletal muscle blood flow, arterial O_2 content (Ca_{O_2}), muscle oxygen delivery (DO_2), and the arterial partial pressure of O_2 (Pa_{O_2}). Data represent a compilation of studies reviewed in Refs. 51, 143, 167, 186, 209, 237, and 302. Note that when not reported, Pa_{O_2} was estimated using the alveolar gas equation, with assumed values for alveolar-arterial gradient (10 mmHg), Pa_{CO_2} (40 mmHg if not reported via blood gases or end-tidal CO_2), and RER (0.8 if not reported). If Ca_{O_2} was not reported, then it was estimated as $1.36 \times Hb \times Sa_{O_2} + 0.003 \times Pa_{O_2}$, where Hb was assumed to be 15 g/100 ml for men and 14 g/100 ml for women if unreported, and Sa_{O_2} was assumed to be 98% in normoxia and 100% in hyperoxia if unreported. When not reported, DO_2 was estimated as the product of blood flow and Ca_{O_2}. Rest, resting values; Ex, exercising values; Max, maximal exercising values; UT, untrained; TR, indicates trained.

regional perfusion heterogeneity has been observed (144). For instance, Smith and colleagues (254, 255) reported that the posterior circulation (posterior cerebral artery velocity) response to hyperoxic incremental exercise was greater than in the anterior circulation (middle cerebral artery velocity). As described above (see *Ventilation*), hyperoxia causes a respiratory stimulus that results in hyperventilation. Given the highly sensitive nature of the cerebral vasculature to arterial blood gases (316), more recent studies have examined the cerebral blood flow response to hyperoxia while maintaining isocapnic blood gases. It was reported in all isocapnic studies that cerebral blood flow was maintained compared with normoxia (3, 66, 144).

The cerebrovascular responses to increased Pa_{O_2} are illustrated in Fig. 8, with the differential reponses of blood flow and DO_2 between poikilocapnic and isocapnic hyperoxia clearly evident. It is noteworthy that, despite marginal increases in Ca_{O_2}, hyperoxia results in impaired DO_2 to tissues, with the only exception being that which demonstrated the greatest increase in Ca_{O_2} due to very high Pa_{O_2} in a hyperbaric environment. Theoretically, increasing Ca_{O_2} should result in greater increases in DO_2, yet hyperoxia causes constriction in various vascular beds, including the coronary, cerebral, and renal arteries. If such hyperoxia is accompanied by a decrease in local perfusion, a seemingly paradoxical situation prevails in which tissues may be at increased risk of hypoxic stress (128, 129). Therefore, in *Medical Uses of Oxygen*, we will further explore the pathologies in which supplemental oxygen is currently used in a clinical setting and also the potential dangers of such use given the integrative physiological reponses to such a stimulus.

HYPEROXIA AND PERFORMANCE

The recreational use of supplemental O_2 is raising controversies similar to the use of hypoxia nearly a decade ago (152). For example, the World Anti-Doping Agency is not regulating its practice anymore, and hyperoxia can be used freely by athletes in a belief that it offers performance-enhancing benefits. However, this problem is somewhat different inasmuch as there is no report of natural hyperbaric training facilities being used by athletes, and, although the use of hypoxia has been deemed safe at least under certain conditions (42), hyperoxia poses unclear health risks (see *Medical Uses of Oxygen*). Overall, the literature about exercise and performance remains scarce, and caution should be applied. Sperlich and coworkers (258, 260) have recently published on the topic of the effect of hyperoxia on performance and recovery (260) as well as its ethical concerns (258). Therefore, although we include more recent work to expand these previous reviews, the present section will essentially offer a brief summary and update of the main literature relating to the acute and prolonged effects of oxygen supplementation on performance. The associated mechanism(s) by which hyperoxia might induce performance benefits will also be highlighted.

Acute Effects on Performance

The protocols used in the existing literature vary largely in terms of the FI_{O_2} (~0.3–1.0) and exercise modalities, making direct comparisons difficult. To date, there is no published consensus on the best approach to use hyperoxia, particularly in terms of the optimum level of oxygenation (260). Nevertheless, the following section aims to provide a simple overview of key results for the main levels of exercise intensities,

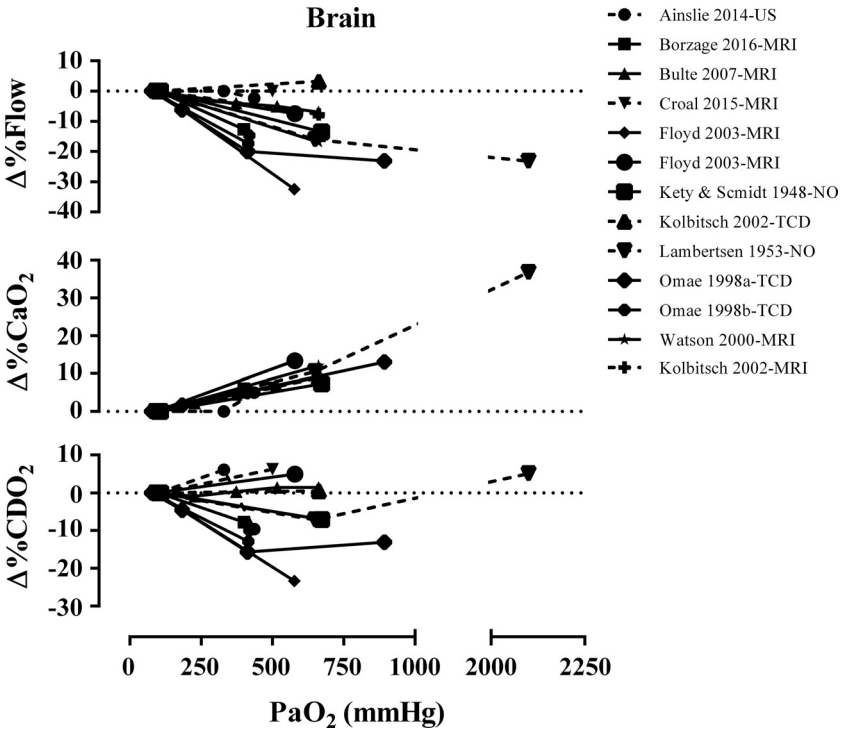


Fig. 8. Relationship between the changes in cerebral blood flow, arterial O_2 content (Ca_{O_2}), cerebral oxygen delivery (DO_2), and the arterial partial pressure of O_2 (Pa_{O_2}). Data represent a compilation of studies reviewed in Refs. 3, 35, 44, 66, 101, 138, 144, 146, 206, and 293. Note that when not reported, Pa_{O_2} was estimated using the alveolar gas equation with assumed values for the alveolar-arterial gradient (10 mmHg), Pa_{CO_2} (40 mmHg if not reported via blood gases or end-tidal CO_2), and RER (0.8 if not reported). If Ca_{O_2} was not reported, then it was estimated as $1.36 \times Hb \times Sa_{O_2} + 0.003 \times Pa_{O_2}$, where Hb was assumed to be 15 g/100 ml for men and 14 g/100 ml for women if unreported, and Sa_{O_2} was assumed to be 98% in normoxia and 100% in hyperoxia if unreported. When not reported, DO_2 was estimated as the product of blood flow and Ca_{O_2}. MRI, magnetic resonance imaging; TCD, transcranial Doppler ultrasound. NO indicates that cerebral blood flow was measured via the nitrous oxide technique (138). Dotted lines indicate studies that were performed in isocapnic conditions.

namely, rest, submaximal, and supramaximal exercise. $\dot{V}O_{2max}$ is the main marker of maximal performance considered in this section, as it is widely considered the best indicator of cardiovascular fitness and aerobic endurance. It is also particularly relevant in the context of hyperoxia, as O_2 delivery is affected by the increase in $F_{I_{O_2}}$.

