

---

# Physiological response to alterations in [O<sub>2</sub>] and [CO<sub>2</sub>]: relevance to respiratory protective devices

W. Jon Williams

National Institute for Occupational Safety and Health, National Personal Protective Technology Laboratory, 626 Cochran Mill Road, P.O.Box 18070, Pittsburgh, PA 15236, USA

E-mail: aun7@cdc.gov

## ABSTRACT

Millions of workers rely on respiratory protective devices (RPD) because of workplace inhalation hazards. Many workers also engage in increased physical activity while wearing RPDs. Demand is placed on the RPD to supply oxygen, purge carbon dioxide produced from the breathing space, and still provide respiratory protection. Moreover, changes in the composition of the breathing atmosphere result in significant physiological responses, mostly affecting the cardiopulmonary systems, which permit short term survival or may result in long term adaptation to the changed atmospheric composition. However, these changes can have a significant impact on the ability to perform occupational tasks and can potentially result in injury and death. This article provides a review of the origin of the earth's atmosphere, the physiology of respiration and responses to changes in environmental concentrations of oxygen and carbon dioxide, impact of exercise, and their relevance to respiratory protection in various occupational settings. In addition, O<sub>2</sub> and CO<sub>2</sub> concentration limit values verses time have also been identified which, if not exceeded, would not be expected to impose physiological distress. However, since changes in the concentrations of these gases in the breathing atmosphere can strongly influence ventilation, RPD function and the physical performance of an individual during respirator wear may be affected. Increased ventilation will place demands on respirators that could result in increased breathing resistance or impact the performance of filter elements. Increased concentration of CO<sub>2</sub> in the breathing space of an RPD may result in a sensation of dyspnea to the degree that the wearer may remove the RPD. Hypoxia may occur unnoticed by the wearer of RPD and the individual may lose consciousness with no warning. This could result in injury or fatality if the loss of consciousness occurred in a dangerous situation (e.g., firefighting, underwater diving, search and rescue activities). Therefore, "scrubbing" or clearing CO<sub>2</sub> from the breathing space, as well as careful monitoring of the atmosphere, is as critical to wearer safety as selection of the proper RPD for the complete protection of the user.

**Keywords:** carbon dioxide, oxygen, hypoxia, hyperoxia, hypercapnia, respiratory protective devices

## INTRODUCTION

Due to the nature of their occupations, millions of workers worldwide are required to wear respiratory protective devices (RPDs) (Roberge et al., 2009, Roberge et al., 2010; US Dept Labor, 2001; NIOSH, 2001). RPDs vary considerably, from air purifying respirators (APRs) or powered air purifying respirators (PAPRs), self-contained breathing apparatus (SCBAs), and underwater breathing apparatus (UBAs), to escape respirators used in emergency situations, such as self-contained self-rescuers (SCSRs). Many of

these devices protect against airborne contaminants without supplying air or other breathing gas mixtures to the user. Therefore, the user may be protected from particulates or other airborne toxins, but still be exposed to an ambient gas mixture that differs significantly from that which is normally found at sea level. RPDs that supply breathing air to the user (SCBAs, UBAs, SCSRs) can malfunction or not adequately remove carbon dioxide from the breathing space, thus exposing the user to an altered breathing gas environment. In special cases, RPDs intentionally expose the user to breathing gas mixtures that significantly differ from the normal atmospheric gas mixture of approximately 79% nitrogen and 21% oxygen with additional trace gases. These special circumstances occur in aviation, underwater diving, and in clinical settings (APRs).

Breathing gas mixtures that differ from normal atmospheric levels can have significant effects on most physiological systems. Many of the physiological responses to exposure to high or low levels of either oxygen or carbon dioxide can have a profound effect on the ability to work safely, to escape from a dangerous situation, and/or on the ability to make clear judgments about the environmental dangers. In addition, alteration of the breathing gas environment can, if severe enough, be deleterious to health or even life-threatening. Therefore, monitoring and control of the breathing gas and limiting user exposure to significant variations in the concentration or partial pressure of oxygen and carbon dioxide is crucial to the safety and health of the worker.

This review briefly discusses the origin of oxygen (O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>) in the Earth's atmosphere, the basic physiology of metabolism as the origin of CO<sub>2</sub> in the body, respiratory physiology and the transport of O<sub>2</sub> to the cells and tissues of the body and the subsequent transport of CO<sub>2</sub> from the tissues to the lungs for removal from the body. Following the basic physiology of respiration, the discussion turns to the physiological responses to altered breathing environments (hyperoxia, hypoxia) and to the effects of excess CO<sub>2</sub> in the blood (hypercapnia). Finally, the discussion turns to the physiological responses to altered partial pressures/concentrations of O<sub>2</sub> and CO<sub>2</sub> during respirator use.

## METHODS

The literature surveyed in this review were obtained through internet searches (PubMed<sup>®</sup>) using key words, electronic database search by a National Institute for Occupational Safety and Health (NIOSH) professional librarian (Index Medicus, OVID), and information contained in contemporary textbooks on physiology and medicine. A list of key word included the following: carbon dioxide, oxygen, physiological exposure limits, high altitude, hypoxia, medical oxygen, hyperoxia, hypercapnia, underwater diving, submarine atmospheres, and confined spaces atmospheres. The search was conducted in order to review the literature published in this topic over the last 25 years. References older than 25 years were also used when the reference was considered relevant to the discussion. A total of 350 general articles out of 1231 were obtained that proved relevant to the present topic. Of the 350 articles on the general topic, the author selected those cited in the present work as the most relevant to a focused review of the literature on the physiological responses to CO<sub>2</sub> and O<sub>2</sub> and the importance to respiratory protection.

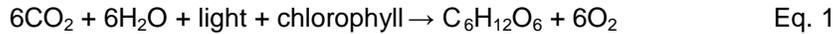
## RESULTS

### The Earth's Atmosphere

Over the last ~ 4 billion years, many physicochemical and later biological processes have occurred that have contributed to the present composition of the Earth's atmosphere (Nunn, 1998; Oró, 1994; Nisbet and Sleep, 2001; Lumb, 2005). The early atmosphere of the Earth began with the cooling of the Earth's crust approximately 3.8 billion years ago. The resulting off-gassing of CO<sub>2</sub> and water vapor eventually comprised the major components of the early atmosphere and, upon the condensation of water, the planet's oceans. The high concentration of atmospheric CO<sub>2</sub> slowly reacted with surface silicates to form

carbonates trapped in the Earth's crust thus greatly reducing the atmospheric partial pressure of CO<sub>2</sub>. The gravitational force of the Earth ( $g = 9.8 \text{ m}\cdot\text{s}^{-2}$ ) was sufficient to allow the retention of heavier gases (CO<sub>2</sub>, O<sub>2</sub>, nitrogen [N<sub>2</sub>]), but not the lighter gases such as hydrogen and helium, thus leading to the loss of these lighter elements to space and leaving a largely N<sub>2</sub> atmosphere.

The development of photosynthetic organisms in the early oceans produced large amounts of atmospheric O<sub>2</sub> as a result of the metabolic process of photosynthesis. Although atmospheric CO<sub>2</sub> now occurs in very low concentrations (~0.03%), its presence is important for photosynthesis as described in the following equation:



This reaction occurs only in the presence of light (and the appropriate chlorophyll molecules) and produces both O<sub>2</sub> and carbohydrates (Stryer, 1981). Essentially all aerobic life on Earth relies on the photosynthetic reaction that supplies not only O<sub>2</sub> to the atmosphere but carbohydrates to the food chain. Over time, the Earth's atmosphere reached its contemporary status composed primarily of 78.8 % N<sub>2</sub> and 20.94% O<sub>2</sub> along with some trace gases with an average sea level barometric pressure of 101.3 kPa (760 mmHg).

Humans have, of necessity, evolved strong physiological defenses (e.g., enzymes such as superoxide dismutase and catalase) against toxic reactive oxygen species (ROS) in order to survive in the oxidizing atmosphere of Earth. This has allowed humans to utilize oxygen and carbohydrates as primary components in the production of energy during aerobic cellular metabolism (Lumb, 2005). This adaptive process has resulted in the physiological responses to CO<sub>2</sub> and O<sub>2</sub> that will be discussed in detail in the following pages.

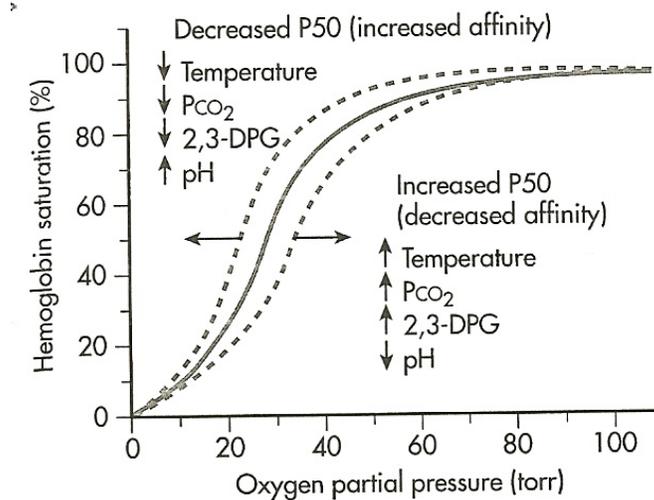
## Oxygen and Carbon Dioxide Gas Exchange in the Lungs

Pulmonary minute ventilation ( $\dot{V}_E$  in L·min<sup>-1</sup>) is generally controlled by neural activity in the respiratory control centers located in areas of the brainstem known as the medulla oblongata and the pons. Gas exchange does not occur in all regions of the pulmonary system. Anatomical dead space (regions where gas diffusion to the blood does not occur) comprises of about 1 ml for each 0.454 kg of lean body mass (~150 ml for a 68 kg person) within the pulmonary system. Physiological dead space is the sum of all parts of the tidal volume (the volume of air inhaled or exhaled in a single breath) that does not participate in gas exchange. In addition, alveolar dead space comprises the volume of air that passes the anatomical dead space and mixes with gas at the alveolar level but does not participate in gas exchange (Lumb, 2005).

Inhaled gas must pass through the regions of dead space to the pulmonary alveoli. Gas exchange occurs in the alveoli (the terminal air sacs of the lung) that are in contact with blood capillaries. The exchange of O<sub>2</sub> into the blood stream and CO<sub>2</sub> out of the blood stream into the alveoli is driven by simple diffusion down a concentration gradient. The partial pressure of O<sub>2</sub> in the alveoli (P<sub>A</sub>O<sub>2</sub>) is approximately 13.3 kPa (100 mmHg) whereas the partial pressure of O<sub>2</sub> in the venous blood (P<sub>V</sub>O<sub>2</sub>) is approximately 5.3 kPa (40 mmHg). Therefore, O<sub>2</sub> will move from the alveoli to the venous blood. O<sub>2</sub> will also be transported into the red blood cells along a similar concentration gradient to be bound to hemoglobin. Conversely, the partial pressure of CO<sub>2</sub> (P<sub>V</sub>CO<sub>2</sub>) in the venous blood is roughly 6.1 kPa (46 mmHg) and is only 5.3 kPa (40 mmHg) in the alveoli. Therefore, CO<sub>2</sub> will move from the venous blood to the alveoli to be exhaled to the atmosphere. After this gas exchange has taken place, arterial blood contains an O<sub>2</sub> partial pressure (P<sub>A</sub>O<sub>2</sub>) of 13.3 kPa (100 mmHg) and a CO<sub>2</sub> partial pressure (P<sub>A</sub>CO<sub>2</sub>) of 5.3 kPa (40 mmHg). The arterial blood arriving at the cells will release O<sub>2</sub> and take up CO<sub>2</sub> based on a similar process of diffusion along a concentration gradient. After O<sub>2</sub> delivery to the cells takes place, the red blood cells have a PO<sub>2</sub> of 5.3 kPa (40 mmHg) and a PCO<sub>2</sub> of 6.1 kPa (46 mmHg). Upon return to the lungs for another round of gas exchange the process is repeated. Proper O<sub>2</sub> delivery to the cells and CO<sub>2</sub> removal from the body will occur as long as a match exists between  $\dot{V}_E$  of the lungs and blood perfusion driven by a robust circulatory system.

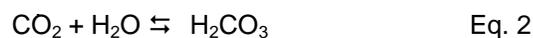
## Oxygen and Carbon Dioxide Transport in the Blood

Oxygen has a very low solubility in the blood and must be transported to the vital organs, working muscles, and brain by a special transport mechanism in the blood. When  $O_2$  diffuses from the alveoli to the circulation, about 98% of the  $O_2$  present in the alveoli is rapidly transported into the red blood cells where it binds to hemoglobin (Hb) to form oxyhemoglobin ( $HbO_2$ ). Oxygen affinity for Hb is very high in the venous blood returning from the general circulation. Oxyhemoglobin in the red blood cells is carried through the arterial circulation to the capillaries where the  $O_2$  is released from Hb and diffuses from the red blood cells to the cells of the target tissues. The  $O_2$  is then utilized in aerobic metabolic energy production. Several factors affect the affinity of  $O_2$  for Hb. For any given  $PO_2$ , an increase in body temperature, blood lactate ( $\downarrow$  pH), increased  $PCO_2$ , or an increase in 2,3-diphosphoglycerate (DPG - a product of anaerobic metabolism in red blood cells), can decrease the affinity of  $O_2$  for Hb (Berne and Levy, 1988). The decreased affinity of  $O_2$  for Hb under these circumstances is beneficial insofar as that it increases the availability of  $O_2$  to tissues under conditions of increased  $O_2$  demand. The effect of  $CO_2$  on the affinity of  $O_2$  for Hb is a phenomenon known as the Bohr Shift (Figure 1).

