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Physiologic Effects of Fluctuations in Oxygen Partial Pressure: A Literature Review

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STATEMENTS

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Abstract

The partial pressure of oxygen (PO_2) delivered to the pilot of a tactical aircraft fluctuates in flight. Regular oscillations with periods of about once per minute have been recorded, as have less frequent but regularly-occurring spikes. The regular oscillations generally fall within the oxygen schedule. Less regular excursions may include mildly hypoxic gas if cabin air is entrained into the mask.

Oxygen partial pressure fluctuations may or may not have physiological effects. Rates of onset differ across the multiple effects of hyperoxia or hypoxia. Thus, fluctuations in inspired oxygen partial pressure might put a pilot into a situation where physiological compensations may lag the environmental conditions. In particular, 1) constriction and dilation of blood vessels with hyperoxia or hypoxia might be inappropriate for the arterial gas composition that prevails; and 2) control of breathing patterns might be slightly impaired. In the absence of direct studies of fluctuating PO_2, information is assembled here primarily from PO_2 step changes.

Executive summary

1) The characteristics of the fluctuations in the oxygen partial pressure (PO_2) supplied to pilots in tactical aircraft have not been disseminated. This review deals with the topic in general.

2) Oxygen partial pressure fluctuations from hyperoxic to normoxic conditions or from more hyperoxic to less hyperoxic conditions are unlikely to change brain blood flow, but may transiently alter oxygen availability to the brain. It requires about two minutes of hyperoxia for brain blood flow changes to begin and more than five minutes before the blood flow reaches its new steady value. The dynamics of brain blood flow during more rapid changes have not been studied.

3) Hypoxia reduces the supply of oxygen to the brain despite the dilation of blood vessels.

   The dynamics of brain blood flow during hypoxia and recovery have not been studied. Thus, the effects during intermittent hypoxia cannot be predicted.

4) After the first or second hypoxic or hyperoxic breath, respiratory minute ventilation (volume of air breathed per minute) increases or decreases, respectively. (The delay can be explained by the circulation time. Blood takes about 6 seconds to go from the lung to the carotid body in a person who is at rest.) However, the stabilization of the respiratory minute ventilation requires a few minutes.

5) Sufficient hyperoxia (inspired oxygen partial pressure greater than about 200 Torr) suppresses peripheral chemoreceptor (carotid body) output. In addition to stimulating ventilation, peripheral chemoreceptors tune the responses of the central chemoreceptors.

   The dynamics have been explored only with step changes, not with rapid fluctuations. With the "wrong" frequency and range of P_IO_2 fluctuation, instabilities in breathing pattern might develop.

6) Periods of intermittent (episodic) hypoxia cause increased respiratory minute ventilation that persists for at least 90 minutes after the end of the exposure. They also increase the ventilatory response to high- or low arterial carbon dioxide partial pressure (P_aCO_2) (increased or decreased minute ventilation, respectively). These effects are probably minor from an operational perspective.

7) During hyperoxia, blood vessels throughout the body constrict. However, chemoreceptor output moderates that effect in the muscles.

   The dynamics of the two processes – vasoconstriction and vasodilation – have not been studied. If the two processes operate at different rates, rapidly varying P_IO_2 could have unexpected effects on blood vessel constriction, effects that could depend on the frequency of the fluctuations. Oxygen-independent reflex control should maintain blood pressure, but there could be implications for the long-term health of aviators.

8) During hypoxia, the opposite occurs: blood vessels throughput the body dilate, but chemoreceptor activity causes some relative blood vessel constriction in the muscles. The constrictor effect on muscles lasts for more than an hour after room air breathing begins.

9) After prolonged episodic hypoxia (fluctuations between normoxia and hypoxia), blood pressure and cholesterol are elevated. Chronic intermittent hypoxia (e.g., sleep apnea) increases oxidative stress without increasing antioxidant production. This is a long-term health effect, not an acute operational concern.

