Hypercapnia in diving: a review of CO_2 retention in submersed exercise at depth

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ABSTRACT

Carbon dioxide (CO_2) retention, or hypercapnia, is a known risk of diving that can cause mental and physical impairments leading to life-threatening accidents. Often, such accidents occur due to elevated inspired carbon dioxide. For instance, in cases of CO_2 elimination system failures during rebreather dives, elevated inspired partial pressure of carbon dioxide (PCO_2) can rapidly lead to dangerous levels of hypercapnia. Elevations in P_aCO_2 (arterial pressure of CO_2) can also occur in divers without a change in inspired PCO_2. In such cases, hypercapnia occurs due to alveolar hypoventilation. Several factors of the dive environment contribute to this effect through changes in minute ventilation and dead space. Predominantly, minute ventilation is reduced in diving due to changes in respiratory load and associated changes in respiratory control. Minute ventilation is further reduced by hyperoxic attenuation of chemosensitivity. Physiologic dead space is also increased due to elevated breathing gas density and to hyperoxia. The Haldane effect, a reduction in CO_2 solubility in blood due to hyperoxia, may contribute indirectly to hypercapnia through an increase in mixed venous PCO_2. In some individuals, low ventilatory response to hypercapnia may also contribute to carbon dioxide retention. This review outlines what is currently known about hypercapnia in diving, including its measurement, cause, mental and physical effects, and areas for future study.

INTRODUCTION

Hypercapnia in diving was first described in the 1920s during an investigation of the dangers of deep diving. A committee appointed by the British Admiralty found that divers often became unconscious or "greatly exhausted" with exertion at depth. Samples taken from the helmets of these divers showed carbon dioxide (CO_2) levels equivalent to 9% CO_2 at the surface (significantly higher than even a normal end-tidal CO_2 of 5-6%)[1]. Later work during the Second World War explored hypercapnia as the cause of "shallow water blackouts." At that time, Royal Navy divers using oxygen rebreathers were found to become significantly impaired or to occasionally lose consciousness in water too shallow to incite oxygen toxicity. These "blackouts" were attributed to the narcotic effects of CO_2 [2]. Subsequent work has confirmed the importance of carbon dioxide in compressed-air narcosis [3, 4]. With prolonged or high levels of exposure to carbon dioxide, studies have demonstrated both physical [5-8] and cognitive impairments

KEYWORDS: carbon dioxide; carbon dioxide retention; hypercapnia; PCO_2; P_aCO_2; $P_{ET}O_2$; diving; Haldane effect

[9-16]. Elevated carbon dioxide also increases the risk for oxygen toxicity [17, 18], likely due to vasodilation of the cerebral vasculature [19], which can lead to oxygen-induced convulsions during dives considered to be within the safe limit for oxygen exposure [20].

Carbon dioxide retention in diving is usually the result of alveolar hypoventilation. Both an increase in dead space and a reduction in overall ventilation contribute to this effect. In some cases, a high inspired partial pressure of carbon dioxide (P_iCO_2) contributes dramatically to elevations in arterial partial pressure of CO_2 (P_aCO_2). This can occur during rebreather dives due to exhaustion or malfunction of the CO_2 absorbent. It is relevant to note that, at rest, partial rebreather failure leading to elevated inspired PCO_2 can be compensated for by a small increase in ventilation [21]. During exercise, however, elevations in inspired PCO_2 are less tolerated and can lead to carbon dioxide retention [22]. The resulting hypercapnia is often tolerated to an extent [23-25], but can lead to incapacitation or to unconsciousness [3, 4, 7, 9, 11, 12, 15]. In divers, such incapacitation is especially problematic and can be deadly [14].

At this time, hypercapnia remains an unpredictable and sometimes lethal risk of diving. Yet, we are aware of only one recent comprehensive review of hypercapnia in diving [26]. This review outlines what is currently known about hypercapnia in diving — its measurement, cause and effects — and further explores two relevant topics: the relationship between end-tidal and arterial PCO_2 under submersed exercise conditions and the role of hyperoxia in the development of diving-related hypercapnia, including a secondary analysis of four previously published studies.

METHODS

Data source

Data were obtained from four previously published studies: Cherry, et al. 2009 [27], Wester, et al. 2009 [28], Peacher, et al. 2010 [29] and Fraser, et al. 2011 [30]. Data points from Cherry, et al. with added external breathing resistance or static lung load were excluded from all analyses to reduce confounding factors.

Subjects

Each study received institutional approval and informed consent. Data from a total of 49 subjects were included in the present analysis, as there was some subject overlap between the four studies. Subject exclusion criteria included: $VO_{2max} < 30\ mL \cdot kg^{-1} \cdot min^{-1}$, ratio of FEV_1 to forced vital capacity < 0.75, or estimated body fat >3% higher than the age- and sex-based upper limits (male < 35 years = 25%, ≥35 years = 28%; female < 35 years = 38%, ≥ 35 years = 41%), contraindications to diving (ear or sinus infection and inability to autoinflate the middle ear), and pregnancy.

Experimental procedures

Experiments were conducted in a small water-filled pool inside a hyperbaric chamber. Submersed exercise took place in the prone position, using an electronically braked ergometer as previously described [27]. In two studies subjects were studied at rest and during submersed exercise at both the surface (1.0 atmosphere absolute (ATA)) and at a simulated depth of 37 meters of sea water (4.7 ATA) [27, 29]. One study examined subjects during submersed exercise only at 1.0 ATA [28], and one study examined subjects during submersed exercise only at 4.7 ATA [30]. Studies during submersed exercise at 4.7 ATA were conducted over a range of inspired oxygen partial pressures (P_iO_2 = 0.21, 0.7, 1.0, 1.3 and 1.75 atmospheres/atm) with some variations in water temperature and work rate between the four experiments. Nitrogen was used as the diluent in all experiments. Expired gas and arterial and venous blood samples were collected at rest and six minutes into exercise, as well as at 16 minutes into exercise for two studies [29, 30].

Statistical analyses

The agreement between end-tidal and arterial PCO_2 was analyzed using Bland-Altman plots (matched pairs analysis, JMP Pro 12, SAS Inc). The association of P_iO_2 with arterial to end-tidal PCO_2 difference was analyzed using a repeated-measures mixed model (mixed model, Statistical Analysis, Software, SAS Inc) that included P_iO_2 as a fixed effect with a random effect for subject. The association of P_iO_2 with minute ventilation (V_E) and P_aCO_2 was analyzed using a repeated-measures mixed model (mixed model, Statistical Analysis Software, SAS Inc) that included P_iO_2 and external work rate as fixed effects with a random effect for subject. Post hoc

Tukey tests were used for pairwise comparisons of all P_iO_2 conditions at 4.7 ATA of depth. The association of depth with V_E and P_aCO_2 was analyzed using a mixed model including depth and external work rate as fixed effects with a random effect for subject (mixed model, Statistical Analysis Software, SAS Inc). Data are displayed as means ± 95% confidence intervals.