The majority of literature indicates there is no change in resting $\dot{V}O_2$ (38, 167, 210, 221); however, other studies indicate an elevation (213) or a decrease (158) in $\dot{V}O_2$. It is noteworthy, however, that the latter study from Lodato (158), as well as the one from Bredle et al. (38), was performed in animals. In Peltonen et al. (213), the observed increase in $\dot{V}O_2$ was >40% at rest, while at maximum exercise the improvement was only 13.6%. This discrepancy seems difficult to explain and brings the validity of the measures into question. Unfortunately, the authors did not discuss their resting data. Alternatively, without any significant change in heart rate, stroke volume, or indeed, cardiac output, it could be speculated that changes in ventilation may have accounted for this observation. The initial increase in ventilation upon exposure to hyperoxia has been discussed earlier in the present review, and this would seem untenable. Regrettably, in the Peltonen et al. (213) study, the resting values are not presented, and maximal ventilation did not differ between conditions. The time when gas exchange was measured could also account for the discrepancies in the literature. Indeed, at least in normoxia, it has been suggested that a 10-min period should be used for baseline measurement and that the first 5 min should be discarded to ensure a "true" steady state (219). For instance, Rousseau et al. (237) observed that there is an initial increase in $\dot{V}O_2$ during the first minute of a 20-min exposure to an $F_{I_{O_2}}$ of 0.58 before returning toward normoxic levels. In contrast, MacDonald et al. (167) and Prieur et al. (221), who did not observe any difference in $\dot{V}O_2$ at rest, had their participants breathing for 5 and 10 min, respectively, before collection of expired gases. Unfortunately, little information about resting measurements is provided in either one of the papers by Peltonen and colleagues (210, 213), but it is understood that the resting period did not last longer than 5 min, and gas samples were measured over a maximum period of 30 s. Often, additional and more complex calibrations of the O_2 analyzers are required when manipulating elevations in $F_{I_{O_2}}$; it is unclear whether these aforementioned studies employed such approaches. Similarly, the time of day could have an effect on the response to hyperoxia; however, little is known about this in healthy participants, which warrants further studies.

During submaximal exercise, the majority of studies report either no change (47, 94, 95, 167, 186, 209, 210, 290, 302, 315) or an increase (172, 207, 209, 213, 221, 290) of ≤15% in $\dot{V}O_2$. These observations are not influenced by the modalities of exercise since both steady-state (47, 94, 95, 172, 209, 210, 302, 315) and incremental (167, 186, 207, 213, 221, 290) exercises have been studied in the literature. During submaximal exercise, blood flow is known to respond to changes in Ca_{O_2}; however, when only a small muscle mass is involved, Ca_{O_2} barely influences blood flow during whole body exercise (49), which could explain why some authors (167, 186, 209) did not observe any positive effect on $\dot{V}O_2$ during knee-extension exercise. Nonetheless, as mentioned above, other studies using whole body exercise (cycling, walking, running) also failed to show evidence of any improvement to breathing hyperoxia during submaximal exercise (47, 94, 95, 210, 290, 302, 315). Another potential explanation relates to the intensity of exercise used in the literature. Indeed, studies using incremental protocols consistently failed to show evidence of any difference in $\dot{V}O_2$ at lower intensities, whereas the difference widens (hyperoxia > normoxia) toward more strenuous intensities

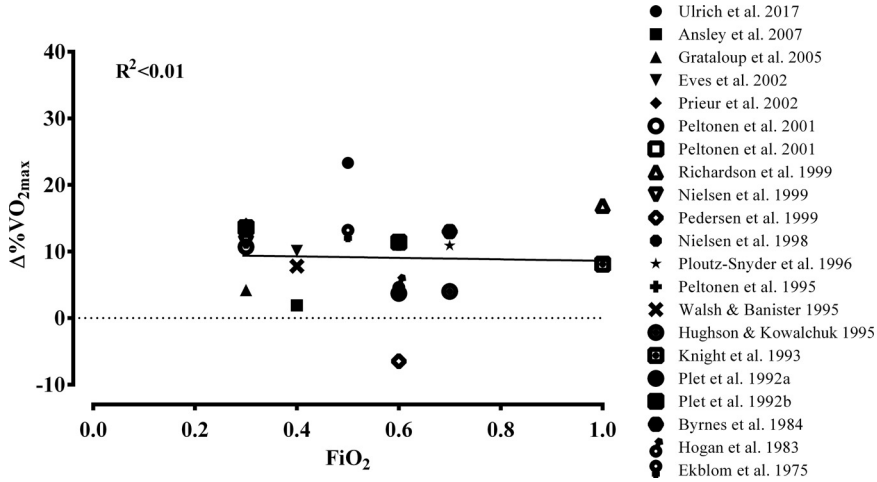


Fig. 9. Relationship between the changes in maximal O_2 uptake ($\dot{V}O_{2max}$) in healthy participants and the inspired fraction of O_2 (FI_{O_2}). $\dot{V}O_{2max}$ data represent a compilation of studies reviewed in Refs. 11, 47, 87, 95, 112, 120, 124, 143, 191, 192, 209, 211–213, 217, 218, 221, 229, 280, and 290.

(207, 221, 290) (50% $\dot{V}O_{2max}$, 70% $\dot{V}O_{2max}$, or above ventilatory threshold). However, this may not be the case during steady-state exercise even at 70% $\dot{V}O_{2max}$ (210).

There is an overwhelming body of evidence suggesting that maximal performance does increase during the breathing of supplemental oxygen (see Figs. 9 and 10). This has been demonstrated during both incremental tests and time to exhaustion (7, 8, 95, 172, 176, 186, 205, 207, 213, 217, 221, 228, 229, 258, 290, 315). Although it has been observed that the magnitude of increase in exercise capacity correlates with the increase in Ca_{O_2} in the hypoxemic range [e.g., exercise-induced arterial hypoxemia (190)], our analysis of the available literature as seen in Figs. 9 and 10 failed to demonstrate a strong linear relationship between markers of performance ($\dot{V}O_{2max}$ or power output) with increasing FI_{O_2}. Thus, previous findings about maximal performance from Sperlich et al. (260) are confirmed but contradict the positive correlation between FI_{O_2} and the changes in power output suggested in another publication by the same author (258). Nevertheless, as acknowledged by Sperlich and colleagues (258, 260) and further extended and confirmed in Figs. 9 and 10 ($\dot{V}O_{2max}$ and power output, respectively), the magnitude of the changes varies greatly. For instance, time to exhaustion seems to be the most substantially affected, with improvements of ≤131% (260) (confirmed in Fig. 10). This is particularly relevant, as time to exhaustion is usually considered a better indicator of "real life" performance than $\dot{V}O_{2max}$. It is also noteworthy that sex differences might exist. For example, Plet et al. (217) reported that when performing an incremental test to exhaustion while breathing a hyperoxic gas mixture containing 50–55% O_2, women exhibited a significant increase in $\dot{V}O_{2max}$ of 12% (vs. 4% in men; not significant) compared with the normoxic test. However, there was no significant sex difference during the time to exhaustion test despite the women exhibiting a ~51% increase, whereas the men improved by only ~33%. The authors suggested the 3% increase in maximal heart rate as well as sex differences in oxyhemoglobin dissociation curve toward an increase in P_{50} (i.e., a decrease in affinity) are potential mechanisms (217). It is well established that hemoglobin concentration usually is lower in females than males; however, this does not seem to influence P_{50} values (125).

The aforementioned literature is essentially relevant to the laboratory setting with potential extrapolation toward clinical populations. However, in the field and in particular during competitions, the exercise must be carried out by breathing normoxic FI_{O_2}. When the exercise test is performed in normoxic/normobaric conditions following acute hyperbaric exposure, no clear increase in $\dot{V}O_{2max}$ or performance is evident

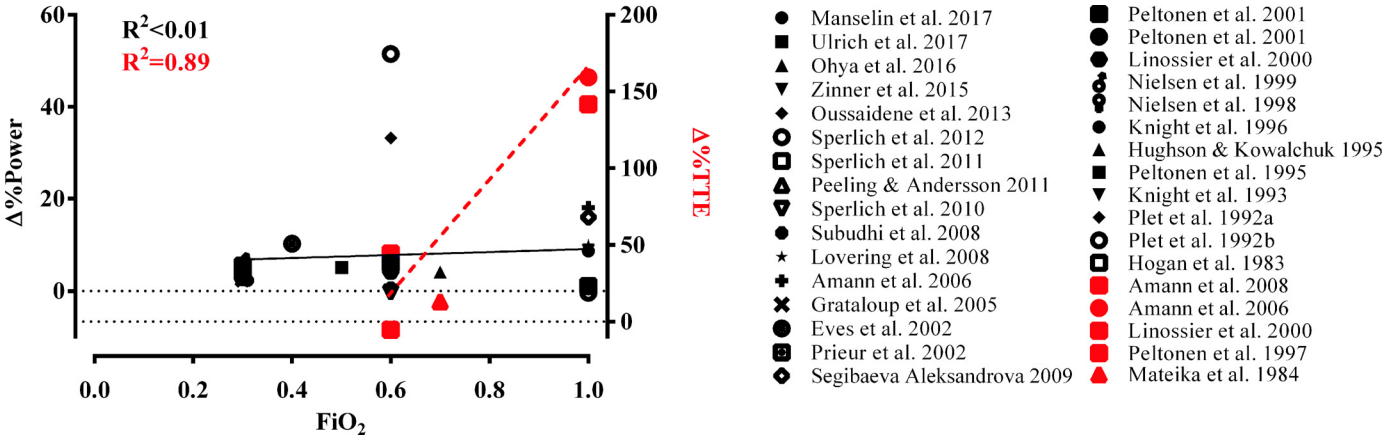


Fig. 10. Relationship between the changes in peak power (*left* *y*-axis) and time to exhaustion (TTE; *right* *y*-axis) in healthy participants and the inspired fraction of O_2 (FI_{O_2}). Peak power/TTE data represent a compilation of studies reviewed in Refs. 7, 95, 112, 120, 124, 142, 143, 153, 164, 172, 192, 205, 207, 211–213, 217, 221, 242, 266, and 280.

irrespective of the fitness level of the participants (177, 259, 301).