Many effects of intermittent hypoxia or intermittent hyperoxia remain unknown. Most are unlikely to affect pilots during flight. Potential research of possible interest to the aviation community are brain blood flow and ventilatory control during intermittent hypoxia, and blood pressure and blood vessel constriction during intermittent hyperoxia.

Introduction

The oxygen partial pressure (PO_2) delivered to pilots in tactical aircraft may fluctuate frequently and rapidly. This literature search was conducted to find any known physiological effects of these fluctuations and effects related to step changes in Po2 and to postulate from those what is important to investigate in relation to tactical aviation.

The frequency, amplitude, and range of PO_2 of the fluctuations that occur in aircraft differ across air frames. Oxygen generators are designed to produce regular, periodic output oxygen fraction (FO_2) fluctuation within the oxygen schedule. Thus, pilots experience either hyperoxic to hyperoxic or hyperoxic to normoxic fluctuations in PO_2, even at constant cockpit pressure. Rapid fluctuations in cabin pressure cause fluctuations in PO_2 even with constant FO_2. Oxygen generators periodically produce spikes to very high oxygen fraction. At high cabin altitude, antisuffocation valves and mask leaks may cause dips in PO_2 to mildly hypoxic levels when cabin air is inhaled in combination with the gas supplied. Accordingly, fluctuations involving hyperoxia and those involving hypoxia were both considered.

For the purposes of this review, normoxia is loosely defined as the breathing of atmospheric air at the altitudes of the various laboratories whose data are reviewed. Hyperoxia is the result of a higher inspired PO_2, but is usually 100% oxygen in the laboratories, and hypoxia refers to PO_2 equivalent to an inspired FO_2 less than 20% at ground level in the various facilities. More details are given for particular studies when the details are available and relevant.

Lung dilution as a smoothing function

Chemoreceptors and blood vessels are exposed to arterial, not inhaled, PO_2. If the alveolar PO_2 does not fluctuate, neither will the arterial PO_2, and changes in inhaled gas are immaterial. The breath-by-breath dilution of the gas in the lungs means that after a step change in inspired gas, alveolar PO_2 (P_AO_2) changes with each breath approximately (ignoring water vapor and CO_2 in the lungs, and differences between breaths), as

$$\Delta P_AO_2|_{\text{breath i}} = (V_T\text{-}V_D) / FRC \cdot (PO_{2\ \text{inspired}} - P_AO_2|_{\text{breath i}}).$$

$$P_AO_2(t) = PO_{2\ \text{inspired}} \cdot (1 - e^{-KN}) = PO_{2\ \text{inspired}} \cdot (1 - e^{-K \cdot f \cdot t}),$$

where N is breath number after the change in gas, FRC is the lung volume at the end of expiration, f is frequency of breathing, t is time, and $K = (V_T - V_D) / FRC$.

The effect of arterial gas composition is further delayed by the time for the blood to reach the target tissues.

Changes in inspired gas that occur once per breath or faster result in a steady alveolar gas composition that is an average of the two inspired gas conditions, with no significant fluctuation. If the inspired PO2 changes every few breaths, small P_aO_2, fluctuations will begin to appear. Only if the oscillations are slow enough that alveolar gas reaches its new steady state after each gas step will the magnitude of the oscillations in arterial gas reach the magnitude in inspired gas, but changes in inspired gas will be smeared and potentially attenuated by the mixing, mixing that will differ across individuals depending on breathing pattern. Conveniently, measured end tidal PO_2 can be used as a measure of P_AO_2 in any experiments.

Hyperoxia

The literature is thin for fluctuating oxygen levels in the range between normoxia and 100% oxygen breathed on the ground. The material covered here is primarily from steady-state hyperoxic exposure and from responses to oxygen step changes. One paper (Kumar et al., 1991) deals both with within-breath fluctuations in peripheral chemoreceptor output, and with those fluctuations when changes in inspired gas were imposed. Kumar et al. used hypoxic to very mildly hyperoxic gas to avoid the hyperoxic suppression of peripheral chemoreceptors (Lahiri and DeLaney, 1975).