The association of P_iO_2 with mixed venous PCO_2 was analyzed using a mixed model (JMP Pro 12, SAS Inc.) with P_iO_2, carbon dioxide production (VCO_2) and P_aCO_2 as fixed effects and with subject as a random effect. This analysis included data from only two studies [28, 29] and only from subjects with paired data (i.e., measurements collected at both P_iO_2 = 0.21 and 1.75 atm). Paired t-tests were used to compare VCO_2, P_aCO_2, oxygen consumption (VO_2) and cardiac output between the two inspired oxygen conditions (matched pairs analysis, JMP Pro 12, SAS Inc). Data are displayed as means ± SEM.

Measuring hypercapnia in diving

While hypercapnia is defined by an increase in arterial PCO_2, it is rarely feasible to measure P_aCO_2 directly. Consequently, both inspired PCO_2 and end-tidal PCO_2 are sometimes used as surrogate measures of hypercapnia. As arterial PCO_2 is directly related to CO_2 delivery to the lungs and indirectly related to alveolar ventilation, an increase in inspired PCO_2 (and therefore CO_2 delivery to the lungs) can often be compensated for by an increase in ventilation. Consequently, inspired PCO_2 is an imprecise tool for representing hypercapnia; it is a particularly poor reflection of end-tidal or arterial PCO_2 at rest [21], but has been associated with increased end-tidal PCO_2 under exercising conditions [22]. End-tidal PCO_2 ($P_{ET}CO_2$) is considered to be a better surrogate and is often reported in the literature in place of P_aCO_2. During rest at 1 ATA, with normal lungs the difference between end-tidal and arterial PCO_2 is small (normally, P_aCO_2 is 2-5 mmHg higher than $P_{ET}CO_2$). In cases of elevated dead space or V_A/Q mismatch (which may be the case under hyperoxic diving conditions (P_iO_2 = 1.75 atm)), $P_{ET}CO_2$ tends to underestimate P_aCO_2. The opposite is true during exercise, where end-tidal PCO_2 has been shown to overestimate arterial PCO_2 by up to around 14 mmHg at high work rates [31]. Discrepancies between arterial and end-tidal PCO_2 during exercise may be due to a lack of temperature correction. Arterial blood gas measurements are made at 37°C irrespective of a subject's body temperature at the time of collection. As body temperature is increased during exercise, the reported values of P_aCO_2 will be lower than the actual P_aCO_2 in the subject, falsely increasing the end-tidal to arterial difference. One study found that correction of P_aCO_2 for body temperature accounted for 44% of the end-tidal arterial difference during exercise [32]. Given the importance of this correction, Henriquez, et al. suggest the following formula for estimating temperature-corrected arterial PCO_2 from $P_{ET}CO_2$ during exercise:

(1) $P_aCO_{2tc} = 8.607 + 0.716 \, x \, P_{ET}CO_2$ [33].

The relationship between P_aCO_2 and $P_{ET}CO_2$ under dive conditions was examined in a study by Mummery, et al., which found that in a dry hyperbaric chamber at 2.8 ATA, the end-tidal arterial PCO_2 difference was smaller at depth versus the surface under both resting and exercising conditions. At 2.8 ATA, $P_{ET}CO_2$ underestimated P_aCO_2 by about 2.21 mmHg during rest and overestimated P_aCO_2 by 2.46 mmHg during exercise. There was also large intersubject variability in end-tidal arterial difference under all conditions [34].

To further elucidate the relationship and agreement between P_aCO_2 and $P_{ET}CO_2$ under diving conditions specifically, Figures 1-3 combine data from four previously published studies in our lab involving submersed exercise at the surface and at depth (4.7 ATA) [27-30]. In this set of studies, mean arterial to end-tidal difference is not significantly different from zero under any of the following conditions:

(1) submersed rest at 1 ATA
    (mean difference= 0.255mmHg, p=0.636);
(2) submersed exercise at 1 ATA
    (mean difference=-0.733mmHg, p=0.171); or
(3) submersed exercise at 4.7 ATA
    (mean difference= 0.693 mmHg, p=0.0780).

P_aCO_2 and $P_{ET}CO_2$ both tend to be higher during exercise at 4.7 ATA than either the resting or exercise condition at 1 ATA (Figure 1). Although the average difference between end-tidal and arterial PCO_2 is small, individual pairs reveal considerable scatter (Figure 2). Interestingly, the precision appears to improve from rest to exercise at the surface and then again from exercise at the surface to exercise at depth. Under all conditions, more than 80% of the values for the end-tidal to arterial difference fall within ±10 mmHg, as demonstrated by

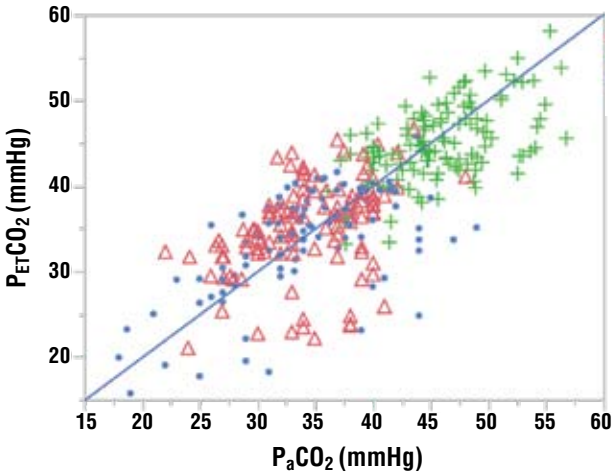


FIGURE 1

End-tidal CO_2 vs. arterial CO_2 during rest and submersed exercise. The line of identity is shown. *From [27-30] excluding data with added resistance or static lung load.* Unusually low PCO_2 values are at rest during cold-water immersion, when subjects are hyperventilating [28].