Prolonged Effects of Hyperoxia on Performance

The mechanisms of action of hyperoxia are numerous, and as such, the more chronic effects of O_2 supplementation (training) can be difficult to decipher. Also, because of the cost and complexity of training and/or living in hyperbaric/hyperoxic environments, there is a certain paucity in the literature. For instance, during the classic Hana Kai II study in the 1970s, five participants were exposed to 17 days at a pressure of 18.6 atm (depth of ~177 m) in a chamber. Because of the hyperbaric nature of the protocol, the 17 days included 1 day of compression and was followed by an extra 7 days of decompression before the postmeasurements could be performed (122). Both maximal and submaximal performance were improved following the dry saturation dive (76). Similarly in other studies, hyperoxia was combined with other stimuli such as hypoxia (57, 185), making the effect of hyperoxia per se difficult to interpret. These studies did not offer any strong evidence supporting ergogenic effects of a combination of hypoxic and hyperoxic training. Indeed, Morris et al. (185) observed an increase in steady-state maximal performance, whereas Chick et al. (57) did not; however, these authors did notice an improvement in submaximal performance (57).

Studies using only hyperoxia as a stimulus also generated inconsistent results. To the best of our knowledge, only six studies used hyperoxic training in healthy humans without mixing it with another stimulus (45, 140, 188, 215, 216, 218). Among these studies, only Burgos et al. (45) and Perry et al. (215) observed an increase in either maximal or submaximal performance, respectively. Kilding et al. (140) even concluded that, in their experimental conditions, hyperoxia had less of an effect on endurance and high-intensity exercise than normoxic training, whereas the remaining studies did not detect any added benefit with hyperoxia (188, 216, 218). The mechanisms driving these potentially positive adaptations also remain unclear. Indeed, Burgos et al. (45) did not observe any alteration in oxidative markers, whereas Perry et al. (215) concluded that peripheral adaptations must be implicated since the cardiorespiratory parameters did not change. Unfortunately, in a followup paper using the same methods, the authors failed to show evidence of any further gain in skeletal muscle enzyme activity with hyperoxia when compared with normoxic training (216).

As previously mentioned, technical limitations and prohibitive running costs undoubtedly limit the time spent under hyperoxic conditions during these training protocols. Indeed, the participants in these six studies (45, 140, 188, 215, 216, 218) spent an average total time of ~10 h over a 5-wk period (average $F_{I_{O_2}} = 0.8$). In comparison, the recommended hypoxic dose during altitude training is ≥12–16 h/day for 4 wk or 336–448 h in total (314).

Mechanisms of Action

The mechanisms involved during exposure to hyperoxia are numerous. One of the most obvious consequences of supplemental O_2 is on the cardiopulmonary and cardiovascular systems, since breathing more O_2 will increase Pa_{O_2} and in turn Ca_{O_2}. Indeed, $\dot{V}_{O_2}$ is bound by the parameters of the Fick equation, $\dot{V}_{O_2} = \dot{Q} \times (Ca_{O_2} - Cv_{O_2})$, where $\dot{Q}$ is cardiac output and $Ca_{O_2} - Cv_{O_2}$ is the arteriovenous O_2 difference. This means that to allow $\dot{V}_{O_2}$ to increase during hyperoxia, one or more of these parameters must also increase. However, at maximum exercise, $\dot{Q}$ does not seem to be altered by hyperoxia (191, 213). Understandably, Peltonen et al. (213) did not observe any changes in heart rate or stroke volume either when comparing hyperoxic ($F_{I_{O_2}} = 0.32$) and normoxic conditions. Since many others (172, 205, 209, 210, 217) made the same observation about heart rate, one can confidently conclude that $\dot{Q}$ remains at best unchanged at exhaustion in hyperoxia. Other studies have even observed a decrease in $\dot{Q}$ at rest (237) or during light exercise (118) in hyperoxia, whereas Peltonen et al. (213) observed a nonsignificant widening of the $Ca_{O_2} - Cv_{O_2}$, which can be seen as a compensatory mechanism for the blunted $\dot{Q}$. Despite the lack of significance, this most likely accounted for the observed improvement in $\dot{V}_{O_{2max}}$. Interestingly, both Pedersen et al. (209) and Mourtzakis et al. (186) did not observe any clear difference in heart rate, $Ca_{O_2} - Cv_{O_2}$ or indeed $\dot{V}_{O_{2max}}$ between normoxia and hyperoxia. According to Fig. 9, there is no correlation between the changes in $\dot{V}_{O_{2max}}$ and the increase in $F_{I_{O_2}}$. Therefore, based on the above discussion, the increase in Ca_{O_2} ultimately appears to have little effect if it is not accompanied by an increase in $Ca_{O_2} - Cv_{O_2}$. In endurance-trained athletes suffering from exercise-induced arterial hypoxemia, however, it appears that breathing a hyperoxic mixture cannot only correct the hypoxemia but also reduce quadriceps muscle fatigue as well as the rise in blood lactate (235). Taken together, these results suggest that whereas in normoxia the limiting factors of performance are traditionally considered convective, when $F_{I_{O_2}}$ is hypoxic or hyperoxic these limitations become more diffusive and peripheral in nature. For instance, Pedersen et al. (209) suggested that peripheral gas exchange could be impaired due to a decrease in O_2 conductance despite the increase in transit time. We have discussed the hemodynamic consequences of hyperoxia extensively in the previous section. Briefly, the compensatory vasodilation usually observed in the vascular beds of exercising muscles does not seem to be as efficient in hyperoxia. Because the offloading of O_2 and the associated decrease in Sa_{O_2} are stimulating this phenomenon, it seems logical that its efficiency is limited under hyperoxic conditions where Ca_{O_2} is elevated in the first place. It also appears that even during exercise involving only small muscle mass, such as an isolated muscle contraction (which would be affected less by a blunted $\dot{Q}$ than whole body exercise), some studies still reported no change (167, 186, 228, 229) or a decrease (209) in blood flow compared with normoxia. This was associated with an increase (228, 229) or no change (167, 186, 209) in performance, suggesting that the incapability to increase flow seems to be compensated at least in part by the increase in Ca_{O_2}.

The aforementioned vasoconstriction leads to an increase in peripheral vascular resistance and also in blood pressure. Baroreceptors will sense this increase in pressure (i.e., stretch), leading to reductions in sympathetic nerve activity and heart rate (131). During normoxic exercise, baroreceptor resetting limits the increase in blood pressure to <20%, whereas cardiac output increases four- to eightfold (134). However, to the best of our knowledge, little is known about the role of baroreceptor

Table 1. *Current recommendations for the uses of medical oxygen*

Pathology	HBO	NBO
Carbon monoxide poisoning	Recommended treatment with correction of hypocapnia (296)	Recommended treatment with correction of hypocapnia (296)
Decompression illness	Recommended treatment (296)	Acceptable treatment (296)
Traumatic brain injury	Recommended treatment in conjunction with NBO (233)	Acceptable treatment when administered as early as possible (278)
Ischemic stroke	Not recommended in the absence of hypoxemia (26)	Not recommended (236)
Hypoxic ischemic brain injury	Not feasible	Not recommended (141, 261)
Cluster headache	Effective treatment (23)	Recommended treatment (23)
Colon surgery	Technically not possible	Effective treatment (107)
Endoscopy	Technically not possible	Recommended treatment (5, 63)
COPD	Not used with out-patients	Recommended treatment (62)
Diabetic foot ulcer	Recommended treatment in refractory wounds (86, 263)	Acceptable treatment in refractory wounds (184)
Perioperative O_2 against infections	Routinely used, but strong evidence is lacking (251)	Not enough evidence to recommend routine use (311)
Acute myocardial infarction	Not enough evidence to recommend routine use (24)	Not recommended in the absence of hypoxemia (265)
CPR after cardiac arrest	Technically not possible	Useful during prolonged CPR (98) but not recommended with hands-only CPR (251)
Compromised flaps and grafts	Recommended use (19)	Not used

HBO, hyperbaric oxygen; NBO, normobaric oxygen; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation.

resetting during exercise in hyperoxia. Nonetheless, since arterial blood pressure does not seem to change drastically (reviewed in Ref. 260), and we have demonstrated that $\dot{Q}$ is not affected during exercise under hyperoxic/hyperbaric conditions, it is plausible that baroreceptors are not further reset. In a recent paper, Joyner and Casey (134) reviewed potential mechanisms, such as enhanced β-adrenergic vasoconstriction or nitric oxide inactivation, that could explain the decrease in blood flow observed in hyperoxia; however, it was concluded that these factors are unlikely candidates and that overall the mechanisms remain poorly understood.