Brain blood flow

Four papers that focus on blood flow to the brain during steady, acute hyperoxia suggest no major changes in oxygen delivery to the brain. The dynamics of the step changes between conditions suggest that an increase in inspired PO_2 causes an initial increase in oxygen availability, but that a relatively slow (longer than 5 minutes) reduction in perfusion brings tissue PO_2 back to baseline. The inference is that brain blood flow remains essentially unchanged during rapid fluctuations in PO_2 in the normoxic to hyperoxic range, but that oxygen availability in the brain follows the changes in inspired gas.

> Early studies (Kety and Schmidt, 1948) used nitrous oxide washout to determine that brain blood flow decreases in resting adults breathing hyperoxic gas. A 13% decrease in mean cerebral flow was accompanied by a similar increase in arterial oxygen content. The rate of oxygen uptake by the brain was unchanged. Mean arterial blood pressure increased during hyperoxic exposure. All measurements were made after 15 or more minutes of exposure.
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> Newer methods permit the examination of regional circulations. Foveal blood flow does not appear to be affected by hyperoxia (Geiser et al., 2009), but grey matter perfusion does (Bulte et al, 2007). When the inspired oxygen fraction (F_IO_2) was increased in 12-minute steps of 20% from room air to 100% oxygen in the laboratory, perfusion to the gray matter, detected by MRI, decreased progressively,

with an overall 7% decrease from air to 100% oxygen (Bulte et al, 2007). (Note that from an oxygen delivery standpoint the increased oxygen content in arterial blood, about 9% with the transition from 21% to 100% oxygen at atmospheric pressure, approximately balances the decrease in perfusion.)

Bulte et al. (2007) changed inspired oxygen sequentially because randomly-selected F_IO_2s caused conflicting results for brain perfusion. Although the end-tidal partial pressure of oxygen ($P_{ET}O_2$) stabilized within 3 minutes of even a large change in F_IO_2, the end tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) changed more slowly, and for large changes in F_IO_2, was still not stable at the end of 12-minutes. Brain blood flow may take a long time to reach steady state after a large swing in F_IO_2 because the drive to breathe, and thus arterial PCO_2, is very sensitive to brain blood flow, brain blood flow is very sensitive to arterial PCO_2, and the system includes the delay for CO_2 to cross the blood-brain barrier. It should be noted that that $P_{ET}CO_2$ depicted on the figures remained grossly normal, but the changes were sufficient to affect the measured brain blood flow.

A fourth paper (Bergofsky and Bertun, 1966) examined, in anesthetized dogs, overall brain blood flow and the oxygen saturation of the blood leaving the brain in comparison to similar measurements for the hind limb and the bowel. Blood flow was calculated by measuring the arterio-venous difference in oxygen between the femoral artery and a jugular vein, a femoral vein, and a mesenteric vein. Blood flow in these three regional circulations (and cardiac output as a whole) decreased across 45 minutes during which the dogs were ventilated with 100% oxygen and kept mostly normocapnic, but blood flow to the brain decreased more than that to the other two regions. At the end of 5 minutes, venous blood oxygen saturation was increased in all regions, indicating early hyperperfusion from an oxygen standpoint. However, after 45 minutes of hyperoxia, jugular vein blood oxygen saturation from the brain was back to control and regional blood flow had decreased by 40%.

More-recent papers indicate that the reduction in brain blood flow with hyperoxia is greater than that reported by Kelte and Schmidt (1948), and that brain oxygen delivery is impacted by 100% oxygen at ground level (Watson et al., 2000). However, other investigators (Ainslie et al., 2008) have shown that hyperoxia has a lesser effect on brain blood flow at high than at low altitude. This may simply be a PO_2 vs. FO_2 effect; 70% inspired oxygen at low altitude has negligible effect on brain blood flow (MacDonald et al., 2018).