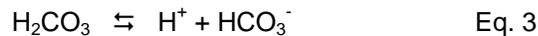


**Figure 1. Shift of the oxyhemoglobin ( $HbO_2$ ) dissociation curve by pH,  $CO_2$  temperature, and 2,3-diphosphoglycerate (2,3-DPG). Reproduced with permission (Berne and Levy, 1988).**

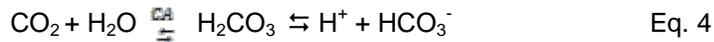
By contrast,  $CO_2$  is about 20-25 times more soluble in blood than  $O_2$ . Carbon dioxide produced as a by-product of aerobic metabolism diffuses from the cells of the tissue to the red blood cells in the circulation along a concentration gradient. In addition,  $CO_2$  combines with Hb to form carbaminohemoglobin ( $HbCO_2$ ). The affinity of Hb for  $CO_2$  increases as  $O_2$  dissociates from Hb during delivery of  $O_2$  to the tissues (Haldane effect). Approximately 5% (arterial) to 30% (arterio-venous difference) of the  $CO_2$  in the blood is transported to the lungs in the form of  $HbCO_2$ . Some of the  $CO_2$  (~5-10%) is carried to the lungs in solution in the blood plasma. Another portion of the  $CO_2$  combines with water to form carbonic acid according to the equation:



This reaction occurs slowly and most of the  $CO_2$  remains in solution in the plasma. However, a small amount of carbonic acid in the plasma dissociates to bicarbonate following the equation:



Whereas the reaction in Eq. 2 occurs in very small amounts in the plasma, it occurs to a very large extent in red blood cells. Red blood cells contain the enzyme *carbonic anhydrase* (CA) which catalyzes the reversible reaction between CO<sub>2</sub> and H<sub>2</sub>O extremely rapidly (approximately 10<sup>6</sup> reactions per second) (Berg et al., 2002) in the following manner:



Approximately 60% (arterio-venous difference) to 90% (arterial) of the CO<sub>2</sub> is transported to the lungs in the form of bicarbonate (West, 1985).

The reaction in Eq. 4 significantly affects respiratory physiology. CO<sub>2</sub>, as a product of aerobic metabolism occurring in cellular mitochondria, increases with an increase in metabolic activity (as with muscular exercise). Although  $\dot{V}_E$  increases linearly with increased O<sub>2</sub> consumption and increased CO<sub>2</sub> production during mild to moderate exercise (e.g., up to ~55% maximal aerobic capacity or  $\dot{V}_{O_2}$  max), the relative P<sub>a</sub>O<sub>2</sub> and P<sub>a</sub>CO<sub>2</sub> do not vary significantly. It is thought that the change in blood pH, and not an increase in molecular CO<sub>2</sub> per se, that stimulates ventilation by action on peripheral chemoreceptors. However, during exercise, the arterial change in pH varies directly with CO<sub>2</sub> content.  $\dot{V}_E$  increases nonlinearly and disproportionately to the exercise effort once the anaerobic threshold is exceeded. The physiological basis for exercise hyperventilation is not completely understood but appears to be related to a decrease in arterial pH that is related to bicarbonate buffering of the increase in metabolic CO<sub>2</sub> production (McArdle et al., 1996).

## Oxygen and Carbon Dioxide and the Control of Respiration

Human life is entirely dependent on an adequate supply of O<sub>2</sub> to support the metabolic processes that produce energy. Because of this, the ability to sense changes in PO<sub>2</sub> has evolved. In addition, although atmospheric CO<sub>2</sub> concentrations are almost negligible, CO<sub>2</sub> is produced as a by-product of metabolism and has a profound effect on the respiratory system. Thus, mechanisms for sensing PCO<sub>2</sub> in the blood have also evolved. Indeed, changes in PCO<sub>2</sub> are more powerful stimulators of respiration than changes in PO<sub>2</sub>. A brief overview of the process is presented in the following pages.

Chemoreceptors exist in both the central nervous system (medulla oblongata in the brain stem) and the peripheral nervous system integrated with the vascular system (i.e., carotid bodies in the carotid artery in the neck and chemoreceptors in the aorta) that sense changes in P<sub>a</sub>O<sub>2</sub> and P<sub>a</sub>CO<sub>2</sub>. When these areas detect changes in P<sub>a</sub>O<sub>2</sub> and P<sub>a</sub>CO<sub>2</sub>, neural signals are integrated into a respiratory response that usually results in a normalization of the P<sub>a</sub>O<sub>2</sub> and/or P<sub>a</sub>CO<sub>2</sub>. Under conditions of hypoxia, the decreased P<sub>a</sub>O<sub>2</sub> is sensed primarily by peripheral chemoreceptors in the carotid bodies and the aortic bodies within the vasculature. The respiratory response is an increase in ventilation in order to increase the O<sub>2</sub> uptake to maintain metabolic energy production. However, if the carotid and aortic bodies are removed or damaged, a decrease in P<sub>a</sub>O<sub>2</sub> can result in a decrease in ventilation because a reduction in brain P<sub>a</sub>O<sub>2</sub> can act directly to depress respiratory cells in the brain. Low P<sub>a</sub>O<sub>2</sub> also increases brain blood flow thereby lowering P<sub>a</sub>CO<sub>2</sub> and [H<sup>+</sup>] and decreasing ventilation. Complete loss of ventilatory drive due to hypoxia has been shown in patients with bilateral resection of the carotid bodies.

Inhalation of supra-atmospheric concentrations of CO<sub>2</sub> also increases pulmonary ventilation. However, the increased P<sub>a</sub>CO<sub>2</sub> stimulates ventilation largely in central chemoreceptors located in the medulla oblongata and pons area of the brainstem and, to a much lesser extent, in the peripheral carotid bodies. The increase in ventilation with increased P<sub>a</sub>CO<sub>2</sub> is exaggerated in the presence of hypoxia. From a functional standpoint, ventilation is stimulated either in the presence of a decreased P<sub>a</sub>O<sub>2</sub> (hypoxia) or an increased P<sub>a</sub>CO<sub>2</sub> (hypercapnia). This results in a ventilatory response that ensures appropriate oxygenation of the blood and elimination of CO<sub>2</sub>.

## Hyperoxia – Physiological Effects

Hyperoxia is defined as an excess of O<sub>2</sub> in the body due to exposure to an O<sub>2</sub> concentration above 21% in the breathing environment or to a normoxic gas concentration under hyperbaric conditions. One does not normally encounter an elevated O<sub>2</sub> level in the atmosphere. Hyperoxia is normally encountered in a clinical setting (breathing 21% - 100% O<sub>2</sub>) or during the use of special gas mixtures for underwater diving or aviation. Hyperoxia has known effects on pulmonary ventilation under normal atmospheric pressures of 1 ATM. Donoghue et al. (2005) have shown that even mild changes in O<sub>2</sub> concentration can effect ventilation.

Exposure to mild hyperoxia can decrease pulmonary ventilation and a small increase can result in an increase in  $\dot{V}_E$  in humans. Breathing mild hyperoxic gas mixtures for a limited period of time is usually not harmful and involves an acclimation process to compensate for the initial increase in ventilation (Donoghue et al., 2005). At sea level, breathing a hyperoxic gas mixture over many hours can result in pulmonary injury through a direct effect of oxidative stress on alveolar cells. Breathing 100% O<sub>2</sub> can result in an initial mild respiratory depression followed by an increase in ventilation due to a paradoxical increase in PCO<sub>2</sub> (Eckenhoff and Longnecker, 1996). The increase in PCO<sub>2</sub> is due to an increase in oxyhemoglobin resulting in a less efficient transport of CO<sub>2</sub> to the lungs for elimination. In contrast, breathing mild hyperoxic gas mixtures under hyperbaric conditions above 1 atmosphere (ATM) can be harmful. Oxygen toxicity can occur when the partial pressure of inspired O<sub>2</sub> reaches a point where neurological or pulmonary changes become pathological. Under greater than 1 ATM (101.3 kPa or 760 mmHg) of pressure, such as occurs during underwater diving, hyperoxic exposure can have effects on the nervous system as manifested by seizures. Seizures will not occur while breathing 100% O<sub>2</sub> at sea level (1 ATM). However, seizures are a potential risk while breathing 100% O<sub>2</sub> at 2 or more ATM ( $\geq$  202.6 kPa or 1520 mmHg) of pressure and, in the US Navy, the threshold for O<sub>2</sub> toxicity which poses a risk for seizures is considered to be between 1.3-1.5 ATM (131.7 – 151.9 kPa or 988 – 1140 mmHg). Although seizures are the most dramatic consequence of O<sub>2</sub> toxicity, other symptoms such as hallucinations, involuntary movements, paresthesias, psychological changes (dysphoria), and vegetative disturbances have been reported (Spigno et al., 2008).

Much of the research on hyperoxia has been performed on the professional underwater diving community. Professional underwater divers are often required to breathe special gas mixtures during deep or “saturation” diving. For instance, hyperoxic gas mixtures can be administered to promote nitrogen washout (i.e., reducing the amount of dissolved N<sub>2</sub> in the body) thereby limiting the potential for decompression sickness (“bends”) and inert gas narcosis (“rapture of the deep”). However, breathing hyperoxic gas mixtures carries the risk of O<sub>2</sub> toxicity since the partial pressure of O<sub>2</sub> increases with depth. The potentially heavy exercise performed by professional divers and an increase in hypercapnia can accelerate the effects of O<sub>2</sub> toxicity (Eckenhoff and Longnecker, 1996). Central nervous system toxicity secondary to hyperoxia is rapidly reversed by a decrease in P<sub>a</sub>O<sub>2</sub> and, in general, no sequelae have been observed assuming, should O<sub>2</sub> toxicity occur, that the diver survives the seizures while still underwater. However, a case report on two recreational underwater divers breathing Nitrox, a hyperoxic breathing gas mixture used for underwater diving, experienced transient global amnesia immediately after surfacing (Spigno et al., 2008). Although the mechanism involved in the induction of transient global amnesia after breathing hyperoxic gas mixtures under hyperbaric conditions is not understood, both divers revealed upon magnetic resonance brain imaging, clinically silent cerebrovascular ischemia. Spigno et al. (2008) suggested that the cerebrovascular ischemia may have been a predisposing feature in these unusual episodes of amnesia after breathing hyperoxic gases mixtures under hyperbaric conditions. The issue remains unresolved.

While at least one study has reported an improvement in maximal exercise during exposure to hyperoxia while wearing a SCBA (Evest et al., 2002), hyperoxia has also been shown to have a negative impact on the cardiovascular system. Recent studies in hyperbaric chambers found reductions in key cardiovascular parameters (heart rate, cardiac output, stroke volume, ejection fraction, total arterial compliance) in military divers subjected to hyperoxic gas mixtures at 1.6-3.0 ATM. These cardiovascular changes are possibly due to a decrease in the force of contraction of the heart as an effect of hyperoxia

or an increase in parasympathetic nervous system activity secondary to hyperoxia (Moléat et al., 2004; Lund et al., 2000). It also appears plausible that the heart is capable of regulating the ratio of O<sub>2</sub> delivery to O<sub>2</sub> consumption to limit hyperoxic damage to cardiomyocytes (Winegrad et al., 1999). General vasoconstriction of the central and peripheral circulation as well as vasoconstriction of the renal and splanchnic regions also results from hyperoxia and the effect appears to be independent of sympathetic neural input (Rousseau et al., 2005; Dean et al., 2003). General, but non-uniform, cerebral vasoconstriction, as evidenced by decreased cerebral blood flow during exposure to hyperbaric hyperoxia, has also been described (Di Piero et al., 2002).

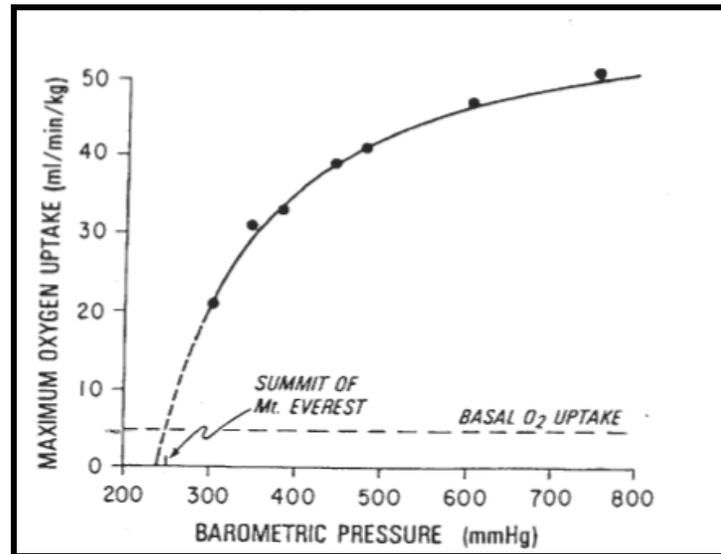
In normoxic emergency clinical settings, sudden retinal artery occlusion is treated by having the patient breath into a paper bag to increase PaCO<sub>2</sub> to induce retinal artery dilation to relieve the occlusion (Mitchell, 2004). However, retinal blood flow is also affected by breathing hyperoxic gas mixtures at 1 ATM (101.3 kPa or 760 mmHg). The decreased blood flow appears to be the result of vasoconstriction that is not mediated by changes in arterial pH (acidosis) and is not counteracted by increased arterial PCO<sub>2</sub> in the systemic circulation (Luksch et al., 2002). Refractive changes can also occur when breathing hyperoxic gas mixtures at >1 ATM. Professional deep sea divers using hyperoxic gas mixtures repetitively over a prolonged period of time (i.e. multiple dives each lasting several hours) have experienced myopia (loss of distance vision) that resolved only after more than one month (Butler et al., 1999).