It has also been demonstrated that hyperoxia can silence peripheral chemoreceptors, thereby decreasing sympathetic nerve activity and contributing to the regulation of blood pressure (241). It is noteworthy that in the experiment by Seals et al. (241) the hyperoxic exposure lasted only 3–4 min, and to the best of our knowledge we do not know whether sympathetic activity remains reduced or not when the exposure to hyperoxia is prolonged beyond this acute phase. Moreover, this sympatho-inhibition tends to fade during exercise (due to baroreceptor resetting and metaboreflex activation) but could still explain at least part of the discrepancies on the regulation of heart rate during submaximal exercise.

Metabolism is also affected by hyperoxia. For instance, it has been reported on several occasions that levels of lactate are lower during both submaximal and maximal exercise when breathing hyperoxia (47, 95, 111, 205, 217, 218). This smaller contribution of the anaerobic metabolism may reflect higher oxidation rates of pyruvate (205, 260). It may also represent a faster lactate clearance in the mitochondrial electron shuttle (137) as well as a slower breakdown of glycogen during exercise (205). There is also evidence from animal studies that cellular respiration is elevated in hyperoxia (119). Similarly, Suzuki (267) recently demonstrated that 1 h of acute exposure to hyperbaria (1 h at 1.3 atm with $F_{I_{O_2}} = 0.21$) and intermittent hyperbaric training (1 h daily 6 days/week for 4 wk) induced an increase in mRNA levels of genes involved in mitochondrial fatty acid oxidation. This effect enhanced performance by promoting oxidative and glycolytic capacities and the expression of proteins involved in mitochondrial biogenesis in mice. Another demonstration of the greater reliance of aerobic metabolism during exercise in hyperoxia is the lower rate of phosphocreatine (PCr) utilization (260). Taken together, these results suggest that the attenuation of metabolic acidosis may contribute to delaying fatigue and in turn improving performance (190). Nonetheless, it also appears that the increased O_2 availability in hyperoxia is reducing mitochondrial efficiency, consequently suggesting that muscle efficiency is unlikely to contribute to any improvement in exercise capacity (150).

MEDICAL USES OF OXYGEN

The use of supplemental oxygen in clinical settings has received greater attention than in applied contexts because its applications are much broader.

Indeed, with various degrees of effectiveness, and not without consequences, supplemental oxygen is used in an attempt to correct tissue hypoxia (e.g., brain ischemia, traumatic brain injury, or carbon monoxide poisoning) as well as to help with wound healing, necrosis, or reperfusion injuries (e.g., compromised grafts). As already mentioned, hyperoxia marginally increases Ca_{O_2}, theoretically increasing tissue DO_2 as long as tissue blood flow remains stable. However, O_2 supplementation causes vasoconstriction in critical vascular beds, including the coronary, cerebral, and renal vasculatures (see Figs. 6 and 8), and if regional perfusion decreases concomitantly with blood hyperoxemia, a seemingly paradoxical situation exists in which the administration of O_2 may cause tissue hypoxemia.

As mentioned in the previous section, hyperoxia or normobaric oxygen (NBO) requires a predetermined gas mixture containing a certain $F_{I_{O_2}}$ (e.g., 0.3–1.0), whereas hyperbaric oxygen (HBO) uses 100% O_2 while exposed to increased atmospheric pressure (296, 297). Typically, depending on the clinical indication, a total pressure of 2 to 3 atm is applied. As a consequence, Pa_{O_2} can exceed 2,000 mmHg and reach 200–400 mmHg in the tissues (271). The main diseases and clinical pathologies in which NBO or HBO is recommended or contraindicated are highlighted in Table 1. Aside from specific scenarios of decompression sickness in diving [described below in *Diving (decompression sickness)*] and carbon monoxide poisoning, where hyperbaric treatment is necessary, the most common methods of delivering hyperoxia in clinical situations

are via nasal cannula or face mask. It is worth noting that although the O_2 percentage in the gas mixture provided is known (usually 100% O_2), the actual $F_{I_{O_2}}$ delivered to the patient can differ depending on the form of administration and flow rate (225). For example, nasal cannulas can deliver an $F_{I_{O_2}}$ of 0.24–0.40 at flow rates of ≤6 l/min, and a simple face mask can provide an $F_{I_{O_2}}$ of 0.35–0.50 at flow rates of 5–10 l/min (136).

Although administration of supplemental oxygen is common, only few randomized clinical trials (RCT) demonstrated benefits in the absence of hypoxemia. Nevertheless, the use of supplemental O_2 is widely considered as safe and, therefore, it constitutes an integral part of clinical practice. For example, in the treatment of cluster headache (23), reducing the oxidative stress associated with colon surgery (107), and the prevention of desaturation during endoscopy (5, 63), the administration of supplemental O_2 is indeed useful. However, because of its many adverse side effects, hyperoxia should only be used to correct hypoxemia with the aim to restore normoxic levels. It is beyond the scope of our review to provide an exhaustive list of every situation in which hyperoxia might be used in clinical practice. Readers are referred to detailed reviews on this topic (12, 62, 135, 251, 271, 286, 297). Rather, the sections outlined next will focus on the utility of hyperoxia in common and somewhat controversial areas. These areas include carbon monoxide poisoning, decompression sickness (DCS), traumatic brain injury (TBI), ischemic stroke, hypoxic ischemic brain injury (HIBI) after cardiac arrest, and chronic hypoxemia. Finally, although oxygen is the "molecule of life," it is also a very potent contributor to oxidative stress for better and worse (251). Therefore, O_2 toxicity and the safety and best practice for the use of supplemental oxygen will also be discussed.

Carbon Monoxide Poisoning

Following a randomized controlled double-blind trial comparing NBO and HBO to treat carbon monoxide (CO) poisoning, Scheinkestel et al. (240) concluded that HBO should not be recommended. Buckley et al. (43) later confirmed following a meta-analysis that it cannot be unequivocally established whether HBO reduces the clinical downstream consequences of carbon monoxide poisoning in vulnerable cerebral tissue. However, these authors acknowledged that the literature remains scarce, and more studies are needed to be fully conclusive. On the contrary, Weaver et al. (298) suggested that three sessions of HBO within 24 h of exposure to acute CO poisoning can reduce the risk of cognitive sequelae for ≤12 mo. At least part of the discrepancy could be reconciled by the fact that HBO seems to be particularly efficient in patients ≥36 yr old or who have had CO exposure intervals ≥24 h (300). Nevertheless, (NBO or HBO) hyperoxia is apparently effective for the treatment of CO poisoning (296). This study from Weaver (296) is a good example of the cost-effective, safe, and simple use of NBO for short-term management before using HBO. However, one should consider CO_2 levels during short-term treatment of CO poisoning with NBO. Indeed, Rucker et al. (238) observed that MCAv decreased below baseline level when participants were recovering from CO exposure with poikilocapnic hyperoxia; however, this reduction in cerebral blood flow was prevented when end-tidal CO_2 ($P_{ET_{CO_2}}$) was maintained to normocapnic level. This is not surprising considering the well-established link between MCAv and $P_{ET_{CO_2}}$ under various physiological stimuli such as exercise (41, 253) or alterations in temperature (16, 279) or inspired gases (4, 121). As a consequence of the increase in ventilation, CO was also cleared out faster during normocapnic hyperoxia.