It should be noted that if brain blood flow decreases with hyperoxia, the delivery of glucose to the brain decreases in proportion to the blood flow even if oxygen delivery remains constant because of the small increase in arterial blood oxygen content.

Watson et al (2000), using magnetic resonance phase contrast angiography of the carotid and basilar arteries, measured a 9% to 31% reduction in cerebral blood flow in resting adults given 100% oxygen in the laboratory. The decrease was

considerably greater than the 7% to 13% reductions reported by others (Bulte et al., 2007, Kelty and Schmidt, 1948). The decrease in flow began 2 to 4 minutes after the breathing gas change and was complete only after about 6 minutes. The flow increased towards baseline once normoxic gas was reintroduced, but again took about 6 minutes to reach its steady value.

Ainslie et al. (2008), in a study of cerebral autoregulation during hypoxia and hyperoxia, measured blood pressure and middle cerebral artery flow velocity (MCAv) using Doppler ultrasound. Studies were done in the laboratory, at 1,400 m (4,600 ft) altitude, and at about 5,400 m (18,000 ft) altitude while subjects breathed hypoxic gas at sea level and air or 100% oxygen at higher altitudes. (The altitude exposure followed 1 to 2 days for acclimation.) Administration of 100% oxygen caused an approximately 12% decrease in MCAv in the laboratory, but only about 5% after acclimation at high altitude. Conversely, mean arterial pressure was unchanged in the laboratory but decreased about 10% at high altitude. Changes when 100% oxygen was administered were evident after 2 minutes, but were not complete until after 6 or more minutes. Dynamic cerebral autoregulation was unchanged by acute, sea-level hyperoxia, and, though not at baseline levels, was less impaired with hyperoxia at altitude than with altitude alone.

The differential effects on MCAv and blood pressure of hyperoxia at altitude and at sea level may be related to acclimation, but may be simply effects of oxygen partial pressures. MacDonald et al. (2018) used arterial spin labelling and phase contrast MRI to check for decreases in cerebral blood flow when 70% oxygen was inspired, and reported negligible changes.

Chemoreceptor control of breathing

Peripheral chemoreceptor output and chemoreceptor sensitivities are modulated by even small changes in inspired gas (Donoghue et al., 2004; Kumar et al., 1991; Gelfand and Lambertsen 1973; Tansley et al., 1997). Peripheral chemoreceptor activation determines central chemoreceptor sensitivity to CO_2 (Smith et al., 2015), and hyperoxia, which deactivates the peripheral chemoreceptors (Lahiri and DeLaney, 1975), reduces the sensitivity of central chemoreceptors to changes in pH and in PCO_2 (Downes and Lambertsen, 1966).

The adjustments to chemoreceptor sensitivity and its dynamic response primarily fine-tune breathing. Responses are unlikely to cause operationally important changes during rapid fluctuations in inspired PO_2, but overall desensitization to changes in arterial PCO_2, whether elevated or decreased, may be a matter of secondary interest. Further, some instabilities in breathing could result if on- and off- responses cannot complete before the next change in gas.

Chemoreceptor outputs oscillate on a breath-by-breath basis, and also, after a lag presumably related to circulatory delivery time, with perturbations to inspired gas PO_2 and PCO_2 (Kumar et al., 1991). Note that inspired PO_2 forcing functions in Kumar et al.'s study ranged from hypoxic to slightly greater than normoxic; hyperoxia inhibits carotid body discharge when PO_2 exceeds about 200 Torr, based on evidence from cats (Lahiri and DeLaney, 1975) The response to forcing functions depends on their timing relative to inspiration (i.e., early or late). From these results one can infer that carotid body output in pilots will follow inspired PO_2 fluctuations, but only if the P_IO_2 remains in a region where the carotid body discharge is not inhibited by hyperoxia.