## Hypoxia – Physiological Effects

Hypoxia occurs when there is insufficient O<sub>2</sub> available for aerobic energy production. Some types of hypoxia can occur when: 1) the atmospheric oxygen concentration or partial pressure is low (such as at altitude), 2) anemic hypoxia where the oxygen transport mechanism in the blood is impaired, and 3) circulatory hypoxia where a stagnant blood supply fails to deliver oxygen to an organ. Much of the physiological research on hypoxia has been performed during high altitude studies (mountain climbing or aviation). In extreme hypoxia, there is not enough O<sub>2</sub> available to maintain basal metabolism and the person dies from asphyxiation.

Predictions regarding reaching the summit of Mt. Everest (altitude at the summit is 8848 m or 29,028 ft) suggested that the PO<sub>2</sub> at that altitude was lower than that needed to sustain basal metabolic needs and, therefore, ascent to the summit could not be performed without supplemental O<sub>2</sub> (West, 2000). Calculations indicated that the maximal O<sub>2</sub> uptake was equal to that required for basal metabolism at the summit of Mt. Everest. Therefore, there was not enough “extra” O<sub>2</sub> available to perform physical work. However, the air density (and therefore the PO<sub>2</sub>) at the summit of Mt. Everest varies seasonally and the first successful ascent to the summit without supplemental O<sub>2</sub> occurred in 1978 (West, 2000). Refined calculations based on data collected indicated that, during the months of May to October, the PO<sub>2</sub> was enough to perform the physical work required to reach the summit whereas during the winter months the PO<sub>2</sub> was not enough. The PO<sub>2</sub> at the summit of Mt. Everest is 6.6 kPa (49.3 mm Hg) (PO<sub>2</sub> at sea level is 21.2 kPa or 159 mm Hg) and is approximately the same as breathing a gas mixture containing only 5-6% (PO<sub>2</sub> = 5.1 – 6.0 kPa or 38 – 45 mmHg) O<sub>2</sub> at sea level (Figure 2).

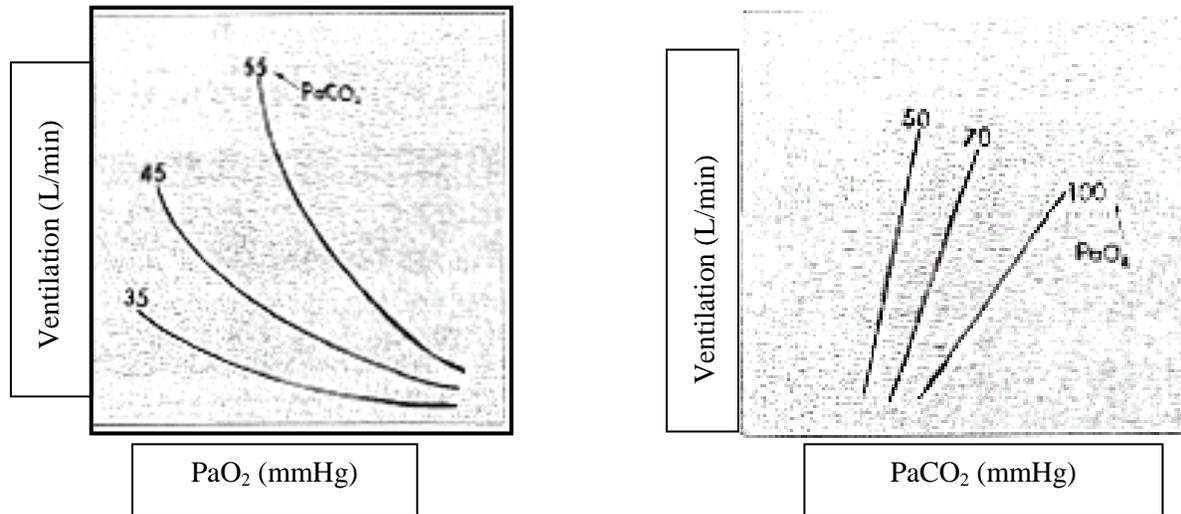
At the summit of Mt. Everest, alveolar PO<sub>2</sub> is 4.7 kPa (35 mmHg) in spite of the low atmospheric PO<sub>2</sub> (Figure 2). This level of alveolar PO<sub>2</sub> is maintained primarily by extreme hyperventilation which results in a decrease in PCO<sub>2</sub> leading to respiratory alkalosis (West, 1993). Nevertheless, the ventilatory suppression normally associated with respiratory alkalosis is overcome by the hypoxic stimulation of ventilation. Whereas measurable adaptive changes in the cerebrovascular response to mild hypoxia occurs over days to weeks (Xu et al., 2006), as the PO<sub>2</sub> falls below a critical value, there is not enough O<sub>2</sub> being transported to the vital organs and the central nervous system to sustain life and health. With atmospheric O<sub>2</sub> concentrations below about 4-5% (PO<sub>2</sub> = 3.9-5.3 kPa or 30-40 mmHg), a loss of consciousness and death will ensue within minutes. The victim is often unaware of the progression to loss of consciousness (Eckenhoff and Longnecker, 1996).



**Figure 2: Maximal  $O_2$  uptake in acclimatized subjects plotted against barometric pressure using the data from Silver Hut expedition. Note that the maximum  $O_2$  uptake at the summit was predicted to be the same as the basal  $O_2$  uptake indicating that no work would be possible. Also note that  $\dot{V}O_{2\max}$  near the summit is exquisitely sensitive to barometric pressure. Reproduced with permission from Blackwell Publishers (West 2000).**

Exposure to hypoxia results in several significant physiological adjustments. Acute hypoxia results in an increased ventilatory response (Crosby et al., 2003) and if the hypoxia is sustained, the peripheral chemoreceptors become hypersensitized and the ventilatory response to hypoxia increases. The increased ventilatory response serves to increase the  $O_2$  content of the blood and eliminate the increased  $PCO_2$  in the lungs (Berne and Levy, 1988) and is accompanied by a concomitant increase in cardiac output as a result of central nervous system stimulation (Eckenhoff and Longnecker, 1996). Although maximal  $O_2$  uptake ( $\dot{V}O_{2\max}$ ) is reduced during exposure to hypoxia (especially for those with a higher  $\dot{V}O_{2\max}$ ), the increase in peripheral chemoreceptor sensitivity during hypoxia results in a smaller drop in  $\dot{V}O_{2\max}$  under hypoxic conditions (Ogawa et al., 2007).

Inhalation of supra-atmospheric concentrations of  $CO_2$  also increases pulmonary ventilation (Berne and Levy, 1988). The increased  $P_aCO_2$  stimulates ventilation largely in central chemoreceptors located in the medulla oblongata and pons area of the brainstem and, to a much lesser extent, in the peripheral carotid bodies. Interestingly, the increase in ventilation with increased  $PCO_2$  is exaggerated in the presence of hypoxia (Figure 3). Thus, from a functional standpoint, ventilation is stimulated either in the presence of a decreased  $PO_2$  (hypoxia) or an increased  $PCO_2$  (hypercapnia) thus ensuring appropriate oxygenation of the blood and elimination of  $CO_2$ .



**Figure 3. The effects of hypoxia and hypercapnia on ventilation. A, At a given PaCO<sub>2</sub>, ventilation increases in a hyperbolic fashion as the PaO<sub>2</sub> is reduced. The ventilatory response to hypoxia is greater the higher the PaCO<sub>2</sub>. B, The ventilatory response to hypercapnia is accentuated by hypoxia. Reproduced with permission (Berne and Levy, 1988).**

Humans can adapt to chronic hypoxia. Some 40 million people live and work at altitudes between 3048 and 5486 m (10,000 - 18,000 ft). Although there are some immediate adaptive responses to exposure to hypoxia (e.g., an increase in ventilation), full adaptation to chronic hypoxia may take months to years. Native populations in the Peruvian Andes and Himalayan mountains reside at altitudes as high as 5486 m (18,000 ft) (McArdle et al., 1996). The barometric pressure at this altitude is approximately 50.6 kPa (380 mmHg) - about one half of that measured at sea level. At this altitude, ambient PO<sub>2</sub> is roughly 10.5 kPa (79 mmHg). The physiological adaptations to this low PO<sub>2</sub> from living at high altitude include increases in the number of pulmonary alveoli at birth, increased blood concentration of Hb and myoglobin (Mb) in the muscle, increased pulmonary ventilation, and a decreased ventilatory response to hypoxia (Eckenhoff and Longnecker, 1996). In spite of an atmospheric PO<sub>2</sub> of 10.5 kPa (79 mmHg), and an arterial PO<sub>2</sub> of 5.1 kPa (38 mmHg), the blood Hb is still 73% saturated. And yet, because the HbO<sub>2</sub> dissociation curve is sigmoidal, even a small decrease in atmospheric PO<sub>2</sub> at this altitude can result in a rapid O<sub>2</sub> desaturation of Hb down to about 50%. Although the great majority of high altitude acclimatized individuals show little or no adverse effects under these circumstances, a small minority of those acclimatized individuals develop Monge's disease (chronic mountain sickness) over time characterized by a poor ventilatory response to hypoxia, low P<sub>a</sub>O<sub>2</sub> and high P<sub>a</sub>CO<sub>2</sub>, high hematocrit, pulmonary hypertension, right heart failure, dyspnea, and lethargy (Lumb, 2005). It should be remembered that the unacclimatized individual rapidly exposed to high altitude would rapidly become incapacitated and probably die from hypoxia.

In acclimation studies conducted by Angerer and Norwak (2003) designed to determine if human subjects could tolerate short-term intermittent exposure to hypoxia, it was revealed that humans could tolerate daily occupational exposure to an atmosphere composed of 13-15% (PO<sub>2</sub> = 13.2 - 15.2 kPa or 99 - 114 mmHg) O<sub>2</sub> (balance nitrogen) for periods of approximately 8 hours without significant physiological or health consequence. The results of this study have been used to support the suggestion that *healthy* workers could function in a hypoxic atmosphere designed for fire suppression with no significant ill-effects. However, the authors cautioned that workers with cardiovascular or pulmonary disease may not tolerate a hypoxic work environment. Moreover, endurance and peripheral limb fatigue have been reported in subjects exposed to acute severe hypoxia (13% O<sub>2</sub> or a PO<sub>2</sub> = 91.7 mmHg). Thus physical activity in the healthy worker would be reduced in a severely hypoxic environment (Romer et al.,

2007). A summary of the effects of hyperoxia and hypoxia at rest and at a high workrate (400 W·m<sup>2</sup>) appear in Table I.

**Table I. The Potential Effects and Limitations on Human Tolerance Imposed by Exposure to Decreased [O<sub>2</sub>] or PO<sub>2</sub> in the Inspired Air at Rest and at High Work Rates (Table constructed from data in Harabin and Survanshi, 1993)**

Average atmospheric %O <sub>2</sub>	Average PO <sub>2</sub> in mmHg	Rest (65 W·m <sup>2</sup> ; $\dot{V}_E=13$ L·min <sup>-1</sup> )		High workrate (400 W·m <sup>2</sup> ; $\dot{V}_E=77$ L·min <sup>-1</sup> )	
		Potential effects and/or Limitations	Exposure Limit (time)	Potential effects and/or Limitations	Exposure Limit (time)
20.9%	79 (Altitude - 5486 m) Andes Mtns	Large increase in ventilation, severe limitations on activity	<30 min	n/a Collapse / unconsciousness	<30 min
20.9%	49 (altitude – 8848 m) Mt. Everest	Large increase in ventilation, severe limitations on activity	<30 min	Collapse / unconsciousness	<30 min
19.5%	148 (1 ATM)	Well tolerated, no symptoms	indefinite	Well tolerated, no symptoms	indefinite
13-15%	99-114 (1 ATM)	Tolerated in the healthy individual, symptoms in the cardiopulmonary patient	hours	Decrease in exercise tolerance, symptoms in the cardiopulmonary patient	<60 min

There is also evidence that hypoxia can affect the thermoregulatory response to cold stressors. Exposure to intermittent hypobaric hypoxia sufficient to cause acclimation resulted in a blunted thermoregulatory response to a standard cold air exposure test at sea level (1 ATM). Much of the response was through peripheral vasoconstriction that may have been driven by hypocapnia due to the increase in the ventilatory response to hypoxia (Launay et al., 2006).

### Hypercapnia - Physiological Effects

The term hypercapnia refers to the presence of excess CO<sub>2</sub> in the blood. The physiological effect of increasing the PCO<sub>2</sub> in the breathing atmosphere has been studied extensively for decades. Hypercapnia actually serves a protective role due to its stimulatory effect on ventilation. As previously noted, alveolar and arterial PO<sub>2</sub> can be maintained by hyperventilation through direct stimulation of the chemoreceptors in the carotid bodies as well as stimulation of the respiratory centers in the brain and brainstem (Berne and Levy, 1988). In addition, studies have demonstrated that increased PCO<sub>2</sub> increases cerebral blood flow and increased regional cerebral oxygenation (Imray et al., 2000). Hypercapnia also is a potent stimulus of peripheral vasculature, but the effect is not as great as on the cerebral vasculature probably due to the critical importance of defending full oxygenation to the brain (Vantanajal et al., 2007). This effect of CO<sub>2</sub> seems, therefore, to increase both the O<sub>2</sub> uptake by stimulating ventilation, but also O<sub>2</sub> delivery through increased cerebral blood flow (probably due to vasodilation of cerebral blood vessels). In fact, when atmospheric CO<sub>2</sub> was chemically scrubbed while human subjects were exposed to simulated high altitude in a hypobaric chamber, both regional cerebral O<sub>2</sub> and peripheral O<sub>2</sub> levels decreased (Imray

et al., 2001). Indeed, breathing gas mixtures containing 3% CO<sub>2</sub> and 35% O<sub>2</sub> have been used at altitude to increase both pulmonary ventilation and cerebral O<sub>2</sub> delivery by increasing cerebral vasodilation and peripheral O<sub>2</sub> delivery to skeletal muscle, thereby increasing human performance (Imray et al., 2003).