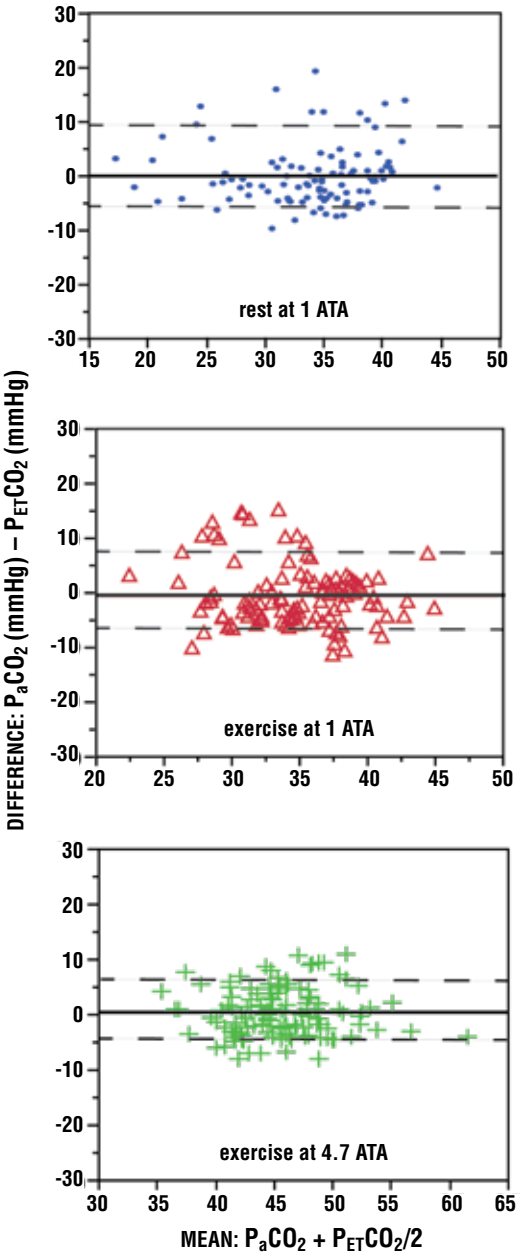


FIGURE 2

Bland-Altman plots for arterial to end-tidal difference during rest and submersed exercise at depth. Solid line shows the mean difference. Dashed lines show 90th percentiles in both directions. *From [27-30] excluding data with added resistance or static lung load.*

the red dashed lines showing the 90th percentiles in both directions.

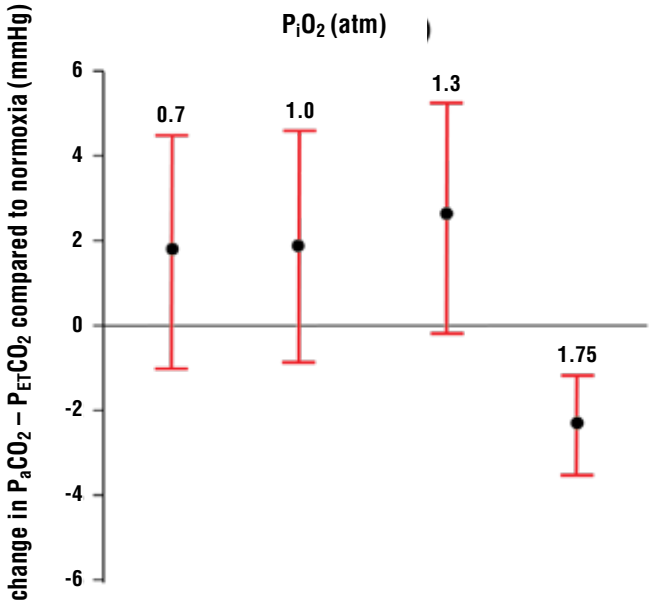
To assess a possible impact of hyperoxia on the relationship between arterial and end-tidal PCO_2, Figure 3 shows the arterial to end-tidal PCO_2 difference for each hyperoxic condition compared to normoxia during submersed exercise at 4.7 ATA. Arterial to end-tidal difference was significantly different from zero at a P_iO_2 of 1.75 atm (mean difference = 3.457 mmHg, $P < 0.0001$) but not significant under any other hyperoxic condition. Overall, end-tidal PCO_2 is an imprecise but relatively unbiased surrogate for arterial PCO_2 and appears to be a better surrogate under most diving conditions (submersed exercise at depth) than under normal resting conditions at the surface. Under very hyperoxic, hyperbaric conditions ($P_iO_2 = 1.75$ atm), end-tidal PCO_2 is more likely to underestimate P_aCO_2 and may be a less appropriate surrogate.

Respiratory physiology and hypercapnia in diving

Under dry, resting conditions at 1 ATA, alveolar ventilation is regulated to maintain an arterial PCO_2 of approximately 40 mmHg [35]. During strenuous exercise at the surface, ventilation increases and P_aCO_2 drops in association with the increased acid production

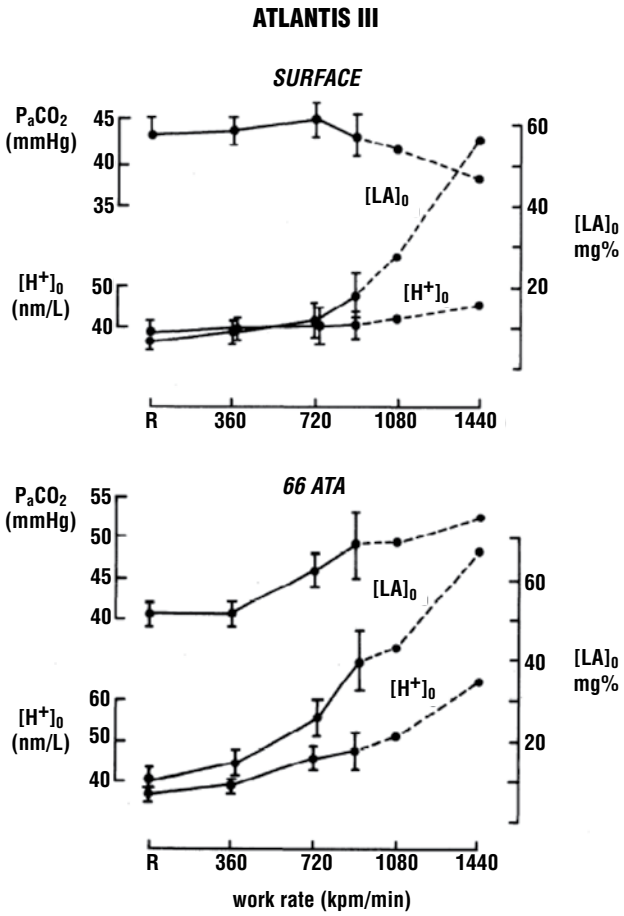
FIGURE 3

Demonstrates the effect of hyperoxia on arterial to end-tidal PCO_2 difference as compared to normoxia during submersed exercise at 4.7 ATA. Red lines indicate 95% confidence intervals. *From [27, 29, 30] excluding data with added resistance or static lung load.*



Lactic acid concentration, hydrogen ion concentration and P_aCO_2 with increasing work rate at 1 ATA (upper plate) and 66 ATA (lower plate) ($P_iO_2 = 0.5$ atm). P_aCO_2 decreases with increasing work at 1 ATA and increases with work at 66 ATA. *Reproduced with permission from Salzano 1984* [36].

FIGURE 4



within working muscles, attenuating the acidemia of exercise (i.e., respiratory compensation for exercise-induced metabolic acidosis). During exercise at pressure, however, minute ventilation and alveolar ventilation (VA) are reduced for any workload compared to the surface. This leads to hypercapnia (rather than the hypocapnia seen with exercise at the surface), which exacerbates exercise-induced acidemia, as shown in Figure 4 [36].