At atmospheric pressure, breathing 100% rather than 16% O_2 (Downes and Lambertsen, 1966) or air (Gefand and Lambertsen, 1973) decreases the ventilatory response to CO_2 and slows the decrease in ventilation when CO_2 is removed from the breathing gas. The dynamic measurements provide evidence for inhibition by hyperoxia of the ventilatory response to hypercapnia at both a central site and at the peripheral chemoreceptors (Gefand and Lambertsen, 1973). The dynamics were described as the sum of three exponentials. The two fastest components, with time constants of 3 to 7 and 8 to 15 seconds, respectively, may be affected by rapid fluctuations of inspired PO_2. However, the magnitude of these changes is unlikely to be important with only metabolically-produced CO_2.

Small, chronic changes in PO_2 alter ventilatory responses to hypoxia (Donoghue et al., 2004). During a 6-day, 10-Torr increase in P_aO_2, the acute hypoxic ventilatory response decreased on the first day and remained depressed, but returned to baseline on the first day of room air breathing. Similarly, during a 10-Torr decrease in P_aO_2, the acute hypoxic ventilatory response increased, but returned to baseline on return to room air. Neither the mildly hypoxic nor the mildly hyperoxic condition affected the acute ventilatory response to carbon dioxide, nor did either cause a measurable change in arterial CO_2 partial pressure (P_aCO_2.)

Long prior exposure to hypoxia also causes an increase in the ventilatory response to hyperoxia (Tansley et al., 1997). After 4 and 8 hours with $P_{ET}O_2$ maintained at 55 Torr, ventilatory responses to a sudden step to $P_{ET}O_2$ of 300 Torr were augmented as compared to those after breathing room air, and the elevated response persisted for at least 8 hours after return to room air breathing. The effects were independent of whether the hypoxic period was normo- or hypocapnic.

Systemic vascular and hemodynamic changes

In addition to their effects on ventilation, the peripheral chemoreceptors influence arterial resistance (Guyenet, 2000). In the absence of other effects, changes in PO_2 from normoxia to hyperoxia would reduce muscle sympathetic nervous activity (MSNA)

(Seals et al., 1991) and permit relaxation (passive dilation) of blood vessels within muscle.

Hyperoxia also deactivates nitric oxide (NO) in blood vessels to cause vasoconstriction (Mak et al., 2002). Systemic vasoconstriction has been shown in the sublingual mucosa of rabbits with normobaric 55% and 100% oxygen (Milstein et al., 2016); both the number of open microvessels and their diameters decreased relative to normoxic values.

The neural effects are fast (changes in less than 0.1 second). The dynamics of destruction and regeneration of NO do not appear to have been studied except under hyperbaric conditions. However, rabbit sublingual mucosa reaches its hyperoxic steady state only after about 10 minutes (Milstein et al., 2016). A cumulative effect of mildly hyperoxic fluctuations on NO, and thus on arterial resistance, currently cannot be ruled out. Because the baroreceptors appear to function even during hyperbaric oxygen (Demchenko et al., 2013), blood pressure should be controlled, but its dynamic responses again are unknown

> During graded hyperoxia (transcutaneous PO_2 of 20, 40, and 60 kPa) in supine resting subjects, cardiac stroke volume declined with a linear, negative dose–response relationship as peripheral vascular resistance increased, but heart rate and mean arterial pressure did not change (Bak et al., 2007).
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> Normobaric 100% O_2 enhanced metaboreflex sensitivity during static exercise (Houssière et al., 2005), as manifested by a greater increase in muscle sympathetic nerve activity (MSNA) and mean blood pressure during static handgrip and post-exercise occlusion with hyperoxia than with normoxia.
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> During one hour of normobaric, normocapnic hyperoxia ($P_{ET}O_2$ = 85%) in semi-recumbent subjects, heart rate, cardiac stroke volume, and cardiac output decreased and systemic vascular resistance increased. The decrease in cardiac output and increase in systemic vascular resistance persisted during a subsequent hour of air breathing (Thompson et al., 2006).