In spite of the use of supplemental CO<sub>2</sub> in both clinical and high altitude settings, there are some drawbacks to breathing elevated concentrations of CO<sub>2</sub>. Stereoacuity and perception of coherent motion are reduced at atmospheric concentrations of only 2.5% CO<sub>2</sub> (Sun et al., 1996; Yang et al., 1997). Breathing CO<sub>2</sub> concentrations ranging from 2.5-8% (balance O<sub>2</sub>) has been shown to reduce retinal blood flow (Luksch et al., 2005), and increase the rate of body core temperature heat loss during snow burial (Grissom et al., 2004). Nevertheless, there appear to be no pronounced disabling physiological effects or clinical symptoms associated with exposures of up to 5% CO<sub>2</sub> (Vercruyssen and Kamon, 1984). Breathing gas mixtures containing >6.5% CO<sub>2</sub> decreased performance on reasoning tasks and subjectively increased both irritability and discomfort (Sayers et al., 1987). Subjects participating in a simulated emergency Space Shuttle egress while wearing the launch and entry suit experienced a build-up of >6% CO<sub>2</sub> in the non-conformal helmet during a 5 minute walk on a treadmill at 3.5 mph. This CO<sub>2</sub> concentration limited the ability of most subjects to complete the simulated egress (Bishop et al., 1999). Breathing 10% CO<sub>2</sub> can result in a resting  $\dot{V}_E$  of 75 L·min<sup>-1</sup> which is maximal for many healthy middle-aged untrained individuals (Simon et al., 2006). Thus, while breathing increased CO<sub>2</sub> concentrations may seem beneficial by increasing cerebral blood flow which serves to protect brain oxygenation during exposure to reduced PO<sub>2</sub> at high altitude this strategy must be tempered with the consideration that CO<sub>2</sub> can also impede performance in a crucial way at sea level. Inhalation of CO<sub>2</sub> is known to induce anesthesia in animals and inhalation of 30% CO<sub>2</sub> can induce anesthesia in humans. However, the administration of CO<sub>2</sub> to achieve anesthesia in humans is complicated by the frequent incidence of seizures during the exposure (Lumb, 2005). Carbon dioxide can induce inert gas narcosis in patients with ventilatory failure probably through changes in intracellular pH that alters the metabolic processes that underlie the narcosis (Lumb, 2005).

Increased concentrations of CO<sub>2</sub> in the breathing environment can limit human performance. Elevated concentrations of CO<sub>2</sub> or increased PCO<sub>2</sub> affects pulmonary minute ventilation disproportionate to the level of exercise, thus increasing the metabolic cost of breathing as well as inducing a sense of "air hunger" (dyspnea) that limits exercise tolerance (Bishop et al., 1999). In addition, higher concentrations of CO<sub>2</sub> in the breathing space may increase the displacement of O<sub>2</sub> from hemoglobin, resulting in shifting the O<sub>2</sub> dissociation curve to the right and reducing the O<sub>2</sub> carrying capacity of the blood (Lumb, 2005). This could exacerbate the effects of concurrent hypoxia. A major concern is the potential of elevated levels of CO<sub>2</sub> to induce cardiac arrhythmias (Lumb, 2005). Usually, these arrhythmias are seldom serious but, in the presence of ischemic heart disease, could be life threatening.

A NIOSH report (PB 266 597 August 1976) summarized 19 studies on the effects of CO<sub>2</sub> on human subjects. Both the physiological responses to acute and longer term exposure were described. For high work rates (exercise on a treadmill at 7 km/hr, 10% grade to simulate escape), exposure to 5% CO<sub>2</sub> during this level of work represented the upper limit of tolerance. Exposure to 3% CO<sub>2</sub> posed no strict limitation on activity. It must be noted, however, that breathing concentrations consistently above 3% reduced the time to exhaustion during high intensity running on a treadmill (Craig et al., 1970). Absolute duration of exposure to CO<sub>2</sub> was also summarized (resting state). Human exposure to 10% CO<sub>2</sub> could only be tolerated for a few minutes before loss of consciousness and exposure to 7% CO<sub>2</sub> was only tolerable for <30 min and usually resulted in a CO<sub>2</sub> induced headache. Exposure to 5% CO<sub>2</sub> was tolerable for up to 8 h and 3% CO<sub>2</sub> could be tolerated for up to 15 h. Exposure to 1.5% CO<sub>2</sub> could be tolerated essentially indefinitely.

The summarized NIOSH data indicate that increasing the environmental (inhaled) concentration of CO<sub>2</sub> significantly attenuates the duration of exercise on a treadmill at a constant rate. This effect has also been corroborated by the aforementioned NASA study which reported that the increase in CO<sub>2</sub> concentration in the breathing space of the non-conformal helmet of the Launch Entry Suit significantly reduced the ability to complete a simulated emergency egress. The effects of 5-6% CO<sub>2</sub> in the breathing space of the non-conformal helmet resulted in only one-third of the subjects wearing the Launch Entry Suit being able to complete the 5 minute walk. The effect was clearly dose-related and exacerbated by

increasing the pressure in the antigravity suit bladders, situated in the lower extremities and abdominal region, to > 6.9 kPa (1.0 psi) (Bishop et al., 1999).

The published literature suggests that the reduction of the duration of exercise with increasing concentrations of CO<sub>2</sub> in the breathing atmosphere could be predicted from the increase in metabolic acidosis as evidenced by a decrease in blood pH, the increase in blood PCO<sub>2</sub>, and the increase in blood potassium and phosphorus (Åstrand et al., 2003; Craig et al., 1970; Menn et al., 1968; Sinclair et al., 1971; Luft et al., 1974). In any case, it is apparent that increased PCO<sub>2</sub> in the breathing space or a hypercapnic physiologic state will result in a decrease in overall physical performance.

Increased CO<sub>2</sub> levels can have psychological effects as well. Carbon dioxide levels of >6.5% affect reasoning time (Sayers et al., 1987). Graded increases in CO<sub>2</sub> can induce anxiety and even panic attacks in the susceptible individual. Indeed, and single breath exposures to 30% CO<sub>2</sub> have been safely used as a provocative test (trigger) to assist in the diagnosis of anxiety disorder (Kaye et al., 2004). All of these effects will impact the ability of an individual to perform tasks while exposed to elevated levels of CO<sub>2</sub> in the breathing atmosphere.

Nevertheless, as in the case of hypoxia, human beings have a remarkable capacity to adapt to long term, low level (1.2%) atmospheric CO<sub>2</sub> exposure leading to hypercapnia (Elliott et al., 1998). Experience in submarine crews, astronauts, and cosmonauts exposed for weeks or months to mild hypercapnia during submarine cruises or in space stations during orbital flight have indicated that metabolic adjustments to hypercapnia can occur within days (Lumb, 2005). One of the most visible physiological responses to hypercapnia is an increase in pulmonary ventilation. Yet, after several days of exposure to elevated CO<sub>2</sub> in the breathing atmosphere, the ventilatory frequency returned to near baseline. The mechanism of this adaptive response appears to be an attenuation in the central chemoreceptor response to CO<sub>2</sub> since the compensatory response to hypercapnia is too rapid to be the result of a blood acid-base buffering system that involves the renal resorption of bicarbonate (Elliott et al., 1998). However, long-term hypercapnia tends to reduce the resorption of bicarbonate in spite of the fact that arterial pH returns toward baseline (Lumb, 2005). The increase in brachial blood flow in response to hypercapnia also gradually decreases to baseline (this effect is not observed in the cerebral vasculature) indicating an adaptive process to hypercapnia (Vantanajal et al., 2007). Unexpectedly, humans can survive exposure to extreme hypercapnia (termed "supercarbia" by the authors) as long as the subject (patient) is well oxygenated with a blood PO<sub>2</sub> ≥ 7.3 kPa (55 mmHg). In the clinical cases in which "supercarbia" in the absence of hypoxia was reported, all patients recovered completely with no evidence of short- or long-term sequelae (e.g., no neurological deficit) (Goldstein et al., 1990; Potkin and Swenson, 1992). The critical fact to bear in mind is the adequate oxygenation of the subject during exposure to the episodes of supercarbia. Should the blood PO<sub>2</sub> have fallen below 7.3 kPa (55 mmHg) (hypoxia), a far more negative clinical outcome would have almost certainly been the result.

## Relevance to the Use of RPDs

### General Comments

Although the use of RPDs in the young, fit population is not associated with significant cardiovascular stress (Johnson et al., 2003), breathing high CO<sub>2</sub> while wearing an RPD can have a significant effect on the cardiovascular system in the susceptible individual. Hypercapnia can induce the release of enough catecholamines (epinephrine and norepinephrine) from the sympathetic nervous system to cause cardiac arrhythmias, and reduce cardiac contractility. Hypercapnia can also result in a decrease in cerebral cortex excitability, and can increase the pain threshold through its effects on the central nervous system. All of the above can promote problems with the ability to think clearly, potentially have a negative impact on the cardiovascular system, and reduce the ability to feel pain.

A sufficient increase in CO<sub>2</sub> or a decrease in O<sub>2</sub> can stimulate the respiratory system and increase ventilation thereby placing an increased physical demand on the wearer of the RPD. A sufficient build up of CO<sub>2</sub> in the breathing space of the RPD can negatively impact the ability to perform tasks. Similarly, a decrease in the O<sub>2</sub> level in the breathing space of a respirator can result in a stimulation of

ventilation and a loss of consciousness if the O<sub>2</sub> level is <5% (PO<sub>2</sub> of 3.9-5.3 kPa or 30-40 mmHg). For O<sub>2</sub> concentrations below about 15% (at 1 ATM), the ability to work is seriously diminished and may induce early symptoms such as chest pain/discomfort in persons with coronary artery disease. However, the duration of exposure is important because it usually influences the severity of the clinical symptoms observed. High levels of O<sub>2</sub> (even up to 100% O<sub>2</sub>) can potentially be toxic, but are generally well tolerated at normal atmospheric pressures for several hours. Breathing increased PO<sub>2</sub> while exposed to greater than 2 ATM also can result in O<sub>2</sub> toxicity and should be avoided (Table I).

It should be noted that the CO<sub>2</sub> and O<sub>2</sub> limitations for respirators stated herein reflect maximal allowable average concentrations in the inspired air. During normal respiration, concentrations of CO<sub>2</sub> in the breathing zone at the end of exhalation can be as high as 8%, particularly during exercise. Then, at the start of the following inhalation, concentrations quickly decrease as the breathing zone is flooded with CO<sub>2</sub>-deficient, O<sub>2</sub>-enriched air. As such, CO<sub>2</sub> levels decrease to near atmospheric conditions in the early stages of inhalation and remain at such levels until inhalation ends and another exhalation begins (Figure 4). As long as this occurs, CO<sub>2</sub> concentration averaged for the complete inhalation phase of a breath is unlikely to exceed maximal allowable concentrations. The example presented in Figure 4 illustrates that with an end exhalation CO<sub>2</sub> concentration in the breathing zone of an APR of roughly 6%, the average concentration for all data of the inspired air was approximately 0.7%. Therefore, it is important to understand that average inspired CO<sub>2</sub> concentrations are not the same as single maximal values normally found at the end of an exhaled breath (end-tidal CO<sub>2</sub>, as the terminal portion of exhalation that has a CO<sub>2</sub> concentration almost equal to that of arterial blood).

Based on respirator CO<sub>2</sub> limitations set forth in US standards (United States Code 42 CFR pt. 84, 2004) and international standards documents (e.g., Japanese Industrial Standard, JIS M 7651, 1996), it is evident that most requirements are below concentrations known to impair physiological or psychological performance, possibly as a built-in margin of error for individuals who may exhibit greater CO<sub>2</sub> sensitivity than others (Roberge, 2009). The 42 CFR pt. 84 is based on a time weighted average of CO<sub>2</sub> exposure ranging from 2.5% for ≤ 30 minutes to 1.0% for 240 minutes. This range has been adopted by the JIS and European standards organizations (BS EN 12941:1998+A2:2008). In the UK, maximal permissible limit for CO<sub>2</sub> is significantly less than in the US, i.e. 1.5% for 15 minutes (BS EN 12941:1998+A2:2008). Although the JIS sets upper limits of exposure to a maximum of 3% CO<sub>2</sub> (JIS M 7651, 1996, in Japanese) for all exposure regardless of time, the practical limit for the JIS is 1% CO<sub>2</sub> exposure. Both the Mine Safety and Health Administration (MSHA) and the Occupational Safety and Health Administration (OSHA) (29 CFR pt. 1910.1000) consider exposure to 5000 ppm CO<sub>2</sub> (0.5%) in the breathable atmosphere to be tolerable over a time weighted average of 8 hours. These limits have been adopted by several European countries (Austria, Belgium, Denmark, Finland, Germany, and Hungary), Australia, the UK, and Japan. NIOSH (30 CFR 11.3(t)) considers that an atmosphere containing 40,000 ppm CO<sub>2</sub> (4% CO<sub>2</sub>) to be immediately dangerous to life and health (IDLH). Nevertheless, the differences between maximal allowable concentrations and concentrations known to significantly impair performance suggest that somewhat higher concentrations of CO<sub>2</sub> could be inhaled without harm for certain respirators and for certain periods of time. For example, a NIOSH respirator certification procedure (Procedure No. CET – APRS-STP-CBRN-0454) allows for up to 2.5% CO<sub>2</sub> V<sub>Dresp</sub> for 15-30 min and 2.0% V<sub>Dresp</sub> for 45-60 min for chemical, biological, radiological, and nuclear (CBRN) APRs used for escape. Further, NIOSH Procedure No. RCT-APR-STP-0063 and 0064 allow for a V<sub>Dresp</sub> of 1.0% CO<sub>2</sub> with the PAPR blower on and 2.0% CO<sub>2</sub> with the blower off, respectively.