The weight of evidence does not support increased ambient pressure as the cause of hypoventilation and hypercapnia seen with exercise at depth. While pressure itself may have some direct effects at very high pressures (e.g. 30 ATA) [37], breathing gas density (which increases in proportion to increases in pressure) is the most important factor in the development of hypoventilation and hypercapnia at the pressures experienced by most recreational or commercial divers (typically up to ~6 ATA) [38]. Immersion, external breathing resistance from a regulator and hyperoxic breathing gas are also contributing factors.

Except for high inspired PCO_2 in rebreather diving, hypercapnia occurs due to alveolar hypoventilation as a result of two main mechanisms: reduced total pulmonary ventilation — due to increased respiratory load and reduced chemosensitivity — and increased physiologic dead space. The following section elucidates these mechanisms and explores the possible impact

of density-related gas exchange impairment and pressure-induced carbonic anhydrase inhibition on diving-related hypercapnia.

Respiratory load in the dive environment

Ventilation is a balance between chemosensitivity and ventilatory work [39, 40]. Respiratory load — including elastic, resistive and inertial load — is increased in diving [41] and can lead to an increased work of breathing (WOB). Immersion, elevated gas density and external breathing resistance from a regulator all contribute to changes in respiratory load and exacerbate the increased WOB in diving. Immersion or submersion contributes to an increased WOB mainly through changes in lung elastic load. During immersion at any depth and in any posture, there is a passive redistribution of blood to the thorax and pulmonary vasculature. Pulmonary vascular engorgement occurs [42] resulting in an increase in lung elastic resistance [43] and necessitating higher negative inspiratory pressures [44].

Immersion in the head-up position exacerbates changes in lung elastance. In head-out immersion or upright water submersion, there is a pressure differential between the mouth and the centroid of the lung equal to roughly -21 cmH_2O [45]. This negative static lung load (SLL) increases elastic load and has been shown to reduce total lung capacity, vital capacity and residual volume [46, 47]. Such reductions in lung volume also result in decreased force produced by a given respiratory effort due to the length-tension relationship of skeletal muscle [48, 49]. Work of breathing is therefore increased at low lung volumes.

Despite the effect of negative static lung load on efficiency and work of breathing, SLL does not appear to affect hypercapnia directly. One study found that an SLL of up to -20 cmH_2O increased subject-reported dyspnea without exerting a significant change in $P_{ET}CO_2$ [50]. Another study using arterial PCO_2 found that there was no effect of either positive or negative SLL (+10 cmH_2O and -10 cmH_2O) on P_aCO_2 during submersed prone exercise [27].

Along with lung elastic load, resistive load increases in diving, mainly due to increased breathing gas density. In large airways with turbulent flow, flow resistance is directly dependent on gas density during both inspiration and expiration. The effects of elevated gas density on flow resistance are manifested by reductions in expiratory flow [34, 51, 52], maximum voluntary ventilation (MVV) [51, 53] (which is also reduced by immersion [54]) and total ventilation with exercise at depth [38]. Changes in peak expiratory flow or in MVV in relation to changes in gas density can be represented by the following equation:

$$A = A_0(\rho/\rho_0)^{-k} \quad (2)$$

where A is either MVV or peak expiratory flow at gas density ρ (related to the ambient pressure of the diver), A_0 is MVV or peak expiratory flow at 1 ATA, ρ_0 is gas density at 1 ATA and k is a constant (valued at 0.4-0.5) [55]. The mechanisms by which diving reduces MVV have been previously explored in detail [26, 41]. Briefly, MVV is reduced in diving due to reductions in both inspiratory and expiratory flow. During expiration of dense gas, a small increase in flow requires a greater increase in pleural pressure [56], partially due to dynamic airway compression at lower flow rates [26]. Inspiratory flow is not affected by dynamic airway compression, but is similarly reduced at high gas densities, contributing to an overall reduction in MVV [51]. As P_aCO_2 increases when exercise ventilation approaches MVV, reductions in MVV at depth may contribute to hypercapnia during immersed exercise in diving.

Flow resistance is further increased in diving by external breathing resistance from a regulator. A small amount of external breathing resistance is unavoidable with currently available breathing gear. This added external resistance does not significantly affect maximum exercise capacity during non-immersed exercise at the surface [57], but at depth increased external resistance has been shown to reduce ventilation [57], increase subject dyspnea scores [58] and increase P_aCO_2 with submersed exercise [27, 45].

Inertial resistance refers to the amount of pressure required to accelerate the respiratory tissues (i.e., lung and thoracic tissues) and the gas stream. Inertial resistance is also increased in diving in proportion to the increase in gas density [59]. However, changes in inertial resistance contribute only minimally to the changes in WOB at depth. The relative impact of elevated inertial resistance on WOB is dependent on breathing frequency; when respiratory rate is less than the resonant frequency of the respiratory system (which is about 6 Hz at the surface and 2 Hz at depth), inertial resistance plays

only a small role in respiratory load. This is the case at depth due to the reduced respiratory rate [41]. Further, when respiratory rate is equal to the resonant frequency, inertial resistance and elastic resistance can actually balance each other to reduce WOB. One study found that divers using a tunable closed-circuit breathing apparatus would adjust their respiratory rates to match the resonant frequency of the system in order to reduce respiratory load [60]. While inertial resistance may account for some increase in respiratory load with a normal breathing apparatus, lung elastic resistance and flow resistance account for the majority of the increased respiratory load and increased WOB experienced during diving.