Hypoxia

The literature regarding hypoxia is considerably richer than that for hyperoxia for long-term effects, step changes, and fluctuating arterial (not inspired) PO_2. Many articles concerning fluctuations in arterial PO_2 relate to episodic hypoxia in the context of sleep apnea.

Most studies have been conducted with isoocapnic hypoxia, that is, with CO_2 added to inspired gas to maintain the baseline end-tidal carbon dioxide partial pressure. While this is important for determining the effects of hypoxia specifically, the degree of

hypocapnia that accompanies hypoxia cannot be controlled in an aircraft cockpit. There, the hypoxic ventilatory response and the corresponding sensitivity of ventilation to reduced arterial carbon dioxide partial pressure (P_aCO_2) will determine the blood gases for any given low inspired PO_2.

Brain blood flow

Oxygen delivery to the brain is reduced during hypoxia, and P_aCO_2 is an important mediator of that delivery (Hampson et al., 1990). No information was found about the dynamics of the changes.

> During progressive hypoxia (arterial oxygen partial pressure from 100 to 29 Torr, S_aO_2 from 99% to 70%), measurements with NIRS showed that although brain blood volume increased, cerebral hemoglobin oxygen saturation and oxidized cytochrome α, α_3 decreased, decreasing the oxygen availability. Oxygen availability was lower during hypocapnic hypoxia (P_aCO_2 from 39 to 27 Torr progressively as P_aO_2 decreased) than during normocapnic hypoxia because of a smaller increase in blood volume and lower cytochrome α, α_3 oxidation for any hemoglobin oxygen saturation relative to the normocapnic condition (Hampson et al., 1990).

Chemoreceptor output

The ventilatory response to a step change from normoxic to hypoxic gas is a steep increase in minute ventilation, mostly through an increase in tidal volume, but ventilation takes a few minutes to reach a new steady value. The off response looks almost exponential. Both responses begin after one or two breaths of the different gas. (Reynolds and Milhorn, 1973). Part of the stimulus response lag (approximately 6 seconds in a person at rest) is the transit time from the lung to the carotid bodes. Some of the response time must correspond to mixing time in the lungs and to establishment of a new equilibrium between pulmonary capillary blood and alveolar gas.

The normocapnic hypoxic ventilatory response is greater after a period of hyperoxia than without the hyperoxic exposure (Gozal, 1998; Honda et al., 1996). This response is masked when inspired CO_2 is not adjusted to control $P_{ET}CO_2$ during measurement of the hypoxic response.

Systemic vascular and hemodynamic changes

During long breath holds (3 minutes or more), subjects become hypoxemic (low P_aO_2). Cardiac magnetic resonance imaging indicates that stroke volume is maintained by an increase in left ventricular volume in the face of falling ejection fraction (Pingitore et al., 2007).

Even during breathing, cardiovascular effects of hypoxia are complex. Chemoreceptor activation increases MSNA, a factor that causes constriction of arteries in the muscular beds, but hypoxia causes vasodilation by an independent mechanism. The effects of hypoxia on blood pressure and heart rate are modified by reflex controls, the set points and sensitivities of which are modified by hypoxia. The hypoxic ventilatory response lowers $PaCO_2$, which introduces other chemoreceptor responses. Data are available to give the outcomes for a number of different exposures, but most are from a single level of hypoxia, and many under artificial, isocapnic conditions. However, it is clear that baroreflex setpoints are changed, that MSNA increases yet overall vascular resistance decreases, and that the changes persist for some time breathing room air.