NIOSH also sets the minimum permissible O<sub>2</sub> level in the breathable air is 19.5% at 1 ATA (hypoxia at sea level – 29 CFR 1910.94) for any duration of time. However, NIOSH does not consider hyperoxia an immediate hazard at 1 ATM absolute (barometric pressure at sea level). The JIS regards 18% O<sub>2</sub> (hypoxia) as the lowest acceptable atmospheric concentration for filtering respirators but also does not consider hyperoxia to be a significant hazard at 1 ATM (JIS M 7651, 1996, in Japanese). At high workloads, the demand for O<sub>2</sub> increases to meet the metabolic demands of working muscles. This increased  $\dot{V}O_2$  is accompanied by increases in heart rate and cardiac output. The increase in O<sub>2</sub> consumption is directly related to workload as shown in Table II. This table is modified from ISO/TS 16976-1 Respiratory Protective Devices – Human Factors – Part 1: Metabolic Rates and Respiratory Flow Rates (ISO/TS 16976-1:2007 [E]).

Individuals engaging in activities within the range of metabolic rates (workloads) outlined in Table II must be able to increase their O<sub>2</sub> uptake to meet the increase in metabolic demand. If that person is wearing a RPD, the RPD must allow for this increase in O<sub>2</sub> consumption. If the person is wearing an APR in a “normal” atmosphere at sea level, then the partial pressure of O<sub>2</sub> is sufficient to allow the person to increase his/her  $\dot{V}O_2$  to meet an increase in metabolic demand. Should a person be using an APR in an “abnormal” atmosphere (e.g., the partial pressure of O<sub>2</sub> is sub-atmospheric) then the person may be protected from particulates by the filter but may not be able to increase his/her  $\dot{V}O_2$  to meet the metabolic demand because the amount of available O<sub>2</sub> in the atmosphere is too low (hypoxia). In a hyperoxic or hypoxic environment, there is no significant physiological difference between wearing an APR and not wearing an APR at all. If the person is wearing an SCBA, and as long as the device is functioning correctly, the wearer should be able to increase his/her  $\dot{V}O_2$  regardless of the atmospheric concentration or partial pressure of O<sub>2</sub>. However, since the air supply is limited, an increased  $\dot{V}O_2$  will deplete the air cylinder supply more rapidly than at a lower  $\dot{V}O_2$ .

**Table II: Metabolic Rates and O<sub>2</sub> Consumption ( $\dot{V}O_2$ ) Associated with 8 Levels of Work Likely to Be Encountered in a Variety of Occupations (Assuming a 1.75 m Body Height, 70 kg Body Weight and a Body Surface Area = 1.84 m<sup>2</sup>; The CO<sub>2</sub> Values ( $\dot{V}CO_2$ ), which Represent the Amount of CO<sub>2</sub> Being Exhaled into the Atmosphere or Respirator Breathing Space, Are Calculated from the Estimated Respiratory Exchange Ratio (RER) at each Exercise Level)**

Metabolic Rate W/m <sup>2</sup>	$\dot{V}O_2$ (mL·kg·min <sup>-1</sup> )	$\dot{V}CO_2$ (mL·kg·min <sup>-1</sup> )
65	~4.91	~4.03
100	~7.54	~6.40
165	~12.46	~11.20
230	~17.36	~16.49
290	~21.90	~21.14
400	~30.20	~30.20
475	~35.86	~37.57
600	~45.30	~52.09

As the O<sub>2</sub> consumption increases in response to increased workload, so will the metabolically produced CO<sub>2</sub>. The increased production of CO<sub>2</sub> ( $\dot{V}CO_2$ ) will be exhaled to either the atmosphere or into the breathing (dead) space of the RPD. If exhaled into the dead space of the respirator, there is the possibility that the CO<sub>2</sub> will not be completely removed from the RPD breathing space and, therefore, will be re-breathed by the user. Whether none, some, or all of the CO<sub>2</sub> is re-inhaled by the wearer depends on such factors as respirator design (e.g., fit of the oral-nasal cavity inside a full-facepiece APR), and internal flow dynamics. In any case, should CO<sub>2</sub> continually increase in the RPD breathing space, re-breathing this accumulated CO<sub>2</sub> will result in hypercapnia and the stimulation of ventilation. Studies using unmanned assessments of respirator CO<sub>2</sub> levels in various RPD and with human subjects wearing various RPD for underwater diving have shown that, depending on the dead space characteristics of the RPD, the greater the workload, the greater the end-tidal CO<sub>2</sub> in the dead space that was being re-

breathed and the greater the stimulation of ventilation (Caretti and Coyne, 2008; Warkander and Lundgren, 1995). If ventilation increases against a RPD-imposed resistance to breathing, the resulting dyspnea could be difficult if not intolerable to the RPD wearer and reduce the time to exhaustion for a given task (see previous discussion). Indeed, increased ventilation while wearing an RPD with specific different inhalation and exhalation resistances has been shown to result in decreases in work performance times, peak flow rates, and O<sub>2</sub> consumption (Caretti et al., 2006).

In any case, whether wearing an APR, a PAPR, or an SCBA, the levels of O<sub>2</sub> within the breathing space must be sufficient to meet the metabolic demands of the user. This will be defined by the physiological responses to hyperoxia, hypoxia, or hypercapnia discussed previously. If the breathing atmosphere contains less than 5% O<sub>2</sub>, regardless of whether it is an environmental (high altitude) or a RPD equipment malfunction, the physiological effect is the same. If the level of CO<sub>2</sub> increases to 10% within the breathing atmosphere, regardless of the cause, the physiological response is the same. Thus, air-supply RPD must be designed to deliver the appropriate amount of O<sub>2</sub> and control the level of CO<sub>2</sub> within the physiological limits discussed above. Should the breathing atmosphere change, the physiological responses will change accordingly. In addition, APRs must be used in an atmosphere that contains sufficient O<sub>2</sub> and a low enough CO<sub>2</sub> level to be compatible with normal respiratory function since the APR does not affect atmospheric concentrations of the breathing gases.

### Machine Tests

*RPD CO<sub>2</sub> Levels Established Using Automatic Breathing and Metabolic Simulator (ABMS)* – Turner et al. (2003), using an ABMS capable of simulating human metabolism,  $\dot{V}_E$ , and breathing waveforms, developed a protocol to characterize the average inhaled CO<sub>2</sub> in the breathing space of a variety of NIOSH certified respirators at six simulated  $\dot{V}_E$  rates. A total of 11 PAPRs, 20 supplied air respirators (SARs), six gas masks, 27 P-100 APRs, and 26 N95 particulate filtering facepiece respirators (FFRs) were tested using the protocol. The results indicated that over the range of  $\dot{V}_E$ , PAPRs CO<sub>2</sub> concentrations averaged between 0.2-0.8%, SARs averaged 0.4-0.5% CO<sub>2</sub>, gas masks averaged 0.9-2.6% CO<sub>2</sub>, P-100 APRs averaged 0.6-2.6% CO<sub>2</sub>, and N95 FFRs averaged 2.3-3.6% CO<sub>2</sub>. This study indicated that inhaled CO<sub>2</sub> levels for all the RPDs, with the exception of the N95 FFRs, were within NIOSH (42 CFR pt. 84) limits for RPD breathing space ( $V_{Dresp}$ ) for use for at least 30 minutes (and up to 4 hours for PAPRs and SARs). N95 FFRs could exceed NIOSH (42 CFR pt. 84)  $V_{Dresp}$  limits for 30 minute exposure for CO<sub>2</sub>. However, as noted in the text, these levels of CO<sub>2</sub> are not regarded as dangerous to healthy individuals but could result in increased  $\dot{V}_E$  and an increase in the possibility of symptoms such as headache. It is important to note, however, that in many machine tests, mean inhaled CO<sub>2</sub> levels were, without exception, greater in tests using human subjects. In one example, in a machine test, the “inhaled” CO<sub>2</sub> level was measured at 0.5% whereas in the human subject tests, the value obtained was 1.2%. Thus, a machine test is likely to underestimate the level of inhaled CO<sub>2</sub> that will be experienced under similar conditions by a human wearer (Morris, 1991).

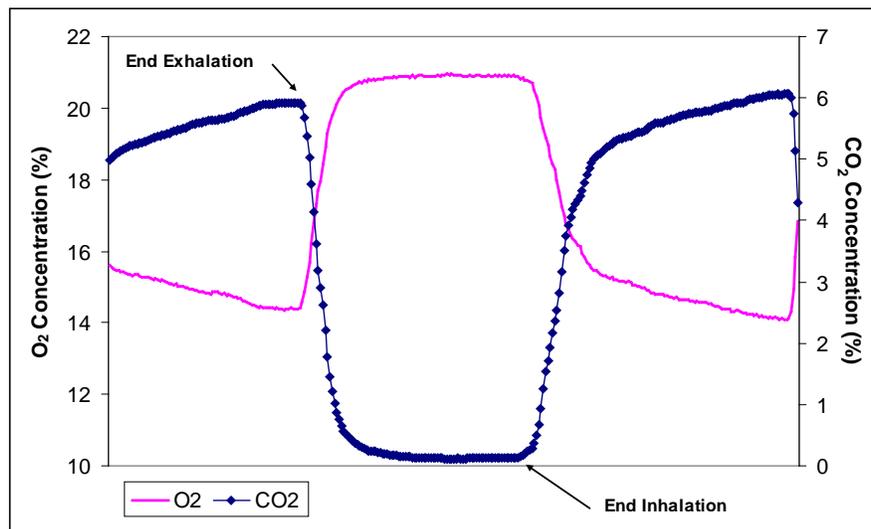
### RPD Issues for the Human Wearer

The physiological responses to O<sub>2</sub> and CO<sub>2</sub> are important for similar and differing reasons depending on the type of RPD being worn and under what circumstances. Therefore, the relevance of the physiological responses to O<sub>2</sub> and CO<sub>2</sub> will be discussed for each RPD type listed as follows.

APRs – The use of respirators while at rest or during exercise have a significant effect on the concentration of inhaled CO<sub>2</sub>. One study has shown that, in subjects wearing military M17 full facepiece APRs and exercising at 80-85%  $\dot{V}_{O_2max}$ , subjects experienced an average of a 19% decrease in physical performance and an 18% decrease in user comfort for each 350 ml (6 dead volumes ranging from 280-1160 ml) increase in external (RPD) dead space (Johnson et al., 2000). In addition, all APRs offer some degree of breathing resistance. Other studies have shown that breathing elevated levels of CO<sub>2</sub> (~3%) against a resistance stimulated ventilation and increased the level of discomfort and distress

in the wearer (Takahashi et al., 1998). Indeed, resistance to breathing while wearing an APR can result in hypoventilation during exercise and the build-up of blood lactate. The buffering of the blood lactate results in increased blood CO<sub>2</sub> and reduced blood O<sub>2</sub>. The increased CO<sub>2</sub> in the APR dead space as a consequence of breathing resistance may contribute more to RPD CO<sub>2</sub> than mask dead space alone depending on the style of the mask (e.g., full facepiece respirator vs. half mask FFR) (Johnson et al., 1996).

Figure 4 is illustrative of the problem of incomplete removal of CO<sub>2</sub> from the APR breathing space discussed previously. In the figure, it is apparent that, with a single breath recording cycle (exhalation followed by inhalation followed by exhalation), the concentration of CO<sub>2</sub> in the breathing space of the APR decreases to nearly zero because of the influx of fresh air during the inspiratory phase of breathing (with a concurrent increase in O<sub>2</sub>). However, for this pattern to continue, essentially all of the CO<sub>2</sub> in the breathing space at the end of expiration must be eliminated to the extent that what remains is similar to atmospheric concentrations. Should any CO<sub>2</sub> remain in the breathing space, it may be re-inhaled with the next breath. Repetition of this pattern could result in a gradual increase in the concentration of CO<sub>2</sub> being re-inhaled into the lungs slowly resulting in hypercapnia. Work in the author's laboratory with subjects wearing N95 FFRs with and without a surgical mask overlay while engaging in treadmill exercise at a low work rate (2.72 km·hr<sup>-1</sup> and 4.0 km·hr<sup>-1</sup>) that the mixed inhalation/exhalation O<sub>2</sub> and CO<sub>2</sub> levels in the V<sub>D</sub><sub>resp</sub> microenvironment exceed the OSHA standards for workplace ambient atmospheres over the course of one hour (Roberge et al., 2010). Although the absolute increase in transcutaneous CO<sub>2</sub> was not significantly different from control levels over the course of one hour, this finding suggests that exhaled CO<sub>2</sub> is not completely removed from the breathing space of a FFR. More research in this area is warranted in order to demonstrate this in a more definitive fashion.



**Figure 4: A typical single breath cycle recording of O<sub>2</sub> and CO<sub>2</sub> concentrations in the breathing zone of an APR during exhalation followed by inhalation while exercising at sea level. The end of exhalation and end of inhalation markings are approximate for the breath. The x-axis is relative time (Caretti, personal communication, reproduced with permission).**

Exercise compounds the effects of respirator CO<sub>2</sub> accumulation due to increased metabolic CO<sub>2</sub> production. At rest,  $\dot{V}\text{CO}_2$  is approximately 2.86 mL·kg<sup>-1</sup>·min<sup>-1</sup>. During moderate to heavy exercise,  $\dot{V}\text{CO}_2$  can increase to 23.6-28.6 mL·kg<sup>-1</sup>·min<sup>-1</sup> while during maximal exercise  $\dot{V}\text{CO}_2$  may exceed 50.0 mL·kg<sup>-1</sup>·min<sup>-1</sup> (Table II). Breathing an atmosphere containing 10% CO<sub>2</sub> can stimulate  $\dot{V}_E$  to approximately 75 L·min<sup>-1</sup> (Simon et al., 2006). At this level of  $\dot{V}_E$  (induced entirely by breathing CO<sub>2</sub> and not due to exercise), issues such as work of breathing and respirator breathing resistance may become significant

dependent upon the type of respirator that is being worn (Johnson et al., 1996; Takahashi et al., 1998). Withdrawal of the CO<sub>2</sub> leads to a rapid reversal of these effects (Eckenhoff and Longnecker, 1996).