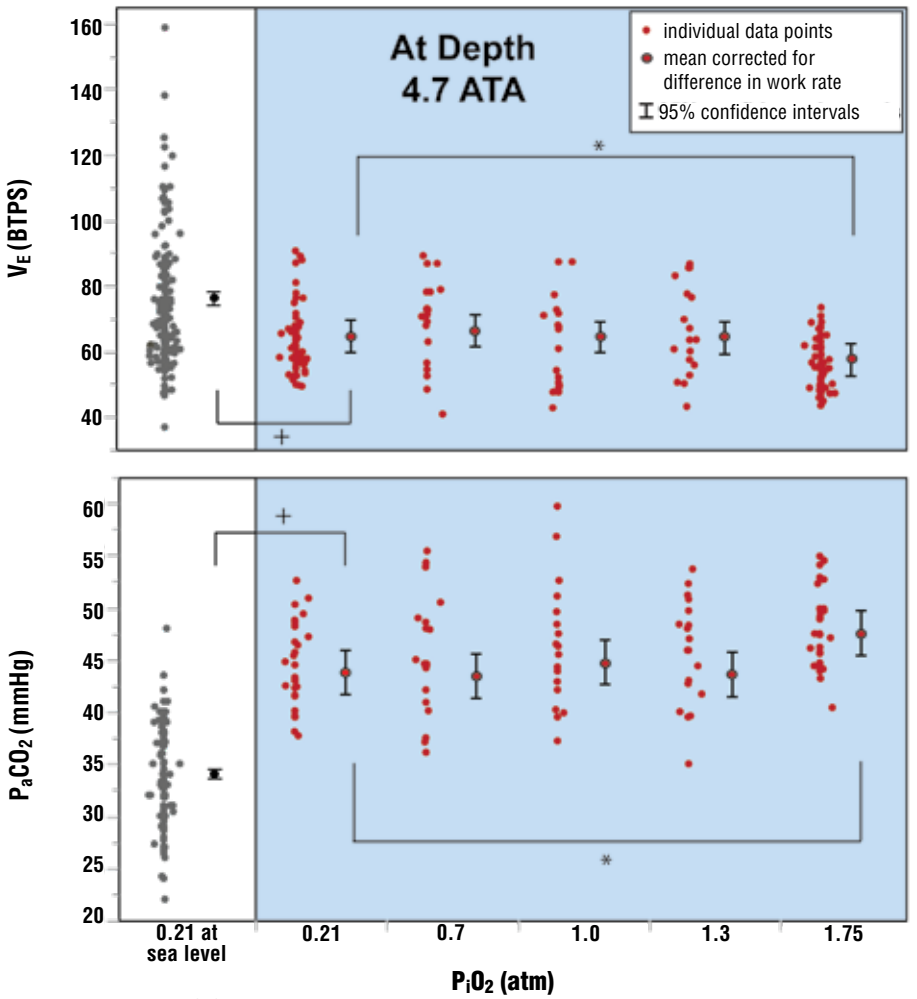
Despite this increased work of breathing, divers are prone to total pulmonary hypoventilation with exercise at depth, leading to progressive accumulation of CO_2. As discussed by Doolette and Mitchell [26], this hypoventilation is not entirely explained by an insurmountable increase in WOB at depth. Hypoventilation and hypercapnia have been shown to occur even during submaximal exercise under hyperbaric conditions [27, 61-63]. Thus, it is unlikely that the increased respiratory load at depth simply surpasses a diver's physical ability to compensate with increased ventilation. Instead, the authors suggest that there is a change in ventilatory control (which continually balances between chemosensitivity and respiratory work) that leads an attenuated response to CO_2. In other words, some control over CO_2 elimination (the key chemosensitive driver in respiration) is sacrificed in order to reduce ventilatory work (in the presence of increased respiratory load) during exercise at depth [64-66]. Additionally, hypercapnic ventilatory response (HCVR) tends to be reduced in divers [67,68]. This furthers supports a diving-related attenuation of CO_2 chemosensitivity and suggests that the changes in ventilatory control that occur under hyperbaric conditions may not be transient.

Hyperoxia and chemosensitivity

The partial pressures of both oxygen and nitrogen are increased during compressed air breathing at depth compared to the surface. For some divers, inspired oxygen partial pressure (P_iO_2) is further increased by the use of oxygen-enriched air mixtures. These changes in gas partial pressure, oxygen in particular, are thought to lead to reductions in respiratory rate due to attenuation of the response of peripheral chemosensors to hypercapnia, and may further exacerbate alveolar hypoventilation and thus carbon dioxide retention.

While hyperoxia is commonly thought to exacerbate carbon dioxide retention, some controversy remains. A recent study by Gill, et al. did not find a significant change in $P_{ET}CO_2$ during exercise at 1.45 ATA with a P_iO_2 of 1.3 atm [11]. Although the authors pointed out that hyperoxia might have changed the relationship between end-tidal PCO_2 and arterial PCO_2 (through a change in V_A/Q distribution), our data do not support such a change in the arterial to end-tidal difference at a P_iO_2 of 1.3 atm (Figure 3). However, our studies were conducted during submersion, while the Gill, et al. study was conducted in a dry chamber. Cherry, et al. also found no significant association between P_aCO_2 during submersed exercise at 4.7 ATA and a range of inspired oxygen pressures (P_iO_2 = 0.7, 1.0, 1.3 atm) [27]. Conversely, two studies by Fraser, et al. and Peacher, et al. found a significant increase in P_aCO_2 during submersed exercise at 4.7 ATA with a P_iO_2 of 1.75 atm compared to normoxia [29, 30]. A third study by Lambertsen, et al. found significant changes in P_aCO_2 during exercise in the dry at a P_iO_2 of 2 atm, although this study did not control for the effect of increased gas density (which would arguably be a small contributor at only 2.0 ATA of pressure) [69]. Figure 5 combines data from Cherry, et al., Fraser, et al., Peacher, et al., and a fourth previously published study performed in our lab by Wester, et al. [27-30]. It demonstrates a significant change in V_E and P_aCO_2 at depth with a P_iO_2 of 1.75 atm when compared to a P_iO_2 of 0.21 atm ($P<0.05$). The remaining oxygen conditions (P_iO_2 = 0.7, 1.0 or 1.3 atm) did not significantly affect V_E or P_aCO_2. Based on these findings, it is plausible that hyperoxia affects hypercapnia in diving but only at extreme levels of inspired PO_2 (e.g., ≥1.75 atm), which are not permitted in usual diving practice.

The mechanism by which hyperoxia induces hypercapnia remains incompletely understood. One suggested mechanism is hyperoxic attenuation of respiratory chemosensitivity. Interestingly, this mechanism is not supported within a clinical context. Some patients with chronic obstructive pulmonary disease (COPD) experience hypercapnia when supplemental oxygen is administered. Originally this phenomenon was attributed to chemosensitive reductions in the hypoxic drive, lead-



	0.21 at sea level	0.21	0.7	1	1.3	1.75
P_aO_2 (mmHg)	104±1	103±3	472±24	616±12	802±20	1045±18
S_aO_2 (%)	96.8±0.1	96.5±0.2	98.2±0.1	98.1±0.1	98.5±0.1	98.4±0.1
P_VO_2 (mmHg)	23.7±0.3	27.2±0.9	29.8±0.8	31.2±0.8	32.7±0.9	35.6±0.6
S_VO_2 (%)	34.0±0.7	39.7±1.7	49.3±2.9	51.7±2.4	52.3±2.1	55.0±1.0

FIGURE 5

V_E and P_aCO_2 during submersed exercise at 4.7 ATA vs. P_iO_2. + P<0.05 vs. normobaric normoxia; * in the figure P<0.05 vs. hyperbaric normoxia. Table: means (±SEM) for arterial and mixed venous PO_2 and saturation. *From [27-30] excluding data with added resistance or static lung load.*

ing to hypoventilation [70]. Later research, however, has refuted hypoventilation as the cause of hyperoxia-induced hypercapnia in COPD patients [71-75]. One study by Aubier, et al. demonstrated elevations in P_aCO_2 in COPD patients after 15 minutes of oxygen administration despite only small reductions in minute ventilation (V_E= 93 ± 6% V_E (mean ± SEM) on room air). Given the maintenance of relatively normal ventilation, the authors attributed elevations in P_aCO_2 to inhomogeneous V_A/Q distribution [73]. A subsequent study, by Sassoon, et al., found that changes in P_aCO_2 with oxygen administration were associated with both decreased V_E and increased V_D/V_T. Reductions in V_E, however, corresponded completely with changes in carbon dioxide production (VCO2) and the increases in P_aCO_2 were therefore explained by changes in V_D/V_T [75]. Most recently, a study by Rialp, et al. demonstrated no significant effect of hyperoxia on respiratory drive or on V_E in patients with COPD [71]. At this time, hyperoxia-induced hypercapnia in patients with COPD is thought to occur due to changes in V_A/Q distribution, elevations in dead space and a direct decrease in blood CO_2 solubility through the Haldane effect. These effects are also applicable to diving and will be explored in a later section.