Diving (Decompression Sickness)

Diving with a self-contained underwater breathing apparatus (SCUBA) is a major physiological stress, and yet the number of recreational, industry, and military divers is increasing. One of the most serious complications of SCUBA diving is DCS, which is often associated with circulating inert gas bubbles resulting from improper decompression (283). These bubbles can block blood supply, cause mechanical damage, or evoke biochemical actions that result in a variety of symptoms ranging from musculoskeletal manifestations (joint and muscle pain), cutaneous manifestations (skin discoloration), neurological manifestations (numbness, dizziness, motor weakness, headache), and vestibular manifestations (vertigo, nausea, vomiting) (72, 283). During descent, the body is able to absorb more nitrogen in the tissues than would be possible at the surface due to breathing at increased ambient pressure, which permits gas to dissolve better in fluids. During ascent, gas supersaturation commonly occurs because of the decrease in ambient pressure, allowing dissolved inert gases to be eliminated from the tissues, resulting in the formation of venous gas emboli (VGE) (84). Asymptomatic VGE are common after resurfacing from SCUBA diving and are normally trapped and eliminated in the pulmonary microcirculation during gas exchange and ventilation (155). Once thought to be the primary cause of decompression sickness, it has been recognized that VGE are quite common even following mild dive profiles such as in recreational dives (156). The traditional view that held VGE responsible for causing decompression injuries has already been disputed (127, 157). Apart from presenting high bubble scores after diving, for VGE to arterialize (arterial gas emboli; AGE), i.e., to cross over from the right to the left side of the circulation, open communication must exist between the venous and arterial circulation either at the level of the heart or in the lungs (18). Intracardiac shunts such as patent foramen ovale (PFO), which are present in ~25–35% of the population (91, 113, 127, 162, 317), have been linked to increased VGE arterialization, and they are still considered an important risk factor for the development of DCS (155). Extracardiac shunts like large intrapulmonary arterial-venous anastomoses (IPAVA) are closed at rest in most individuals but are increasingly recruited as exercise intensity increases and open during submaximal and maximal exercise in 90% of the human population (18, 89, 163, 170). Yet the incidence of DCS that is linked to these events is only 0.01 to 0.019% in recreational divers, 0.03% in US Navy divers, and 0.095% in commercial divers (283).

Although gas bubbles may be present in large quantities during DCS, their presence alone is not an indicator of DCS, as high bubble loads are frequently observed following conservative dives with no clinical implications (85). The central role of bubbles as an inciting factor for DCS is widely accepted, but other pathophysiological responses are also involved in the development of this syndrome (275). SCUBA diving exposes

divers to stresses that are unique to the underwater environment, such as increased ambient pressure, water temperature, increased work of breathing, hyperoxia, and psychological stress (202, 270). These factors are present either during descent, at depth, or during ascent. During descent, with every 10 msw (meters of sea water) ambient pressure increases by 1 atm. Inert gases become more soluble and are taken up by tissues more than at surface pressure. Although breathing compressed air at depths, nitrogen narcosis (a feeling of dizziness and mild euphoria) can appear. As pressure increases, the volume of the lungs decreases, thereby increasing the partial pressures of gases. The partial pressure of oxygen also rises, leading to hyperoxia and inducing oxidative stress accompanied by detrimental physiological consequences on hemodynamic and vascular functions (37, 78, 174, 203). In very high concentrations, oxygen can also show toxic effects on the central nervous system (leading to generalized tonic-clonic convulsions that may result in drowning). At depth, water temperature, physical activity while swimming, and psychological stress of being in an unnatural environment also contribute to cardiovascular alterations (165, 270). While ascending, the solubility of the gases decreases as pressure reduces, and the gases come out of solution, appearing as gas bubbles in the circulation.

In addition to venous and arterial gas emboli, the aforementioned diving-related stress factors can lead to pathophysiological consequences such as hyperoxia-induced oxidative stress (182), impaired endothelial function (202), damaged endothelial integrity with shedding of microparticles (272), and platelet and neutrophil activation promoting inflammation (273–275, 320). Depending on the severity of the diving stress, these alterations can last from hours to days (169, 202, 273). Other than peripheral endothelial damage, markers of blood-brain barrier damage and elevations in intracranial blood flow velocities have also been demonstrated following SCUBA diving, suggesting that oxidative stress and gas emboli can harm the cerebral circulation as well (17, 31). The vast array of physiological consequences of diving are illustrated in Fig. 11.

To prevent the complications described above, divers take decompression stops at different depths while ascending to allow gas bubbles to be eliminated. During these stops the higher arterial oxygen will increase the gradient for inert gas elimination from the tissues (283). As such, high oxygen levels reduce the total tissue gas tension, decreasing the degree of supersaturation, i.e., the probability of gas bubble formation and the risk of DCS. The use of 100% oxygen as a measure of first aid relies on the principle that it can "wash out" inert gas, increasing the partial pressure gradient for inert gas from inside to outside a bubble (283). Some evidence indicates that intravenous injection of lidocaine (297) as well as saline (283) may also be helpful; however, due to the low rate of occurrence, scarce information on best practice is available. Protocols using pressures ranging from 1.9 to 10 atm have been used, and the US Navy uses a pressure of 2.8 atm (equivalent to a depth of 18 m). Vann et al. (283) provided a comprehensive description of the recommended strategy. It is also recommended that recompression is applied as soon as possible, but HBO has been shown to be efficient even when applied many hours after AGE in the brain (33). Overall, HBO seems to be the preferred choice to treat DCS, but NBO has the advantage of being more readily available and is sufficient to wash out inert gases from the body, at least initially.

Supplemental Oxygen and the Cerebrovasculature

As mentioned previously, cerebral DO_2 is the product of CBF and Ca_{O_2}. In healthy adults, hyperoxia decreases CBF by 10–30% (Fig. 8) and marginally increases Ca_{O_2}. Therefore, administration of high oxygen concentrations is likely to decrease cerebral DO_2 (Fig. 8). This might seem somewhat counterintuitive, as one would expect the decrease in CBF to compensate for the increase in Ca_{O_2} to maintain DO_2. This discrepancy can be resolved when considering the respective effects of hyperoxia and CO_2. Indeed, as discussed earlier, after ~5 min of exposure to hyperoxia, one starts to hyperventilate, leading to a decrease in $P_{ET_{CO_2}}$ and vasoconstriction (44, 101, 144). Alternatively, hyperoxia alone leads to vasoconstriction in a dose-dependent manner (101, 144). Taken together, the cumulative effects of hyperoxia and hypocapnia contribute to the decrease in DO_2 described in Fig. 8.

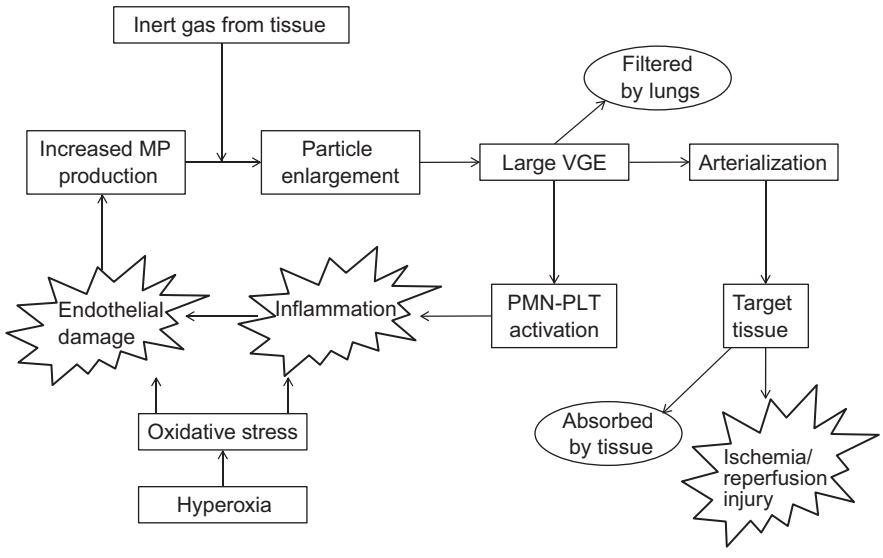


Fig. 11. After surfacing, because of the decrease in ambient pressure, inert gases previously taken up by tissues get released in the form of small gas bubbles. Bubble-mediated shear stress and hyperoxia-induced oxidative stress activate platelets (PLT) and neutrophils [polymorphonuclears (PMN)] that lead to inflammatory vascular injuries that further increase microparticle (MP) production. Because of the influx of inert gases, MPs can become bubble nucleation sites and particles can enlarge in diameter, further increasing stress and related injuries. In most cases, venous gas emboli (VGE; gas bubbles on the venous side of the circulation) get eliminated through the lungs, but they can arterialize and end up in target tissues, where they either get absorbed or lead to ischemia-reperfusion injuries as part of decompression sickness.

The cerebrovascular effects of hyperoxia are limited in clinical populations pertaining to neurocritically ill patients. In these clinical disease states such as TBI, ischemic stroke, or hypoxic ischemic brain injury (HIBI) after cardiac arrest, adequate Ca_{O_2} is necessary to prevent secondary brain injury. Without adequate cerebral DO_2, cellular ischemia stemming from secondary injury can lead to irreversible cell death and necrosis. Here, we summarize the evidence for and against the use of hyperoxia in TBI, ischemic stroke, and HIBI after cardiac arrest.