Whereas resistance to breathing at rest and low workloads is negligible while wearing an FFR or APR, assuming that the pressure drop across the breathing media does not exceed 17 cm H<sub>2</sub>O (Bentley et al., 1973), wearing an APR inevitably decreases exercise performance during higher workloads because of the resistance to air flow across the filter media (Caretti et al., 2004; Caretti and Whitley, 1998). The degree of breathing resistance depends on the type of respirator being worn and the level of workload. The increased breathing resistance will have three potential results: 1) decrease in exercise performance, 2) hypoventilation, and 3) increased production of CO<sub>2</sub> (Caretti et al., 2004, Craig, et al., 1970). Hypoventilation is one of the most important causes of hypercapnia (Babb et al., 1989). The increased resistance to breathing at any given workload will, in turn, increase CO<sub>2</sub> production and end-tidal CO<sub>2</sub> (ET-CO<sub>2</sub>), heart rate, and a reduced tolerance for work (Craig et al., 1970; Raven et al., 1979; Caretti et al., 1998). Paradoxically, the greatest percent change in the decreased workload tolerance occurred at the lighter workloads. Many occupations that do not involve heavy workloads but require the use of APR are also affected significantly by increased breathing resistances imposed by the APR. Indeed, should the resistance to breathing involve a decrease in breathing frequency concurrent with a decrease in tidal volume the result will be hypercapnia (Raven et al., 1979). Nevertheless, other significant factors such as a requirement for long-duration APR use, level of discomfort imposed by the APR, individual susceptibility to sensations of claustrophobia, individual sensitivity to CO<sub>2</sub> exposure, and the increased awareness of each of these factors also significantly affect the wearer. As the metabolic CO<sub>2</sub> increases (i.e., increased  $\dot{V}CO_2$ ), ventilation will be stimulated but may not increase in the presence of an increased breathing resistance imposed by the respirator. Thus, a negative cycle is initiated by the increased breathing resistance which induces hypoventilation leading to increased hypercapnia. The resulting hypercapnia stimulates ventilation and increased re-breathing of CO<sub>2</sub> which further exacerbates the hypercapnia. Eventually, dyspnea caused by hypercapnia may be so great as to be intolerable. Further research in this area is required to determine the degree to which this putative cycle influences respirator wearers in dangerous environments. In any case, Babb et al., (1989) demonstrated that an increased respirator breathing resistance in conjunction with an increased level of CO<sub>2</sub> (3%) in the breathing space resulted in a decrease in physical performance. Further, attempts to maintain a certain level of ventilation against a breathing resistance could lead to a sense of dyspnea and physical and psychological stress (anxiety or panic) in the susceptible individual (Kaye et al., 2004).

Thus, these combined factors will increase the amount of CO<sub>2</sub> exposure to the APR wearer. Some investigators have shown that breathing comfort and performance time did not differ significantly between resistances below 0.39 kPa (3.9 cm H<sub>2</sub>O) but did decrease by 35% at the highest resistance (0.49 kPa or 4.9 cm H<sub>2</sub>O) (Caretti and Whitley, 1998). Other investigators maintain that there does not seem to be a threshold APR resistance below which there is no effect on metabolic measures (e.g., CO<sub>2</sub> or O<sub>2</sub> levels) or exercise performance during exercise (Johnson et al., 1999). The differences in these findings may be due to the use of half masks by Caretti and Whitley (1998) and the use of a full military facepiece by Johnson et al. (1999). However, the effect of CO<sub>2</sub> on the physiology will be the same whether or not the person is wearing an APR or breathing an atmosphere that contains an elevated concentration or partial pressure of CO<sub>2</sub>. In any case, it is clear that the resistance to breathing offered by FFRs and other types of APRs clearly impact the metabolic response to exercise and the level of comfort experienced by the wearer.

From the previous discussion, it is apparent that the breathing resistance characteristics of an APR during inhalation or exhalation, is an extremely important factor in the user comfort and acceptance (Bentley et al., 1973; Raven et al., 1979). Therefore, APR design changes have been implemented to reduce the breathing resistances inherent in wearing APR. FFRs have demonstrated a low breathing resistance (9-12 mm H<sub>2</sub>O – inhalation and 7-11 mm H<sub>2</sub>O exhalation) (Jones, 1991). In addition, the development of the “electret” (electrostatically-charged) filter has resulted in an ultra-low breathing resistance in APRs (Barrett and Rouseau, 1998). As mentioned previously, it has been estimated that 90% of the users could wear an APR without experiencing distressing symptoms as long as the breathing resistances were below 17 cm H<sub>2</sub>O (Bentley et al., 1973). Although there does not seem to be a way to completely eliminate breathing resistances in APRs, the advent of electret filters have significantly

reduced the resistances for wearers engaged in most low to medium levels of activity. Moreover, the decrease in breathing resistances will reduce the potential for hypoventilation which is a significant factor in increased  $P_A\text{CO}_2$  and increased  $\text{ET-CO}_2$  exhaled into the breathing space of the respirator. This will reduce the potential for  $\text{CO}_2$  stimulation of ventilation during APR use. The addition of exhalation valves in respirators to increase the elimination of  $\text{CO}_2$  from the breathing space have met with limited success. APRs are designed to protect the wearer against particulates or vapors in the atmosphere. These RPDs are worn typically in an atmosphere containing the normal partial pressures of  $\text{O}_2$ ,  $\text{N}_2$ , and  $\text{CO}_2$ . Because APRs do not provide an independent air supply to the wearer, they cannot be safely worn in a hypoxic atmosphere or an atmosphere containing high (>10%) concentrations or partial pressures of  $\text{CO}_2$ . For instance, workers have died of asphyxiation after environmental gas displacement by vaporization of liquid nitrogen into a confined space creating a hypoxic atmosphere.  $\text{N}_2$  is an inert gas and is, by itself, not toxic. The death of the worker was caused by displacement of atmospheric  $\text{O}_2$  by  $\text{N}_2$  thus creating a hypoxic environment leading to asphyxiation (Gill et al., 2002). The worker would not have been protected against this hypoxic hazard while wearing an APR. Similarly, a research scientist died after entering a cold room with no working ventilation in which workers had stored dry ice which subsequently sublimated into  $\text{CO}_2$  gas. The resulting high concentration of  $\text{CO}_2$  in this confined space not only displaced the atmospheric  $\text{O}_2$ , but had an immediate toxic effect on the scientist that entered the chamber. Again, wearing an APR will not protect against the resulting hypoxic state or against the direct toxic effects of breathing high concentrations of  $\text{CO}_2$  (Gill et al., 2002).

PAPRs – A PAPR is an APR that uses a blower to force the ambient air through air-purifying elements to the inlet covering. The blower sends air to the facepiece or hood from the external atmosphere. The PAPR air blower may limit the problems of breathing resistance over most exercise intensities, purge exhaled  $\text{CO}_2$  from the breathing space, as well as the flow of air offers some level of cooling to the wearer. However, the PAPR only purifies the atmosphere of particulates or toxic vapor in a manner similar to FFRs and APRs. Thus, a PAPR will not protect the wearer in a hypoxic environment or an  $\text{O}_2$  or  $\text{CO}_2$  enriched atmosphere.

RPDs with Independent Air Supply – There are several classes of RPDs that utilize an air supply that is independent of the ambient atmosphere. These RPDs are generalized under the categories of Supplied Air Respirators (SARs) or an atmosphere-supplying respirator for which the source of breathing air is not designed to be carried by the user. These RPDs are connected by an airline connected to a compressed air cylinder or other source of compressed air. Other RPDs that fall into this category are SCSRs, SCBAs, and other UBA. These RPDs have a supply of air or oxygen that is carried on the wearer, can be used in hypoxic, toxic, or underwater environments, and thus do not rely on atmospheric oxygen to sustain the life of the wearer.

SARs can have several configurations: half-mask, full facepiece, helmet, hood, and full supplied-air suit (level "A" protection). The SAR is used in hazardous or immediately dangerous to life and health (IDLH) environments. Assuming the air source supplies clean air to the breathing space of the halfmask or full facepiece SAR, the issue of hypoxia or high levels of  $\text{CO}_2$  (or other inhalation hazards) in the external atmosphere is irrelevant. With each breath, the SAR provides fresh air from the compressed source and each exhalation will eliminate the metabolically produced  $\text{CO}_2$  from the breathing space. However, in SAR hoods, helmets, or air-fed suits, the increased dead space created by the hood, helmet, or suit can allow for the accumulation of exhaled  $\text{CO}_2$ . Studies have shown that in SAR hoods and helmets during light workload (48W external work) and airline flow rates of  $100\text{-}200\text{ L}\cdot\text{min}^{-1}$ , re-inhaled  $\text{CO}_2$  concentrations remained below 0.3% but increased to 0.4-0.53% at external workloads of 96 W resulting in a marginal increase of  $P_a\text{CO}_2$  to 47 mmHg (normal range of 35-45 mmHg) (Comte and Koradecka, 1981). It should be noted that for any RPD, the  $\text{CO}_2$  level increasing to 0.3% begins to create an unfavorable diffusion gradient from the blood to alveoli making the elimination of metabolically produced  $\text{CO}_2$  more difficult and is initially compensated for by an increase in  $\dot{V}_E$  (Morris, 1991). When inhaled  $\text{CO}_2$  increases above 1-2%, increased ventilation is ineffective in removal of excess  $\text{CO}_2$  and arterial hypercapnia results (Morris, 1991). In any event, the failure of the air supply will allow for the increase in the concentration of  $\text{CO}_2$  within the SAR dead space or a state of hypoxia within the SAR.

SCSRs are designed with a canister containing the chemical compound potassium superoxide ( $\text{KO}_2$ ) that will generate oxygen in the presence of water ( $\text{H}_2\text{O}$ ) in the exhaled breath through the following reaction:



The generation of  $\text{O}_2$  in the presence of  $\text{H}_2\text{O}$  will continue until the  $\text{KO}_2$  reactant is exhausted. According to the federal regulations, the SCSR must provide a supply of  $\text{O}_2$  to the user for at least 60 minutes under escape conditions but the  $\text{O}_2$  supply may last up to four hours under resting conditions (30 CFR 75.1714). Thus, the duration of the supply of  $\text{O}_2$  to the user beyond 60 minutes will depend on the rate of  $\text{O}_2$  consumption at a specific activity level (escape), body weight and physical fitness. The dependence on water makes a second equation equally important and critically dependent on  $\text{CO}_2$ . The following reaction is dependent on  $\text{CO}_2$  to form water:



The water formed in the above reaction is dependent on the presence of  $\text{CO}_2$  and makes water available for the reaction in Eq. 5 which is, again, critical for the production of oxygen. Since metabolically produced  $\text{CO}_2$  will be transported in solution in the blood to be exhaled by the lungs, then the  $\text{CO}_2$  exhaled by the lungs will be involved in Eq. 6 in the formation of water, which in turn will be involved in the formation of oxygen by reacting in Eq. 5.

The SCSR is carried on the person and  $\text{O}_2$  is transported from the chemical reactant canister through an air hose to a mouthpiece. The SCSR  $\text{KO}_2$  evolves  $\text{O}_2$  continuously, cannot be regulated, and will expose the wearer to hyperoxic conditions. However, exposure to hyperoxia for a short period of time (60 min) usually does not present a significant physiological threat. In fact, the hyperoxia may improve physical performance (Evest et al., 2002) which, however, may be offset by a negative influence on the cardiovascular system and a mild depression in  $\dot{V}_E$  and decreased retinal blood flow (Luksch et al., 2002). These physiological effects could have a negative impact on the wearer during a mine emergency escape scenario. Hyperoxia may also result in the displacement of carbon monoxide on the Hb molecule thereby limiting the toxic effects of this gas (Simon et al., 2006).

Metabolically produced  $\text{CO}_2$  is scrubbed by soda lime placed in series with the air flow of the SCSR. Under normal operating conditions, the wearer of an SCSR should not experience any adverse effects from the hyperoxic state or from re-breathing metabolically produced  $\text{CO}_2$ . However, a malfunction of the system or exhaustion of the soda lime could expose the wearer to elevated levels of  $\text{CO}_2$  fairly quickly since large amounts of  $\text{CO}_2$  are produced metabolically during the high intensity of exercise experienced under conditions of emergency escape (Table II). Should the wearer be exposed to high levels of  $\text{CO}_2$ , the stimulation of  $\dot{V}_E$  may result in the premature exhaustion of the  $\text{O}_2$  supply before the wearer completed the escape from the mine as well as the reduction of the physical work capacity of the wearer.