Unlike COPD patients, hyperoxia does appear to affect ventilatory rate in divers. Hyperoxia has been shown to reduce minute ventilation during exercise at the surface and at depth (Figure 5) [29] and to reduce hypercapnic ventilatory response (HCVR) [76-78]. Hyperoxia-induced hypoventilation was previously attributed, at least in part, to the attenuation of exercise-induced metabolic acidosis: i.e., higher tissue PO_2 reduces muscle acid production leading to a higher arterial pH and reduced respiratory compensation (ventilation) [29, 69]. A study by Peacher, et al., however, found that compared to normoxia (P_iO_2 = 0.21 atm) there was no change in arterial pH with exercise under hyperoxic conditions (P_iO_2 = 1.75 atm). Reductions in metabolic acidosis were balanced by increases in respiratory acidosis, resulting in a constant arterial pH [29]. Thus the respiratory suppression in hyperoxia cannot be explained completely by reductions in metabolic acidosis. Instead, hyperoxia is also thought to directly inhibit ventilation through its interactions with chemoreceptors and the hypercapnic ventilatory response.

While there is a ventilatory response to hypoxia, ventilation is primarily determined by PCO_2 within arterial blood and the brain. Therefore, hyperoxia affects ventilation mainly through its interactions with CO_2 chemoreceptors. These chemoreceptors are divided into peripheral chemoreceptors, primarily in the carotid body, and central chemoreceptors in the medulla oblongata [79]. The responses of these two types of receptors are not entirely independent. Studies of neural circuitry suggest that afferent input from the carotid body modulates central receptor chemosensitivity to carbon dioxide [80,81]. Regardless of this subtle modulation, the chemosensory response to carbon dioxide under conditions of normoxia or hypoxia essentially occurs in two phases corresponding to separate and sequential responses of the two different receptor types. The rapid reflex ventilatory response is mediated mainly by peripheral chemoreceptors, while the slow reflex response is mediated by central chemoreceptors [77]. In hyperoxia, the rapid response to carbon dioxide (peripheral chemoreceptor response) is attenuated [82] or even eliminated [77, 83], while the slow reflex response is preserved. This results in a longer latency of response to hypercapnia under hyperoxic conditions [84] and could contribute to hypoventilation, though at higher pressures of inspired oxygen than typically encountered in diving.

In addition to oxygen, partial pressures of nitrogen are increased during compressed-air breathing. Nitrogen narcosis was once thought to contribute to carbon dioxide retention at depth, but is not currently considered a main factor in the phenomenon [85].

Effects of diving on dead space

The geometry of the human lung is uniquely suited for air breathing at the surface. Cyclic gas flow into an individual lung unit in response to a cyclic driving pressure is a function of its time constant (a number derived from the product of that unit's resistance and compliance). In spite of large variations in distance between conductive airways and gas exchange units, time constants are approximately equal across different lung units at 1 ATA. Thus ventilation remains reasonably homogenous in healthy individuals [86]. As gas density increases, however, changes in flow resistance lead to an increase in time constant variability [87], and ventilation becomes more heterogeneous [45]. Regional differences in pleural pressure also increase at depth. At baseline,

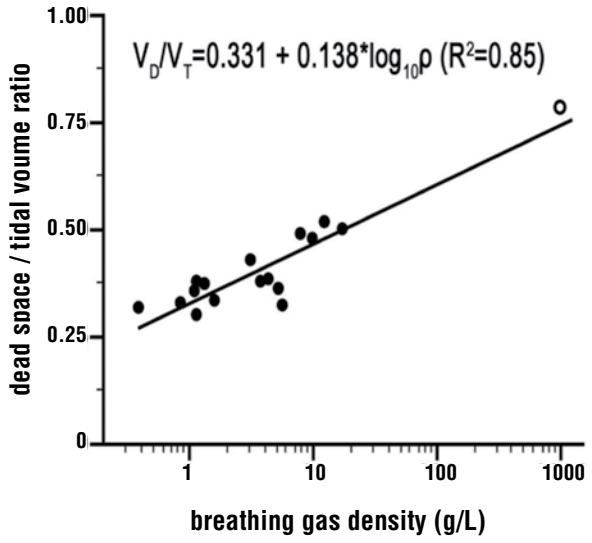


FIGURE 6

Dead space/tidal volume ratio vs. gas density

Demonstrates an increase in fractional dead space with increasing gas density. ° is from a liquid-breathing experiment in dogs. *Reproduced with permission from Moon 2009 [45].*

some variation in pleural pressure exists between the upper and lower lobes of the lung [88]. Elevated gas density exacerbates these differences in pleural pressure and may further contribute to increased heterogeneity of ventilation. Although ventilation becomes more heterogeneous, oxygen exchange actually improves at elevated gas density (as evidenced by a decrease in alveolar-arterial O_2 difference). This phenomenon may be explained by increased cyclic perfusion of the lungs at high gas density [89, 90]. Due to the large pleural pressures swings experienced during dense gas breathing, lung perfusion adopts a cyclical flow that tracks with the breath cycle, which could lead to better V_A/Q matching at any point in time. While cyclic lung perfusion may benefit oxygen exchange, it has been shown to have only a small effect on CO_2 exchange (likely due to the high solubility of CO_2 in blood) [90].

In fact, high gas density likely contributes to elevations in P_aCO_2 through an increase in dead space. During exercise with high breathing gas density in the dry, there is an increase in fractional dead space (V_D/V_T) (Figure 6), likely due to increased variability of ventilation within the lung [27, 34, 36, 91]. It is possible that increased gas density could also augment regional inhomogeneity due to both gravitational effects and interlobar variability [92]. Interestingly, submersion appears to attenuate the effect of gas density on dead space [27, 29], except under some hyperoxic conditions (e.g., P_iO_2 = 1.75 atm) [29]. Two studies (Cherry, et al. and Peacher, et al.) measured V_D/V_T during submersed exercise with air at depth and found no change in V_D/V_T [27, 29]. However, Peacher, et al. also explored the effects of hyperoxia on dead space and found that V_D/V_T did increase significantly during submersed exercise at 4.7 ATA with a P_iO_2 equal to 1.75 atm (Figure 7) [29]. As hyperoxia has been shown to cause general pulmonary vasodilation [93], the authors suggested that the increase in fractional dead space seen with hyperoxia could be due to pulmonary vasodilation leading to an increase in ventilation perfusion (V_A/Q) mismatch. Specifically, non-selective pulmonary vasodilation would divert perfusion from well-ventilated lung units to less well-ventilated units (which may be vasoconstricted under normoxic conditions). Due to the decreased perfusion of well-ventilated lung units and increased perfusion of poorly ventilated units, V_A/Q mismatch and physiologic dead space would both increase. Studies in patients with COPD support increased V_A/Q mismatch and physiologic dead space as contributors to hyperoxia-induced hypercapnia [72-75].