Traumatic Brain Injury

In TBI, the cerebrum and adjoining central nervous system structures undergo a mechanical injury followed by secondary brain injury, which is a significant determinant of clinical outcome. Post-TBI cerebral ischemia is a major factor known to exacerbate secondary brain damage and ultimately lead to neuron loss (29). The critical ischemic threshold for oligemia has been established at 15 to 20 ml·100 ml^{-1}·min^{-1} (67), and alterations in CBF are observed in the majority of patients with TBI, leading to potentially irreversible damages. Within the array of therapeutic options, NBO and HBO remain significant areas of interest after TBI. Importantly, after TBI, susceptible regions of the cerebrum, including pericontusional tissue, have demonstrated increased endothelial swelling and perivascular edema, thereby increasing the diffusion gradient of DO_2 from the intravascular space to the mitochondria of neurons (180). Therefore, neurons can remain hypoxic even in lieu of optimal CBF and hemoglobin concentrations. Hence, the use of NBO to overcome this diffusion barrier has been suggested as a way to ensure adequate cerebral DO_2 (180).

It also appears that the metabolic state before hyperoxic administration impacts the hyperoxic treatment itself (284). Furthermore, it seems relevant to identify regional differences. Indeed, Nortje et al. (195) noted that in brain regions where the baseline (i.e., posttrauma) cerebral metabolic rate of oxygen ($CMRO_2$) was reduced below 37 μmol·100 ml^{-1}·min^{-1}, hyperoxia increased $CMRO_2$ from 23 to 30 μmol·100 ml^{-1}·min^{-1}, whereas no changes in global CBF or O_2 extraction fraction were observed, therefore suggesting that hyperoxia essentially affects at-risk tissues. Sahoo et al. (239) recently confirmed this site-specific response, observing that cerebral oxygen saturation was not only solely improved in the operated cerebral hemisphere (following severe TBI) but also that this increase was linked with impaired cerebral autoregulation. It was postulated that the ability of the cerebrovasculature to vasoconstrict in response to hyperoxia is impaired following TBI, in turn allowing oxygenation to increase. However, although not reflecting local perfusion, middle cerebral artery velocity was not different from the intact cerebral hemisphere. It is also noteworthy that impaired cerebral autoregulation is associated with worse outcome following TBI (239).

Although logistically more complex, HBO has also been suggested as an efficient treatmeant for TBI notably by stimulating angiogenesis, which improves perfusion to the injured structures and eventually reaps beneficial effects on cognitive impairments (even months to years after injury) (269). According to Rockswold et al. (234), 1 h of HBO treatment every 8 h 2 two wk reduced mortality from 32 to 17%, whereas the time frame seems critical for the use of NBO. Indeed, in a rodent model, when HBO was applied >6 h after a stroke, both histological and clinical ischemic injuries were aggravated (160). Additionally, it has been suggested that reaching a tissue Pa_{O_2} of ≥200 mmHg seems to be the minimum to observe an increase in $CMRO_2$. Based on the physiological responses described above, it is more likely to reach these levels with HBO than NBO. As a matter of fact, this threshold was reached in 51% of the patients treated with 1 h of HBO against only 5% in patients treated with 3 h of NBO (234). It has also been proposed that the most beneficial effects of HBO do not occur during treatment but in the hours following the treatment (233). Indeed, a single 60-min session of HBO treatment at 3 atm immediately after a TBI in a rat model appears to alleviate brain damage for ≤12 h post-TBI; multiple sessions may help extend this duration further (291). In a recent article, Rockswold et al. (233) demonstrated that treatments combining both HBO and NBO are the most efficient by increasing markers of oxidative cerebral metabolism and decreasing intracranial hypertension. This suggests synergistic effects between the two treatments leading to reduced mortality at 6 mo. Although animal studies report some favorable effects of HBO or NBO on cognitive decline and stroke outcomes (30, 295, 321), in part via pre-conditioning mechanisms (154), a systematic review published in the *Cochrane Database of Systematic Reviews* concluded that there is little clinical evidence demonstrating the benefits of HBO in treatment of TBI (25). For instance, Brenner et al. (39) concluded from a retrospective study of 1,547 patients with severe TBI that hyperoxia when administered at some point within the first 24 h of hospitalization is associated with worse short-term functional outcomes and higher mortality. Unfortunately, the Pa_{O_2} values used to define hyperoxia were an average of the 24 h of hospitalization, whereas it has been clearly highlighted above that the time frame is critical.

Ischemic Stroke

Despite published recommendations (2) and the known effect of hyperoxia on CBF and, therefore, cerebral DO_2 (Fig. 8), patients with stroke, even those with satisfactory arterial saturations, are administered oxygen routinely (132). In a pilot study, Singhal et al. (250) reported transient improvement in patients with ischemic strokes. However, findings from an RCT revealed that survival at 7 mo for patients with mild or moderate strokes tended to be higher (not significant) in the control group than in patients who received NBO ($FI_{O_2} = 1.0$) for 24 h after they entered the hospital (236). Consistent with these findings, Bennett et al. (26), in a systematic review of 11 RCTs conducted in 2014, concluded that, based on current evidence, HBO cannot be recommended in clinical practice for early treatment of stroke in the absence of hypoxemia.

Hypoxic Ischemic Brain Injury after Cardiac Arrest

HIBI after cardiac arrest (CA) is a leading cause of mortality and long-term neurologic disability in survivors (243). Following a series of events, the pathophysiology of HIBI manifests in secondary brain injury and neuronal cell death. As we have reviewed recently (243), HIBI begins with primary injury to the brain caused by the immediate cessation of CBF after CA. The secondary injury of HIBI then takes place following the initial CA and restoration of the innate cardiac output. Second-

ary injury is due to a variety of factors, including a compromise in cerebral autoregulation, microcirculatory dysfunction, reperfusion injury, hypoxemia, hyperthermia, unstable Pa_{CO_2}, concomitant anemia, and hyperoxia. Although these factors have been covered in greater detail elsewhere (243), we briefly summarize the utility of hyperoxia in the treatment of HIBI.

Although HBO is likely not feasible due to clinical monitoring, studies that have evaluated NBO in HIBI have produced conflicting results (for a detailed review, see Ref. 243). In brief, however, examination of the Project IMPACT database revealed that, compared with the subjects in the normoxia group, subjects with normobaric hyperoxia (Pa_{O_2} >300 mmHg) had higher associated in-hospital mortality (141). Unfortunately, this finding is hampered by significant unmeasured confounding factors, and the independent effect of NBO on adverse outcome remains controversial. Both Spindelboeck et al. (261) and Bellmomo et al. (22) reported that both hyperoxia and hypoxia were associated with increased mortality, findings consistent with other studies (130); however, after adjustment for $F_{I_{O_2}}$ and relevant covariates, the relationship was no longer significant (22). This latter finding is consisent with those reported by Ihle et al. (126) and Lee et al. (151), who also failed to show an association between normobaric hyperoxia and adverse neurological outcomes with concomitant hypothermia. Thus, although not induced in all of the aforementioned studies, concomitant hypothermia may play a role in modifying the detrimental effects of NBO in HIBI.

Chronic Hypoxemia

Long-term oxygen therapy is widely accepted as the standard treatment for chronic hypoxemia of any origin. Although chronic obstructive pulmonary disease (COPD) is the most common cause of chronic hypoxemia (222), many other forms exist (e.g., lung fibrosis, severe congestive heart failure, life at high altitude, etc.). When appropriately prescribed and correctly used, long-term oxygen therapy has clearly been shown to improve survival in hypoxemic COPD patients. However, as already mentioned, O_2 to correct the hypoxemia must be used judiciously to ensure the appropriate minimal $F_{I_{O_2}}$ to elicit Sa_{O_2} = 90–95% (264). When used appropriately, O_2 therapy is the only "drug" that can prolong survival in hyoxemic COPD patients (people with a mean Pa_{O_2} of 55 mmHg) (264), and only continuous (on average 19 h/day) O_2 administration is effective (194).