Isocapnic hypoxia causes a reflex increase in heart rate, no changes in mean blood pressure but a small increase in pulse pressure and a decrease in the augmentation index suggestive of vasodilation. The effective vasodilation is confirmed by a decrease in systemic vascular resistance in the face of increased cardiac output. (Thompson et al., 2006).

Acute hypoxia causes a large shift in the heart rate baroreflex set point, for a higher blood pressure with higher heart rate than during normoxia, despite a decrease in systemic vascular resistance, but the set point depends on the inspiratory time. The slope of the RR interval (inverse of heart rate) as a function of blood pressure also decreases with hypoxia; RR interval responds less briskly to changes in blood pressure when a person is hypoxic. During hypoxia epinephrine concentration is increased, as are MSNA levels; enhanced clearance of norepinephrine keeps its circulating levels at normoxic levels. (Steinback et al., 2009).

During hypoxia, the elevated heart rate at a given blood pressure is accompanied by elevated MSNA, in other words, a different set point for the sympathetic baroreflex. However, the sympathetic baroreflex gain is not changed by hypoxia. Both resets are independent of tidal volume and respiratory frequency (Halliwell et al. 2003).

After 20 minutes of hypoxia with hypercapnia, a condition mimicking the effects of breathing in a small, closed space, MSNA remained elevated for at least 20 minutes in 8 subjects and for at least 1 hour in two subjects for whom measurements were made at that time; in all subjects, measurements ended before the after-effects had resolved. The other variables that were elevated during the exposure returned to baseline as soon as the breathing did, almost immediately on the removal of the stimulus. The long-term effect relates to hypoxia, not to hypercapnia; in hypercapnic hypercapnia, MSNA, though increased during the exposure, returned to baseline within 10 minutes of room air breathing, as did minute ventilation (Morgan et al., 1995).

Somers et al. (1989) measured MSNA during two levels of hypoxia (14% O_2, 10% O_2) during breathing, and during breath holds after breathing each of the gas

mixtures. The 10% O_2 measurement was repeated with CO_2 added for isocapnia. During breathing, 14% O_2 caused little apparent perturbation other than an increase in heart rate and minute ventilation. Breathing 10% O_2 caused increases in minute ventilation, heart rate, and MSNA, with greater MNA with hypocapnic hypoxia (no added CO_2) than with isocapnic hypoxia, but with blood pressure increases only during isocapnic hypoxia. Apnea caused greater increases in MSNA than those seen during breathing. Ventilatory movements modulated the MSNA response to hypoxia.

Hypoxic – normoxic fluctuations

The pattern of dynamic changes in ventilation with changes in inspired gas raises the question of the ventilatory response time during episodic hypoxia. With low frequency (long-duration) hypoxic episodes, ventilation can respond completely to each gas change. If the gas composition changes rapidly, the response will be dominated by gas mixing in the lungs. Between the two extremes of timing, the off response will interrupt the on response, and vice versa, and the ventilatory response will never be complete. No work appears to have been done on this subject.

Hypoxic episodes are possible in tactical aviation during breath holds at altitude, either voluntary ones performed during anti-G straining maneuvers, or involuntary ones during interruptions of the breathing gas supply. Episodic hypoxia at altitude is also a possibility with valve malfunction of an on-board oxygen concentrator if the wash-out gas vents into the breathing circuit instead of overboard.

Effects of intermittent hypoxia last beyond the end of the exposure. So-called respiratory plasticity is observed in the form of post-exposure increased breathing in response to isocapnic hypoxia or isocapnic room air breathing at rest (Garcia, 2000; Foster et al., 2005; Beaudin et al, 2015).

When PCO_2 was allowed to vary in sleeping subjects, response to hypoxia after intermittent hypoxia was not enhanced but the ventilatory sensitivity to hypocapnia was enhanced and spontaneous ventilation produced lower $P_{ET}CO_2$. The post-exposure increase in ventilation lasted at least 90 minutes (Chowdhuri et al., 2009). After episodic hypoxia, ventilatory sensitivity to CO_2 is enhanced in men and women, but more in men than in women (Morelli et al 2004).