The Haldane effect, which causes a slight reduction in CO_2 solubility with elevated oxygen levels, has been suggested to exacerbate the effects of hyperoxia on dead space [94] and is commonly considered to be a main contributor to carbon dioxide retention in both COPD patients on oxygen and healthy divers. While CO_2 solubility is measurably reduced from hypoxia to normoxia, the reduction in CO_2 solubility from normoxia to hyperoxia is insignificant [95]. The impact of the Haldane effect on CO_2 solubility within arterial blood is thus more profound under hypoxic conditions (for example, in patients with COPD or other underlying pulmonary conditions) [74, 75] and would not contribute directly to an increased P_aCO_2 in healthy divers. However, studies within our lab show that the Haldane effect may increase mixed venous PCO_2 in healthy individuals. During submersed exercise at 4.7 ATA, mixed venous PCO_2 is higher with a P_iO_2 of 1.75 atm compared to normoxia even after controlling for differences in P_aCO_2 and CO_2 production (VCO_2) between the two oxygen

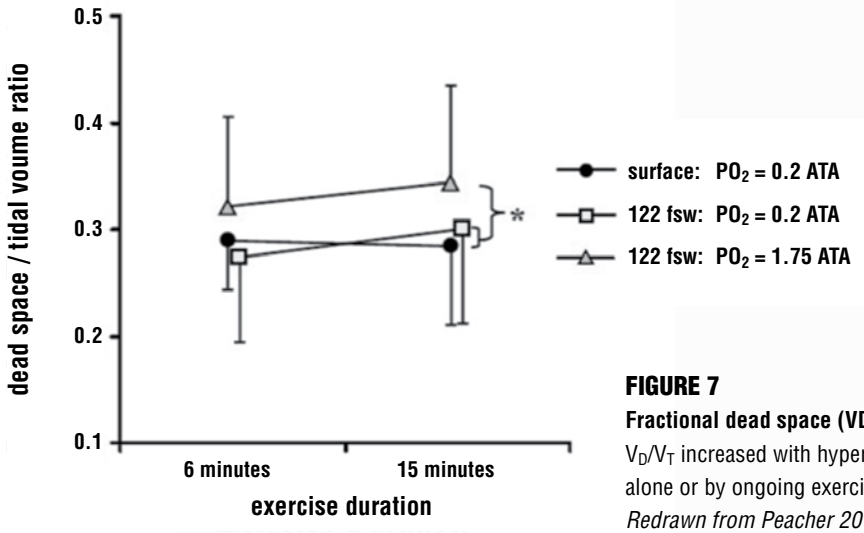


FIGURE 7
Fractional dead space (VD/VT) during exercise trials.
V_D/V_T increased with hyperoxia. It was not affected by depth alone or by ongoing exercise (6 minutes to 15 minutes). *Redrawn from Peacher 2010 [29] with permission.*

	inspired PO_2 (atm)		
	0.21	1.75	p-value
mixed venous PCO_2 (mmHg)	65.79±1.40	70.08±1.37*	0.0003
VCO_2 STPD (L/min) (dm^3/min)	2.20±0.06	2.01±0.05*	<0.0001
P_aCO_2 (mmHg)	44.33±0.76	48.06±0.66*	<0.0001
VO_2 STPD (L/min) (dm^3/min)	2.31±0.08	2.21±0.07	0.3655
Fick cardiac output (L/min) (dm^3/min)	18.89±1.39	17.16±0.58	0.2179

TABLE 1.
Effect of hyperoxia (P_iO_2 = 1.75 atm) on mixed venous PCO_2 during submersed, prone exercise at 4.7 ATA
Values shown are group means ± standard error means. * significant difference from normoxic exercise condition (P_iO_2 = 0.21 atm). *Data from [29] and [28].*

conditions (Table 1). The downstream effects of a Haldane-related increase in venous PCO_2 remain unclear. It is plausible that the increase in mixed venous PCO_2 could contribute to an increase in dead space through an increase in alveolar PCO_2 (P_ACO_2). Fractional dead space can be calculated using the Bohr equation:

(3) $V_D/V_T = (P_ACO_2 - P_ECO_2) / P_ACO_2$

where P_ECO_2 is the mixed expired PCO_2. An increase in venous PCO_2 might increase P_ACO_2 and therefore increase fractional dead space. Overall, however, the Haldane effect likely plays a smaller role in carbon dioxide retention for divers than was historically thought; it does increase mixed venous PCO_2 but does not directly increase arterial PCO_2.

Carbon dioxide and oxygen exchange at high gas density

Diffusion limitation at high gas density has been suggested to cause impairment in gas exchange at depth. A phenomenon thought to contribute to diffusion limitation of carbon dioxide specifically is functional screening of distal alveoli. As oxygen diffuses along an

acinus, it is absorbed by the proximal alveoli and may not reach more distal alveoli. This effectively "screens" distal alveoli from gas exchange and reduces the total area available for diffusion of gases. Functional screening of alveoli could contribute to the hypercapnia seen in diving as screening affects carbon dioxide exchange to a greater extent than oxygen exchange [96] and as screening is exacerbated by elevated gas density [97]. A study by Kylstra, et al. found that there was diffusion limitation of both oxygen and carbon dioxide during ventilation of dogs with hyperoxygenated saline. However, the authors were still able to achieve adequate arterial PO_2 and PCO_2 during ventilation with a liquid. This suggests that diffusion limitation occurs but does not significantly impact gas exchange, even at the highest densities [98], and therefore does not play a significant role in hypercapnia in diving.

Effects of pressure on carbonic anhydrase

The impact of increased ambient pressure on carbon dioxide retention can be primarily explained by elevated gas density at depth. However, at extreme depths, pressure itself may contribute directly to increased P_aCO_2 through reduced functioning of carbonic anhydrase, the enzyme that catalyzes the conversion between carbon dioxide and carbonic acid. A study of red blood cells in simulated saturation dives to 30.6 ATA revealed a decrease in carbonic anhydrase within red cells at extreme pressure. This reduction was due, in part, to binding of the enzyme to the red cell membrane [37]. Reduced carbonic anhydrase function could disrupt the conversion of CO_2 to carbonic acid and contribute to carbon dioxide retention at depth. As this effect was observed only at very high pressures, it does not apply to the shallower depths experienced by most recreational and commercial divers.