Ever since the 1980s, O_2 has been the only drug universally accepted as effective in prolonging survival and improving other outcomes in patients with COPD-related respiratory failure. As reviewed in detail elsewhere (62), the mechanisms by which these beneficial effects of correction of hypoxemia occur are numerous but include improving symptoms of dyspnea, attenuating secondary polycythemia, increasing body weight (i.e., an attenuation of skeletal muscle wasting and weakness), stabilizing and sometimes reversing the progression of pulmonary arterial hypertension with beneficial effects on chronic cor-pulmonale, diminishing cardiac arrhythmias and electrocardiographic findings indicative of myocardial ischemia, enhancing neurophysiological function (*i.e.* relieving depression, improving cognitive function), and eliciting other favorable effects on other generic outcomes (i.e., quality of life, exercise capability, and frequency of hospitalization). It should be noted that long-term O_2 therapy only has a compelling indication when Pa_{O_2} is ≤55 mmHg; however, this therapy should also be considered for patients with less marked hypoxemia (between 55 and 60 mmHg), especially in the presence of pulmonary hypertension (15) or heart failure (223). The aim of long-term O_2 therapy is to maintain a peripheral O_2 hemoglobin saturation >90%.

When compared with healthy individuals, patients with COPD demonstrate lower maximum exercise capacities and lower levels of peak $\dot{V}O_2$ (200, 230). The lowest levels of exercise capacity are observed in patients with more severe COPD (230), but patients with mild COPD also commonly exhibit a reduction in exercise capacity (200). Even in patients who present with normal Pa_{O_2} values at rest, exercise-induced arterial hypoxemia (EIAH; defined as reductions in Pa_{O_2} to <55 mmHg or Sa_{O_2} <88%) is not uncommon (10, 208, 277), suggesting that baseline Sa_{O_2} alone is not a good predictor of EIAH (10, 208). Alternatively, EIAH seems to be a good predictor of mortality in COPD patients, whereas other measures, for example, forced expiratory volume in 1 s (FEV_1), are not (277). The causes for EIAH in COPD include *1*) $\dot{V}_A/\dot{Q}$ mismatching, *2*) diffusion-type limitation, *3*) right-to-left shunt (including intrapulmonary, intracardiac, bronchial, and Thebesian shunts), *4*) alveolar hypoventilation, and *5*) low mixed venous P_{O_2} (208, 288). It should be noted that the latter two mechanisms likely do not have much impact on pulmonary gas exchange at rest or during exercise in healthy individuals (288). However, in some COPD patients, inadequate ventilatory reponses to exercise (i.e., relative alveolar hypoventilation) can cause Pa_{O_2} to fall, thus widening the $A-aP_{O_2}$. Moreover, due to impaired cardiac function in many COPD patients, increases in $\dot{V}O_2$ during exercise can exceed cardiac output and, therefore, lower mixed venous P_{O_2}, which also contributes to widening of the $A-aP_{O_2}$, thus leading to EIAH (289).

Patients with COPD typically also experience dyspnea due to lung hyperinflation during exercise (93, 104, 200); however, the reasons forcing these patients to terminate exercise vary markedly across the population (214). The majority of patients with COPD stop exercise because of dyspnea; however, others are limited by leg fatigue or a combination of dyspnea and leg fatigue. Although the exact proportion varies among studies, leg fatigue appears to be a major limiting factor during cycling (74). Indeed, this will be the symptom causing about one-third of patients with COPD to cease exercise (9, 149). To help reduce dyspnea and improve exercise capacity, COPD patients are often referred to pulmonary rehabilitation programs (e.g., see Refs. 197 and 231).

The following question then arises: is there a clear role for O_2 therapy to improve exercise performance and capacity in patients with COPD and other hypoxemic pathologies? Although other therapeutic approaches such as noninvasive ventilatory support (e.g., see Ref. 201) and low-density gases (i.e., heliox; see Refs. 56 and 147) have been successfully employed as nonpharmacological adjuncts to exercise training to enhance the ability of patients with COPD to exercise, we focus on the putative benefits of supplemental O_2 (92, 257). Here, the use of supplemental O_2 during exercise seems to improve performance in people with bronchial obstruction and mild hypoxemia (mean Pa_{O_2} between 68 and 75 mmHg) (103). Thus, as

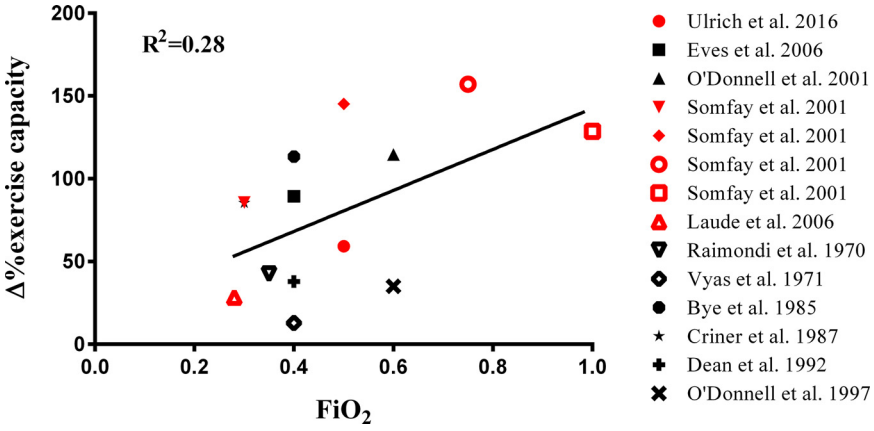


Fig. 12. Relationship between the changes in exercise capacity (either time to exhaustion or distance walked) in chronic obstructive pulmonary disease patients and the inspired fraction of O_2 (FI_{O_2}). Data represent a compilation of studies reviewed in Refs. 46, 65, 70, 93, 147, 198, 199, 224, 257, 281, and 287. Note that red data points indicate nonhypoxemic patients at rest, whereas all others are hypoxemic.

shown in Fig. 12, O_2 seems to generally improve exercise capacity, defined either as time to exhaustion at a constant work rate or as total distance covered in a walk test. Perhaps more importantly is that O_2 also reduces shortness of breath with consequent benefits on quality of life. Notwithstanding the limitation of using regression analyses on between-group data, unlike the relationship in otherwise healthy indiviudals and athletes, it is of interest that in hypoxemic patients there is a general linear relationship between increases in FI_{O_2} and performance. As such, in Fig. 12, this seems to not be necessarily related to preexisting hypoxemia. It would seem that the mechanism(s) by which hyperoxia might affect performance differ between young healthy individuals and elderly individuals with COPD. Although the current evidence demonstrates that supplemental O_2 can increase exercise capacity in both hypoxemic and nonhypoxemic COPD patients (via improved Sa_{O_2}, peripheral tissue oxygenation, and dyspnea), the effects vary considerably among individual patients (reviewed in Refs. 88, 116, 183, and 256). Interestingly, Emtner et al. (92) observed that supplemental O_2 improves acute exercise tolerance in nonhypoxemic patients. Moreover, this approach benefits patients even more during exercise training such as pulmonary rehabilition. However, to date, the use of supplemental O_2 during exercise training for nonhypoxemic patients is not routine clinical practice.

The risk of O_2 therapy is that it not only corrects the hypoxemia but causes hyperoxemia. Unlike in otherwise healthy humans, the use of hyperoxia in clinical conditions of hypoxemia depresses the respiratory drive, putting the patient at risk of respiratory depression, hypercarbia, and carbonarcosis (227). Those exposed to such an effect are patients with chronic respiratory insufficiency of any origin, but in particular COPD patients are extremely prone to CO_2 retention. Besides depressing the ventilation, hyperoxia can directly affect gas exchanges by promoting the collapse of metastable alveoli (1), i.e., of alveoli having a long time constant. Indeed, the inhaled O_2 replaces the other gases in the alveoli and, being quickly absorbed into the blood, decreases the residual volume and prevents the expansion of the alveoli (117). Furthermore, unless remodeling has occurred (166), hyperoxia can reverse the hypoxia-driven vasoconstriction. In hypoventilated alveoli, this means that perfusion increases in otherwise poorly ventilated lung units, thus increasing the ventilation/perfusion unevenness and, ultimately, worsening gas exchange (232). As a consequence, the dead space ventilation increases from 77 to 82% (14). Ultimately, despite the increase in ventilation (following the transient and well-established initial decrease) Pa_{CO_2} rises significantly (40). This makes patients with COPD at special risk of further respiratory function impairment secondary to hyperoxia. However, it should be noted that, in rats exposed to an FI_{O_2} of 1.0 for 7 days, hyperoxia per se (i.e., not when used to correct hypoxemia) can also lead to both anatomic changes in the form of a decrease in the artery to alveoli ratio or a reduction in the lumen of the arteries and pulmonary hypertension (133). Moreover, upon return to normoxic conditions, pulmonary artery pressure increased further.