Intermittent hypoxia has long-term cardiovascular effects as seen in patients with sleep apnea and in mice treated with intermittent normocapnic hypoxia – elevated plasma catecholamines (e.g., epinephrine/adrenaline), elevated blood pressure, impaired vasodilation, elevated plasma cholesterol and triglycerides, and enhanced respiratory motor activity (Prabhakar and Semenza, 2012). Chronic intermittent hypoxia increases oxidative stress without increasing antioxidant production (Pilaloux et al, 2002;

Prabhakar and Semenza, 2012) through an increase in activation of hypoxic inducible factor HIF-1α and a decrease in the activation of HIF-2α (Prabhakar and Semenza, 2012); HIF-1 is an activator of oxidative enzymes, and HIF-2, of antioxidants. The concentration of markers of oxidative stress is strongly correlated to the increase in acute hypoxic ventilatory response, indicating an increase in the carotid body sensitivity to hypoxia (Pialoux et al., 2002). Arterial chemoreceptors excite the sympathetic nervous system simultaneously with ventilatory output (Guyenet, 2000), indicating perhaps that the long-term facilitation of respiratory muscle drive after chronic intermittent hypoxia is matched by a long-term enhancement of MSNA.

> In rats treated with recurrent episodic hypoxia (FO_2 of 2% or 3% supplied to the cage for 3 to 6 seconds once every 30 seconds for 7 hours per day), blood pressure increased (Fletcher et al., 1992 a,b;1999). The sympathetic nervous system is involved in the blood pressure increase and in an increase in hematocrit; sympathetic nervous system denervation blocked both. However, cardiac hypertrophy developed independent of the sympathetic nervous system blockade (Fletcher et al., 1992a). Intact carotid bodies are needed for episodic hypoxia to cause elevated BP (Fletcher, 1992b). The renin-angiotensin system also is involved; the increase in blood pressure could be reversed using an angiotensin 1 receptor blocker or by renal denervation (Fletcher et al., 1999).

Conclusions

Physiological effects of oxygen oscillations cannot be determined from the data about response times that can be found in the literature, but some speculation is possible. We know that different systems have different dynamic responses. For example, brain vasoconstriction begins about 2 minutes after a change from room air to 100% oxygen in the laboratory then slowly reaches steady-state vasoconstriction, sometimes in about 6 min (Watson et al., 2000) and sometimes after more than 12 minutes (Bulte et al., 2007). Peripheral vasoconstriction in response to hyperoxia is complete in 10 minutes (Milstein et al., 2016), but may not require that much time. The dynamics of oxygen delivery to the tissues after a change in inspired gas concentration result from a combination of gas mixing in the lungs and circulation time, functions of rate and depth of breathing and external work rate. At rest, blood gases reach steady state 90 seconds to 2 minutes after a step change (MacDonald et al., 2018). The peripheral chemoreceptors respond almost instantaneously, causing dilation or constriction of blood vessels in muscle in less than a tenth of a second. The modulation of ventilatory sensitivity to arterial PCO_2 is also very rapid, but the changes in PCO_2 resulting from changes in breathing are slow to reach the central chemoreceptors. The ventilatory response to hypoxia in arterial blood has both a very fast component and a secondary one that takes about 10 minutes to stabilize, perhaps because of interactions with PCO_2 and brain blood flow.

Only the fast components of any of these effects will be evident during oscillations in PO_2, but a cumulative effect of some of them cannot be ruled out without experimental evidence. Further, the interactions of responses may alter timing. Cumulative effects are seen after long-term steady or intermittent hypoxia, when ventilation and MSNA stay elevated for more than 90 minutes. Until measurements to sample all relevant PO_2 oscillations are complete, the physiological effects of those oscillations remain unknown.

The views expressed in this article reflect the results of research conducted by the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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