SCBAs are typically worn by firefighters but can also be worn under HAZMAT suits. The SCBA consists of a wearable compressed air cylinder that supplies breathable air through a hose to a full facepiece respirator. These RPDs can be worn in very hazardous environments characterized by hypoxia, high atmospheric  $\text{CO}_2$  concentrations, or toxic gases. Because the supply of air contains normal atmospheric concentrations of  $\text{O}_2$ ,  $\text{N}_2$ , and  $\text{CO}_2$ , the ventilatory response will not be affected by breathing these gases. In addition, under low to moderate workloads, breathing resistance offered by the SCBA facepiece will not be an issue. However, at high rates of  $\dot{V}_E$  ( $112 \text{ L}\cdot\text{min}^{-1}$ ) SCBA regulators present an increased inhalation and exhalation breathing resistance and increased work of breathing (Butcher et al., 2006). Thus, it is possible that increased breathing resistance and work of breathing will result in an increase in  $\text{ET}\text{-CO}_2$  that may be available to be re-inhaled. If symptoms become severe enough, the wearer may be motivated to remove the SCBA even in a dangerous environment. However, an interesting strategy has been used to reduce the effects of the breathing resistance and work of breathing at high workloads using an SCBA. Butcher et al. (2007) have employed a low density heliox gas mixture

(21% O<sub>2</sub> and 79% He) to reduce the breathing resistances and work of breathing at high breathing rates and workloads.

UBAs are worn during underwater diving and are a unique form of RPD. The apparatus, like an SCBA, consists of a compressed air cylinder that supplies air to the diver via pressure regulator/air hose/mouthpiece assembly. The UBA usually supplies normal atmospheric air to the wearer during underwater diving excursions. This is true for most "sport diving" in which the depth attained on any given dive is less than 30 m (4 ATM). However, the use of "normal" air can be toxic at depth. Increasing PO<sub>2</sub> in a "normal" atmosphere that occurs with increasing pressure at depth can result in O<sub>2</sub> toxicity and inert gas narcosis (due to a concomitant increase in the PN<sub>2</sub>). To offset this problem, special breathing gas mixtures are used by the commercial diving community, in sport "technical" diving (SCUBA dives deeper than 40 m), and by military divers. However, military divers have used oxygen re-breathers in which the diver is breathing a hyperoxic gas mixture. Because of the potential for O<sub>2</sub> toxicity with these devices, military O<sub>2</sub> re-breathers can only be used at depths no greater than 10 m (1 ATM of sea water). The issue of CO<sub>2</sub> toxicity usually does not appear since the partial pressure of CO<sub>2</sub> in a "normal" atmosphere is so low that increasing depth will not substantially increase the partial pressure of CO<sub>2</sub> to pose a significant physiological problem for the diver. Should an equipment malfunction occur, thus delivering a hyperoxic mixture to the diver at depth, the toxic effects of O<sub>2</sub> may result in a fatal outcome for the diver. An equipment malfunction could also result in a hypoxic exposure to the diver. At depth, the increased partial pressure may relieve the effects of hypoxia but as soon as the pressure is reduced, hypoxia could become significant.

One cause of an increase in CO<sub>2</sub> exposure in the breathing space while using UBA is related to increased breathing resistance. Studies have shown that increased breathing resistance, particularly during inspiration, can result in hypoventilation and increased CO<sub>2</sub> retention (Warkander et al., 2001). Therefore, significant increases (0.8-1.2 kPa·L<sup>-1</sup>·sec<sup>-1</sup>; 8-12 cm H<sub>2</sub>O·L<sup>-1</sup>·sec<sup>-1</sup>) in inspiratory resistance, especially during deep dives (690 kPa; 190 fsw), represents an unacceptable level of breathing resistance. Moreover, under these conditions of breathing resistance and depth, some divers have experienced sudden reactions to the resulting high end-tidal PCO<sub>2</sub> (P<sub>ET</sub>-CO<sub>2</sub>; ~70 mmHg) that could prove fatal. In at least two cases, divers under conditions of high resistance, depth, and high P<sub>ET</sub>-CO<sub>2</sub> experienced sudden onset of loss of motor skills, inability to respond to commands, and sudden loss of consciousness. These divers apparently did not have the usual onset of dyspnea associated with increasing hypercapnia and experienced no other warning signs of impending physiological distress (Warkander et al., 1990). Research has indicated that increased breathing resistance increases the work (power) of breathing (Warkander et al., 1992). These investigators demonstrated that the P<sub>ET</sub>-CO<sub>2</sub> could be minimized when breathing resistance was low enough in the UBA to keep the power of breathing below 1.5-2.0 J·min<sup>-1</sup> within a ventilation range of 30-75 L·min<sup>-1</sup> (Warkander et al., 1992).

## RPDs and the Pregnant Female

Millions of women serve in occupations that require the use of RPDs. Since pregnancy does not generally preclude women from working throughout most of gestation, it is likely that a significant number of women will continue to work in the health care field after becoming pregnant. It is fairly well documented that pregnancy results in an increased metabolism both at rest and during exercise and an increased ventilatory sensitivity to CO<sub>2</sub> (Roberge, 2009; Jensen et al., 2005; Jaque-Fortunato et al., 1996; Garcia-Rio et al., 1996). The increased ventilatory sensitivity to CO<sub>2</sub> is probably due to the changes in estrogen-dependent progesterone receptors in the hypothalamus which then, in turn, stimulate the respiratory centers in the medulla oblongata (Jensen et al., 2005; Jaque-Fortunato et al., 1996). The altered  $\dot{V}_E$  is also due to some of the anatomical changes that occur in the thoracic cage during pregnancy (Jaque-Fortunato et al., 1996) as well as to changes in chemosensitivity to CO<sub>2</sub> during pregnancy (Garcia-Rio et al., 1996). These anatomical and physiological changes will have a significant impact on the use of FFRs and APRs in the pregnant worker.

The pregnant female also demonstrates hypersensitivity to hypoxia that appears to be linked to an increased level of progesterone. The increase in progesterone appears to increase the carotid body

neural output resulting in an increased ventilatory response to hypoxia (Jensen et al., 2005). In addition, the decrease in expiratory reserve volume and the resulting decrease in O<sub>2</sub> reserves secondary to an elevated diaphragm during pregnancy render the pregnant woman more susceptible to the development of hypoxia (Roberge, 2009). The increased metabolic O<sub>2</sub> utilization by the pregnant female also contributes to the sensitivity to hypoxia (Steinbrook, 2002).

The physiological and anatomical changes that occur in pregnancy are, therefore, problematic for the pregnant female who is required to wear an RPD occupationally or voluntarily. Hypersensitivity to both hypercapnia and hypoxia may cause an adverse response to the pregnant worker exposed to an RPD induced increase in CO<sub>2</sub> exposure or a hypoxic breathing atmosphere. At the minimum, the hypersensitivity to elevated CO<sub>2</sub> or decreased O<sub>2</sub> may limit the tolerance to wearing the RPD and, therefore, limit the amount of time spent on the job. A greater concern is that if the tolerability of the RPD is so low, the pregnant worker may remove the RPD to obtain relief and inadvertently become exposed to an inhalation hazard. These issues must be taken into consideration when the pregnant worker is required to wear an RPD for occupational safety (or any other) reasons.

## Acknowledgements

This manuscript was developed in part as a Technical Specification while the author served as a science advisor for the US Technical Advisory Group to an International Standards Organization Committee on respiratory protection. The author was an employee of the US Government during the entire development of the present manuscript. Therefore, the costs incurred during the development of this manuscript were paid for by the US Government. While this manuscript is the work of the author who is solely responsible for its content, the author would like to acknowledge the contributions of the members of the Project Group 5 Committee on Human Factors chaired by Mr. Michael Thomas, MBE of the British Standards Institute and the Lincolnshire Fire and Rescue Department, Lincoln, UK. The author would also like to extend his appreciation to Dr. Ron Shaffer, David Caretti, M.S., and Dr. Nina Turner for their extensive review and comments on the manuscript.

## Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of commercial product or trade name does not constitute endorsement by the National Institute for Occupational Safety and Health.

## REFERENCES

- Angerer P., Norwak D., 2003. Working in permanent hypoxia for fire protection – impact on health. *Int. Arch. Occup. Environ. Health* 76, 87-102.
- Åstrand P-O., Rodahl K., Dahl H.A., Strømme S.B., 2003. Fatigue. In: *Work Physiology*. fourth ed. Human Kinetics. Champaign, IL, pp. 453-477.
- Babb T., Turner N., Saupe K., Pawelczyk J., 1989. Physical performance during combinations of hypercapnic, resistive, and hot air breathing. *Am. Ind. Hyg. Assoc. J.* 50 (2), 105-111.
- Barrett L.W., Rousseau A.D., 1998. Aerosol Loading Performance of Electret Filter Media. *Am. Indust. Hyg. Assoc. J.* 59, 532–539.
- Bentley R.A., Griffin O.G., Love R.G., Muir D.C.F., 1973. Acceptable levels for breathing resistance of respiratory apparatus. *Arch. Environ. Health*. Oct. 27, 273-280.
- Berg J.M., Tymoczko J.L., Stryer L., 2002. In: *Biochemistry*. sixth ed. WH Freeman and Co. San Francisco, pp. 103.
- Berne R.M., Levy M.N., 1988. *Physiology*. second ed. The C.V. Mosby Company, St. Louis, MO.

- Bishop P.A., Lee S.M.C., Conza N.E., Clapp L.L., Moore A.D., Williams W.J., Williams M.A., Greenisen M.C., 1999. Carbon dioxide accumulation, walking performance, and metabolic cost in the NASA Launch and Entry Suit. *Aviat. Space Environ. Med.* 70 (7), 656-65.
- British Standards Institute/European Standards; BS EN 12941:1998+A2:2008.
- Butcher S.J., Jones R.L., Eves N.D., Petersen S.R., 2006. Work of breathing is increased during exercise with the self-contained breathing apparatus regulator. *Appl. Physiol. Nutr. Metab.* 31, 693-701.
- Butcher S.J., Jones R.L., Mayne J.R., Hartley T.C., Petersen S.R., 2007. Impaired exercise ventilatory mechanics with the self-contained breathing apparatus are improved with heliox. *Eur. J. Appl. Physiol.* 101, 659-669.
- Butler F.K. Jr., White E., Twa M., 1999. Hyperoxic myopia in a closed-circuit mixed-gas scuba diver. *Undersea Hyper. Med.* 26(1), 41-45.
- Caretti D.M., Whitley J.A., 1998. Exercise performance during inspiratory resistance breathing under exhaustive constant load work. *Ergonomics.* 41(4), 501-511.
- Caretti D.M., Gardner P.D., Coyne K.M., 2004. Workplace breathing rates: Defining anticipated values and ranges for respirator certification testing. ECBC-TR-316, Research and Technology Directorate, Edgewood RDECOM, September, pp. 1-66.
- Caretti D.M., Coyne K., Johnson A., Scott W., 2006. Performance when breathing through different respirator inhalation and exhalation resistances during hard work. *J. Occup. Environ. Hyg.* 3, 214-234.
- Caretti D.M., Coyne K., 2008. Unmanned assessment of respirator carbon dioxide levels: comparison of methods of measurement. *J. Occup. Environ. Hyg.* 5, 305-312.
- Comte T., Koradecka D., 1981. Optimum physiological parameters for respiratory tract protection equipment. *Medycyna. Pracy.* 32, 35-43.
- Craig F.N., Blevins W.V., Cummings E.G., 1970. Exhausting work limited by external resistance and inhalation of CO<sub>2</sub>. *J. Appl. Physiol.* 29(6), 847-851.
- Crosby A., Talbot N.P., Balanos G.M., Donoghue S., Fatemian M., Robbins P.A., 2003. Respiratory effects in humans of a 5-day elevation of end-tidal PCO<sub>2</sub> by 8 Torr. *J. Appl. Physiol.* 95, 1947-1954.
- Dean J.B., Mulkey D.K., Garcia III, A.J., Putnam R.W., Henderson III R.A., 2003. Neuronal sensitivity to hyperoxia, hypercapnia, and inert gases at hyperbaric pressures. *J. Appl. Physiol.* 95, 883-909.
- Di Piero V., Cappagli M., Pastena L., Faralli F., Mainardi G., Di Stani F., Bruti G., Coli A., Lenzi G.L., Gagliardi R., 2002. Cerebral effects of hyperbaric oxygen breathing: a CBF SPECT study on professional divers. *Eur. J. Neurol.* 9, 419-412.
- Donoghue S., Fatemian M., Balanos G.M., Crosby A., Liu C., O'Connor D., Talbot N.P., Robbins P.A., 2005. Ventilatory acclimatization in response to very small changes in PO<sub>2</sub> in humans. *J. Appl. Physiol.* 98, 1587-1591.
- Eckenhoff R.G., Longnecker D.E., 1996. The Therapeutic Gases: oxygen, carbon dioxide, nitric oxide, helium, and water vapor. In: Hardman J.G., Limbird L.E., Molinoff P.B., Ruddon R.W., Gilman A.G., (Eds.) Goodman and Gilman's The Pharmacological Basis of Therapeutics, ninth ed. McGraw-Hill, New York, pp. 349-359.
- Elliott A.R., Prisk G.K., Schöllmann C., Hoffmann U., 1998. Hypercapnic ventilatory response in humans before, during, and after 23 days of low level CO<sub>2</sub> exposure. *Aviat. Space Environ. Med.* 69(4), 391-396.
- Evest N.D., Petersen S.R., Jones R.L., 2002. Hyperoxia improves maximal exercise with the self-contained breathing apparatus (SCBA). *Ergonomics.* 45(1), 829-839.
- García-Río F., Pino J.M., Gómez L., Alvarez-Sala R., Villasante C., Villamor J., 1996. Regulation of breathing and perception of dyspnea in healthy pregnant women. *Chest.* 110, 446-453.
- Gill J.R., Ely S.F., Hua Z., 2002. Environmental gas displacement. Three accidental deaths in the workplace. *Am. J. Forensic Med. Pathol.* 23(1), 26-30.
- Goldstein B., Shannon D.C., Todres I.D., 1990. Supercarbia in children: clinical course and outcome. *Crit. Care Med.* 18, 166-168.