The use of O_2 supplementation in cardiac care continues to be commonplace; however, its effectiveness remains equivocal (244). A recent Cochrane review found that there is no evidence to support the use of O_2 adminstration in patients arriving at the emergency department with acute myocardial infarction (AMI) (48). Although O_2 supplementation was traditionally part of routine care, the potential for high O_2 delivery to worsen myocardial ischemia has recently brought its use into question (189, 313). It is typically recommended that O_2 be given only if a patient presents as hypoxemic; however, in light of the known risks of hyperoxia, some guidelines have recently removed its recommendation of supplemental O_2 for AMI (319). One of the main mechanisms limiting the potential benefit of O_2 therapy in cardiac patients relates to the negative hemodynamic changes associated with hyperoxia due to the reduction in nitric oxide bioavailability. We have described in detail hyperoxia-induced vasoconstriction in PHYSIOLOGICAL EFFECTS OF HYPEROXIA. This systemic vascular resistance leads to an increase in blood pressure and afterload, thereby reducing stroke volume and cardiac output, which ultimately leads to a decrease in coronary sinus blood flow (171) when a FI_{O_2} of 1.00 is used in both healthy individuals and in congestive heart failure (see Fig. 6). Decreases in stroke volume and subsequent cardiac output have been observed even at very mild levels of hyperoxia ($FI_{O_2} = 0.24$) (114). Moreover, because the hyperoxia-induced vasoconstriction is at least in part mediated by an increase in oxidative stress, it has been postulated that antioxidants could have a positive effect on the coronary circulation. Indeed, there is evidence that the infusion of vitamin C before an acute exposure to hyperoxia ($FI_{O_2} = 1.0$) promptly restores coronary blood velocity and resistance to prehyperoxic levels in both healthy participants (106) and patients with ischemic

heart disease (179). Nevertheless, although promising, this warrants further research about the chronic effects of antioxidant supplementation.

Oxygen Toxicity and Safety

Oxygen toxicity has been well defined and described in many other research articles, including that of Thomson and Paton (276). Therefore, only a brief overview will be provided here. Paul Bert, in the famous book *La Pression Barométrique: Recherche de Physiologie Expérimentale*, originally published in 1878, was the first to describe the toxic effects of hyperbaric oxygen. The formation of free radicals as a by-product of O_2 metabolism, as opposed to oxygen itself, is widely considered the biochemical basis of oxygen toxicity. Protons are transported along the electron transport chain in the mitochondria, resulting in the acceptance of an electron by molecular oxygen, which is then reduced to produce water. However, some of these electrons are incompletely reduced, resulting in the formation of the superoxide radical. Superoxide can react with nitric oxide to form peroxynitrite. Both can react with lipids, DNA, and proteins. Excessive superoxide can cause apoptosis and premature cell death. Similarly, iron-containing proteins (e.g., hemoglobin) can react with hydrogen peroxide and ultimately produce the highly toxic hydroxyl radical via the Fenton reaction (73). Short exposures to high partial pressures can lead to CNS toxicity. Divers and patients under HBO are most commonly affected. Longer exposures to NBO seem to result in pulmonary and ocular toxicity (276).

Visual changes, nausea, dizziness, and confusion are among the first signs of CNS toxicity, which can occur in as little as 10 min at pressures of 4–5 atm. Seizures are the most dramatic signs of O_2 toxicity but are reversible as the inspired P_{O_2} is reduced. According to de Jonge et al. (68), there is a U-shaped relationship between mortality in ICU and Pa_{O_2}, with a nadir between 110 and 150 mmHg. Mortality seemed to increase dramatically when Pa_{O_2} fell below 67 mmHg or exceeded 225 mmHg. More recently, Eastwood et al. (82) confirmed the harmful impact of hypoxemia, but not of hyperoxemia, as long as Pa_{O_2} does not exceed 300 mmHg. Taken together, it seems that hyperoxia might be relevant to treat global hypoxemia, but caution should be exerted for regional hypoxia/hypoxemia.

METHODOLOGICAL CONSIDERATIONS AND FUTURE RESEARCH DIRECTIONS

Theoretically, it is possible to supply the body's requirements for oxygen using only plasma-dissolved oxygen (even in the absence of hemoglobin), but a P_{O_2} of $\sim$3 atm is required. For instance, the typical HBO therapy, independent of the pathology being treated, uses treatments of 1.5 to 2 h at pressures between 2 and 3 atm (271), in line with the 2.5 atm pressure recommended by the Committee of the Undersea and Hyperbaric Medical Society (318). However, it is well established that pressure $>$1 atm will increase the production of ROS (271). To alleviate this hyperoxia-induced increase in ROS production, it has been suggested that it should be supplemented with antioxidants. Indeed, Deb et al. (71) advised a combination of vitamin C and E for saturation divers who are exposed to prolonged confinement within a hyperbaric, hyperoxic environment. Furthermore, Obad and collagues (203, 204) have reported that acute and long term predive supplementation with vitamins C and E alleviate the magnitude and duration of postdive endothelial dysfunction. However, whereas targeting oxidative and nitrosative stress has been suggested for neuroprotection in acute stroke (53), to the best of our knowledge, no study has specifically investigated the combined effect of hyperoxia and antioxidants.

As described earlier in this review, hyperoxia induces vasoconstriction, in turn reducing perfusion (especially in the heart, brain, and muscle). On the other hand, CO_2 is a known vasodilator, thus improving blood flow. It has been observed in healthy children that adding 5% CO_2 to 95% O_2 mitigates the central consequences of hyperoxia (168), at least over the short term. Indeed, when breathing 100% O_2, hyperoxic hyperventilation triggered immediate and extensive responses from cerebral structures projecting to hypothalamic areas mediating both autonomic and hormonal regulation. The addition of 5% CO_2 nearly abolished these responses and elicited responses in additional areas such as the dorsal midbrain involved in respiratory control. Similarly, Xu et al. (318) observed that HBO with an identical gas mixture containing 95% O_2 and 5% CO_2 decreased the infarct size by 32% in stroke induced by transient, embolic, or permanent middle cerebral artery occlusion animal models. There is also preliminary evidence suggesting that patients who are mildly hypercapnic following cardiac arrest have a greater likelihood of discharge than those presenting with hypocapnia or who have been treated with hyperoxia (83). Future studies might consider the addition of CO_2 to potentially offset some of the detrimental effects of hyperoxia. Indeed, the long-term consequences of such an approach remain unclear but should be employed judiciously.

Finally, hyperoxia is more effective for the treatment of CO poisoning if the accompanying hypocapnia is prevented (238). However, hypercapnia or isocapnia should not be considered as the panacea. For instance, Freiberger et al. (102) observed in a study simulating diving injury that CO_2 can impair motor performance and as such plays a role in CNS toxicity. Taken together, when used in the right conditions, CO_2 could potentially be beneficial; however, it appears evident that the effects of normocapnic or hypercapnic hyperoxia deserve further investigation.

CONCLUSION

Oxygen supplementation is often used as a means to nonselectively improve DO_2 to tissues of particular interest, e.g., the skeletal muscles to enhance physical performance, and the brain following stroke or TBI to prevent ischemia. Theoretically, increasing Ca_{O_2} should increase tissue DO_2, assuming blood flow remains constant. However, a paradoxical phenomenon occurs in which hyperoxia induces both hyperventilation and vasoconstriction in many vascular beds. This combination of physiological responses to high Pa_{O_2} offers some benefits but also presents potentially dangerous health implications. Skeletal muscles appear to maintain their DO_2 relatively better than other organs, which manifests practically as improvements in acute exercise performance, albeit with variable effectiveness in healthy individuals. Importantly, O_2 therapy in COPD rehabilitation appears to be generally useful for improving exercise endurance. Conversely, O_2 therapy in the ICU may be detrimental due to an increase in oxidative stress as well as large reductions in blood flow, particularly in the brain

and heart, that fail to compenstate for the marginal increases in Ca_{O_2}, thus impairing DO_2. Hyperoxia may still be useful in certain scenarios (e.g., CO poisoning), but it should be used judiciously and with the primary goal to relieve hypoxemia without inducing hyperoxemia. From an evoluationary perspective, should another atmospheric surge in O_2 concentration occur again (see Fig. 1), it will be of great interest to see if adaption and generation of new forms of life occur.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.V.B. and P.N.A. conceived and designed research; G.B.C. and P.N.A. prepared figures; J.V.B., G.B.C., O.F.B., Z.D., M.S.S., and P.N.A. drafted manuscript; J.V.B., G.B.C., O.F.B., Z.D., M.S.S., and P.N.A. edited and revised manuscript; J.V.B., G.B.C., O.F.B., Z.D., M.S.S., and P.N.A. approved final version of manuscript.

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