- Grissom C.K., Radwin M.I., Scholand M.B., Harmston C.H., Muetterties M.C., Bywater T.J., 2004. Hypercapnia increases core temperature cooling rate during snow burial. *J. Appl. Physiol.* 96, 1365-1370.
- Harabin A.L., Survanshi S.S., 1993. A statistical analysis of recent Navy Experimental Diving Unit (NEDU) single-depth human exposures to 100-percent oxygen at pressure. Bethesda, M.D. Naval Medical Research Institute Report NMRI, pp. 93-59.
- Imray C.H.E., Brearey S., Clarke T., Hale D., Morgan J., Walsh S., Wright A.D., and the Birmingham Medical Research Expeditionary Society, 2000. Cerebral oxygenation at high altitude and the response to carbon dioxide, hyperventilation and oxygen. *Clin. Sci.* 98, 159-164.
- Imray C.H.E., Clarke T., Forster P.J.G., Harvey T.C., Hoar H., Walsh S., Wright A.D., and the Birmingham Medical Research Expeditionary Society, 2001. Carbon dioxide contributes to the beneficial effect of pressurization in a portable hyperbaric chamber at high altitude. *Clin. Sci.* 100, 151-157.
- Imray C.H.E., Walsh S., Clarke T., Tiivas C., Hoar H., Harvey T.C., Chan C.W.M., Forster P.J.G., Bradwell A.R., Wright A.D., and the Birmingham Medical Research Expedition, 2003. Effects of breathing air containing 3% carbon dioxide, 35% oxygen or a mixture of 3% carbon dioxide/35% oxygen on cerebral and peripheral oxygenation at 150 m and 3459 m. *Clin. Sci.* 104, 203-210.
- ISO TS 16976-1 Respiratory Protective Devices – Human Factors. Part 1: Metabolic rates and respiratory flow rates. ISO/TS 16976-1:2007 (E), pp. 1-16.
- Jacque-Fortunato S.V., Wiswell R.A., Khodiguian N., Artal R., 1996. A comparison of the ventilatory response to exercise in pregnant, postpartum, and nonpregnant women. *Seminars in Perinatology.* August 20(4), 263-276.
- Japan Industrial Standard (JSA JIS M 7651), 1996. Closed-Circuit Oxygen Self Rescuers).
- Jensen D., Wolfe L.A., Slatkowska L., Webb K.A., Davies G.A.L., O'Donnell D.E., 2005. Effects of human pregnancy on the ventilatory chemoreflex to carbon dioxide. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288(5), R1369-R1375.
- Johnson A.T., Dooly C.R., Dotson C.O., 1996. Respirator mask effects on exercise metabolic measures. *Am. Ind. Hyg. Assoc. J.* 56, 467-473.
- Johnson A.T., Scott W.H., Lausted C.G., Benjamin M.B., Coyne K.M., Sahota M.S., Johnson M.M., 1999. Effect of respirator inspiratory resistance level on constant load treadmill work performance. *Am. Ind. Hyg. Assoc. J.* 60, 474-479.
- Johnson A.T., Scott W.H., Lausted C.G., Coyne K.M., Johnson M.M., 2000. Effect of external dead volume on performance while wearing a respirator. *Am. Ind. Hyg. Assoc. J.* 61, 678-684.
- Johnson A.T., Scott W.H., Caretti D.M., Danisch S.G., 2003. Do respirators stress the cardiovascular system? *J. Int. Soc. Resp. Prot.* 20, 26-36.
- Jones J., 1991. The physiological cost of wearing a disposable respirator. *Am. Ind. Hyg. Assoc. J.* 52(6), 219-225.
- Kaye J., Buchanan F., Kendrick A., Johnson P., Lowry C., Bailey J., Nutt D., Lightman S., 2004. Acute carbon dioxide exposure in healthy adults: evaluation of a novel means of investigating the stress response. *J. Neuroendocrin.* 16, 256-264.
- Launay J.-C., Besnard Y., Guinet-Lebreton A., Savourey G., 2006. Acclimation to intermittent hypobaric hypoxia modifies the responses to cold at sea level. *Aviat. Space Environ. Med.* 77, 1230-1235.
- Luft U.C., Finkelstein S., Elliot J.C., 1974. Respiratory gas exchange, acid-base balance, and electrolytes during and after maximal work breathing 15 mmHg PICO<sub>2</sub>. In: Nahas G, Schaefer KE (Eds.), *Topics in Environmental Physiology and Medicine—Carbon Dioxide and Metabolic Regulations.* New York, Springer-Verlag Inc., pp. 282-293.
- Luksch A., Garhöfer, Imhof A., Plolak E., Polska E., Dorner G.T., Anzenhofer S., Wolzt M., Schmetterer L., 2002. Effect of inhalation of different mixtures of O<sub>2</sub> and CO<sub>2</sub> on retinal blood flow. *Br. J. Ophthalmol.* 86, 1143-1147.
- Lumb A.B., 2005. In: *Nunn's Applied Respiratory Physiology.* sixth ed. Elsevier Butterworth Heinemann, Philadelphia, pp. 327-333.
- Lund V., Kentala E., Scheinin H., Klossner J., Sariola-Heinonen K., Jalonen J., 2000. Hyperbaric oxygen increases parasympathetic activity in professional divers. *Acta. Physiol. Scand.* 170, 39-44.

- McArdle W.D., Katch F.I., Katch V.I., 1996. Exercise at medium and high altitude. In: Exercise Physiology: Energy, nutrition, and human performance. fourth ed. Williams & Wilkins, Baltimore, pp. 481-498.
- Menn S.J., Sinclair R.D., Welch B.E., 1968. Response of normal man to graded exercise in progressive elevations of CO<sub>2</sub>. Report No. SAM-TR-68-116. Brooks Air Force Base, Texas, US Air Force, Aerospace Medical Division (AFSC), USAF School of Aerospace Medicine, pp. 1-16.
- Mitchell J.D., 2004. Ocular Emergencies. In: Tintinalli J.D., Kelen G.D., Stapczynski J.S. (Eds.). Emergency Medicine. A Comprehensive Study Guide, sixth ed. McGraw-Hill, New York, pp. 1460-1461.
- Molénat F., Boussuges A., Grandfond A., Rostain J.-C., Sainty J.-M., Robinet C., Galland F., Meliet J.L., 2004. Haemodynamic effects of hyperbaric hyperoxia in healthy volunteers: an echocardiographic and Doppler study. Clin. Sci. 106, 389-395.
- Morris L.A., 1991. Dead space and inhaled carbon dioxide levels in respiratory protective equipment. HSE Contract Research Report No. 27, pp. 1-34.
- National Institute for Occupational Safety and Health Publication No. 2001-123. Women's health and safety issues at work. Available at [www.cdc.gov/niosh/01-123.html](http://www.cdc.gov/niosh/01-123.html) Accessed February 3, 2010.
- NIOSH Criteria for a recommended standard. 1976. Occupational exposure to carbon dioxide. Prepared by the Standard Research Institute for the National Institute for Occupational Safety and Health. NIOSH PB 266 597 August.
- Nisbet E.G., Sleep N.H., 2001. The habitat and nature of early life. Nature 409, 1083-1091.
- Nunn J.F., 1998. Evolution of the atmosphere. Proc. Geol. Assoc. 109, 1-13.
- Ogawa T., Hayashi K., Ichinose M., Nishiyasu I., 2007. Relationship between resting ventilatory chemosensitivity and maximal oxygen uptake in moderate hypobaric hypoxia. J. Appl. Physiol. 103, 1221-1226.
- Oró J., 1994. Early chemical stages in the origin of life. In: Bengston S. (Ed.): Early Life on Earth. Nobel Symposium No. 84 Columbia U.P. New York; pp.48-59.
- Potkin R.T., Swenson E.R., 1992. Resuscitation from severe acute hypercapnia. Determinants of tolerance and survival. Chest. 102, 1742-1745.
- Raven P.B., Dodson A.T., Davis T.O., 1979. The physiological consequences of wearing industrial respirators: a review. Am. Ind. Hyg. Assoc. J. 40, 517-534.
- Roberge R.J., 2009. Physiological burden associated with the use of filtering facepiece respirators (N95 Masks) during pregnancy. J. Women's Health. 18(6), 819-876.
- Roberge R.J., Coca A., Williams W.J., Palmiero A.J., Powell J.B., 2010. Physiological impact of filtering facepiece respirators ("N95 masks") use on healthcare workers. Respiratory Care 55(5):569-577, 2010.
- Romer L.M., Haverkamp H.C., Amann M., Lovering A.T., Pegelow D.F., Dempsey J.A., 2007. Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R598-R606.
- Rousseau A., Bak Z., Janerot-Sjöberg B., Sjöberg F., 2005. Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man. Acta Physiol. Scand. 183, 231-240.
- Sayers J.A., Smith R.E.A., Holland R.L., Keatinge W.R., 1987. Effects of carbon dioxide on mental performance. J. Appl. Physiol. 63(1), 25-30.
- Simon B.A., Moody E.J., Johns R.A., 2006. Therapeutic gases: oxygen, carbon dioxide, nitric oxide, and helium. In: Brunton L.L., Lazo J.S., Parker K.L. (Eds.) Goodman & Gilman's The Pharmacologic Basis of Therapeutics, eleventh ed. McGraw Hill, New York, pp. 387-399.
- Sinclair R.D., Clark J.M., Welch R.E., 1971. Comparison of physiological responses of normal man to exercise in air and in acute and chronic hypercapnia, In: Lambertsen C.J. (Ed). Underwater Physiology. New York, Academic Press, pp 409-417.
- Spigno F., De Lucchi M., Migliazzi L., Cocito L., 2008. Transient global amnesia after breathing hyperoxic mixtures in otherwise regular dives. Clin. Neurol. Neurosurg. 110, 259-261.
- Steinbrook R.A., 2002. Anaesthesia, minimally invasive surgery and pregnancy. Best Pract. & Res. in Clin. Anaesth. 16(1), 131-143.

- Stryer L., 1981. *Biochemistry*. second ed. W.H. Freeman and Company, San Francisco, CA.
- Sun M., Sun C., Yang Y., 1996. Effect of low-concentration CO<sub>2</sub> on stereoacuity and energy expenditure. *Aviat. Space Environ. Med.* 67(1), 34-39.
- Takahashi M., Mano Y., Shibayama M., Yamami N., 1998. Effects of breathing resistance while inhaling 3% carbon dioxide during steady state exercise. *J. Occup. Health.* 40, 213-217.
- Turner N., Sinkule E., Hota S., 2003. Automated Breathing and Metabolic Simulator (ABMS) CO<sub>2</sub> Test for Powered and Non-Powered Air-Purifying Respirators, Airline Respirators and Gas Masks. Presented at the National Occupational Research Agenda Symposium, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Arlington, VA; June 23-24.
- United States Code of Federal Regulations, 29 CFR 1910.94-424, 2008. Occupational Health and Environment Control, Ventilation.
- United States Code of Federal Regulations, 29 CFR 1910.1000, 2008. Occupational Health and Environment Control, Ventilation.
- United States Code of Federal Regulations, 30 CFR 11.3(t), 2009. Testing, Evaluation, and Approval of Mining Products.
- United States Code of Federal Regulations, 30 CFR 75.1714, 2009, Mandatory safety standards--underground coal mines.
- United States Code of Federal Regulations, 42 CFR 84.87;c,d., 2004. Respiratory Protective Devices.
- United States Department of Labor. Bureau of Labor Statistics. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Respirator usage in private sector firms, 2001. Available at [www.cdc.gov/niosh/docs/respsurv/](http://www.cdc.gov/niosh/docs/respsurv/) Accessed February 3, 2010.
- Vantanajal J.S., Ashmead J.C., Anderson T.J., Hepple R.T., Poulin M.J., 2007. Differential sensitivities of cerebral and brachial blood flow to hypercapnia in humans. *J. Appl. Physiol.* 102, 87-93.
- Vercruyssen M., Kamon E., 1984. Behavioral effects of one-hour breathing of high concentrations of CO<sub>2</sub> and O<sub>2</sub> while doing physical work. *J. Intl. Soc. Resp. Protect.* 2, 63-89.
- Warkander D.E., Norfleet W.T., Nagasawa G.K., Lundgren C.E.G., 1990. CO<sub>2</sub> retention with minimal symptoms but severe dysfunction during wet simulated dives to 6.8 atm abs. *Undersea Biomed. Res.* 17(6), 515-523.
- Warkander D.E., Norfleet W.T., Nagasawa G.R., Lundgren C.E.G., 1992. Physiologically and subjectively acceptable breathing resistance in divers' breathing gear. *Undersea Biomed. Res.* 19(6), 427-445.
- Warkander D.E., Lundgren C.E.G., 1995. Dead space in the breathing apparatus: interactions with ventilation. *Ergonomics.* 38(9), 1745-1758.
- Warkander D.E., Nagasawa G.K., Lundgren C.E.G., 2001. Effects of inspiratory and expiratory resistance in divers' breathing apparatus. *Undersea Hyper. Med.* 28(2), 63-73.
- West J.B., 1985. *Respiratory Physiology*. third ed. Williams & Wilkins, Baltimore.
- West J.B., 1993. Acclimitization and tolerance to extreme altitude. *J. Wilderness Med.* 4, 17-26.
- West J.B., 2000. Human Limits for Hypoxia. The physiological challenge of climbing Mt. Everest. *Ann. N.Y. Acad. Sci.* 899, 15-27.
- Winegrad S., Henrion D., Rappaport L., Samuel J.L., 1999. Self-protection by cardiac myocytes against hypoxia and hyperoxia. *Circ. Res.* 85, 690-698.
- Xu K., LaManna J.C., 2006. Chronic hypoxia and the cerebral circulation. *J. Appl. Physiol.* 100, 725-730.
- Yang Y., Sun C., Sun M., 1997. The effect of moderately increased CO<sub>2</sub> concentration on perception of coherent motion. *Aviat. Space Environ. Med.* 68, 187-191.