Physical and cognitive impact of hypercapnia

Compressed-air narcosis has long been known to cause behavioral and physical changes that can be dangerously incapacitating for divers. While nitrogen is considered the main cause of narcosis, elevations in carbon dioxide have been shown to contribute additively (or even synergistically) to this effect [3, 4]. Even when considered separately from nitrogen narcosis, carbon dioxide is thought to lead to its own mental and physical impairments. In fact, at very high levels (over about 10% inspired CO_2), hypercapnia is known to uniformly cause unconsciousness [99]. Conversely, at low levels, hypercapnia is often tolerated [23-25]. At levels between these two extremes, hypercapnia is thought to exert both physical and mental effects, although there is some inconsistency with regard to its observed cognitive effects.

Physical symptoms of hypercapnia

Hypercapnia is often a physically uncomfortable as well as a physically incapacitating experience. Reported symptoms of breathing carbon dioxide include anxiety [9], shortness of breath, sweating, heart palpitations, chest pressure, tingling and dizziness [7]. Hypercapnia can cause headache and increased intracranial pressure due to cerebral vasodilation, as well as muscle twitching of the extremities or face [6], or psychomotor slowing [3]. A rapid return to breathing room air or oxygen following exposure to carbon dioxide can cause vomiting, headache and discomfort [8].

Hypercapnia has additional implications for the heart. In vitro, CO_2 causes a direct reduction in myocardial contractility [100]. In vivo, however, carbon dioxide triggering of peripheral chemoreceptors causes an increase in circulating catecholamines and counteracts this cardiac depression [101-103]. Elevated arterial PCO_2 also causes coronary vasodilation in animals and humans [104-106]. Given the normally tight coupling between coronary vasodilation and myocardial oxygen demand, non-specific vasodilation increases myocardial O_2 delivery, as demonstrated by a decrease in the arteriovenous PO_2 difference [104, 107-110]. For this reason, elevated arterial PCO_2 may provide some protective effects for the heart following ischemia [111, 112]. Despite these positive effects on the cardiopulmonary system, carbon dioxide has dangerous neurological effects for divers. Chronic exposure to even low levels of carbon dioxide ($P_iCO_2 = 0.7\%$ and 1.2% for 26 days) may cause transient visuomotor decrements [13] and, at high levels, carbon dioxide uniformly leads to unconsciousness [99]. In fact, carbon dioxide is used as an effective and rapid anesthetic for animals [5]. In diving, unconsciousness from carbon dioxide retention can prove fatal [14]. Additionally, elevated carbon dioxide increases the risk for oxygen toxicity [17, 18]; Hypercapnia lowers the hyperbaric, hyperoxic seizure threshold and can lead to oxygen-induced convulsions during dives considered to be within the safe limit for oxygen

exposure [20]. This likely occurs due to increased cerebral blood flow and increased oxygen delivery to the brain under hypercapnic conditions [19], as carbon dioxide is a potent, cerebral vasodilator [113]. Cerebral blood flow increases by 50% during inhalation of 5% CO_2 and by 100% during inhalation of 7% CO_2 [114].

Cognitive impairments

While the anesthetic properties of CO_2 are undeniable at very high levels, there remains some controversy regarding the cognitive and psychomotor effects of CO_2 at intermediate levels. Some studies support reduced cognitive performance with moderately elevated amounts of inspired or end-tidal CO_2. Hesser, et al. found that an increase of 10 mmHg in $P_{ET}CO_2$ at depth was associated with a significant decrease in performance on arithmetic and manual dexterity testing [3]. A study by Sayers et al under normobaric conditions found that a $P_{ET}CO_2$ greater than approximately 51 mmHg was associated with a significant increase in time to complete reasoning tests [15]. Henning, et al. measured simple and choice reaction time before, during and after exposure to 6% inspired CO_2 under normoxic conditions and hyperoxic conditions. The authors found no significant change in reaction time during CO_2 exposure, but did find significant decrements in performance immediately after exposure (24). Most recently, Freiberger, et al. examined the relationship between arterial PCO_2 and a number of cognitive performance tests—including tests of memory, attention, planning and motor performance — as measured by MATB-II flight simulator software. Elevated P_aCO_2 was not associated with impairments in memory or attention, but was significantly associated with impaired motor and planning performance [10].

Hyperoxia has been suggested to attenuate the mental effects of hypercapnia, although this hypothesis remains questionable. Henning, et al. found that hyperoxia did not significantly change reaction time [24]. In the study by Freiberger, et al., hyperoxia (P_iO_2 = 0.925 atm) was found to attenuate the cognitive impairments associated with hypercapnia at the surface. However, at increased ambient pressure, high PO_2 (1.22 atm) actually worsened memory, attention and motor performance [10]. In another study by Gill, et al. [11], hyperoxia was found to attenuate reductions in N-back performance [115] associated with elevated $P_{ET}CO_2$. It remains unclear, however, if hyperoxia simply attenuated the hypercapnia itself in this study, as hyperoxia improved cognitive performance through an elevation in minute ventilation and a reduction in $P_{ET}CO_2$ [11].

Two studies within the last decade demonstrated no significant effect of carbon dioxide exposure on cognitive or psychomotor performance. In a study by Vercruyssen, et al., subjects were exposed to three carbon dioxide conditions (room air, 3% CO_2 or 4% CO_2) at sea level for 60 minutes during rest and exercise. Performance on grammatical reasoning, addition, multiplication and postural sway testing was not significantly affected by inspired carbon dioxide before, during or after exercise [25]. In a subsequent study by Haran and Lovelace, U.S. Navy Divers were exposed to up to 2% surface equivalent value (SEV) CO_2 with an imposed external breathing resistance of up to 1.8 kPa (gauge, equivalent to 13.5 mmHg) during endurance exercise testing at a depth of 12 fsw (1.35 ATA). While physical symptoms such as headache increased with both higher resistance and higher inspired CO_2, there was no significant change in cognition (measured before and after exercise by a subset of Automated Neuropsychological Assessment Metrics) or in balance [23].

A number of studies demonstrate cognitive effects of carbon dioxide only above a threshold level. A study by Hesser, et al. (1971) found that carbon dioxide contributed significantly to compressed-air narcosis only with CO_2 alveolar tensions above 40 mmHg [4]. Similarly, Inouye, et al. found that subjects breathing up to 5% CO_2 did not experience a significant change in mental performance, as measured by a modified Kraepelin's test. At 7% CO_2, however, subjects showed significant reductions in mental performance, as well as reductions in hearing and in fusion frequency of flicker (a psychophysical phenomenon) [12].

Several theories may explain the discrepancies within the literature regarding the cognitive effects of hypercapnia. Findings such as those of Inouye, et al. [12] and Hesser, et al. [4] suggest that there may be a threshold of hypercapnia below which carbon dioxide exerts minimal effects on cognition and psychomotor abilities. It is also possible that the cognitive effects of carbon dioxide are subtle at intermediate levels and have not been accurately assessed by all protocols; specifically, hypercapnia is though to affect cognition by reducing an individual's ability to multitask, in which case single-

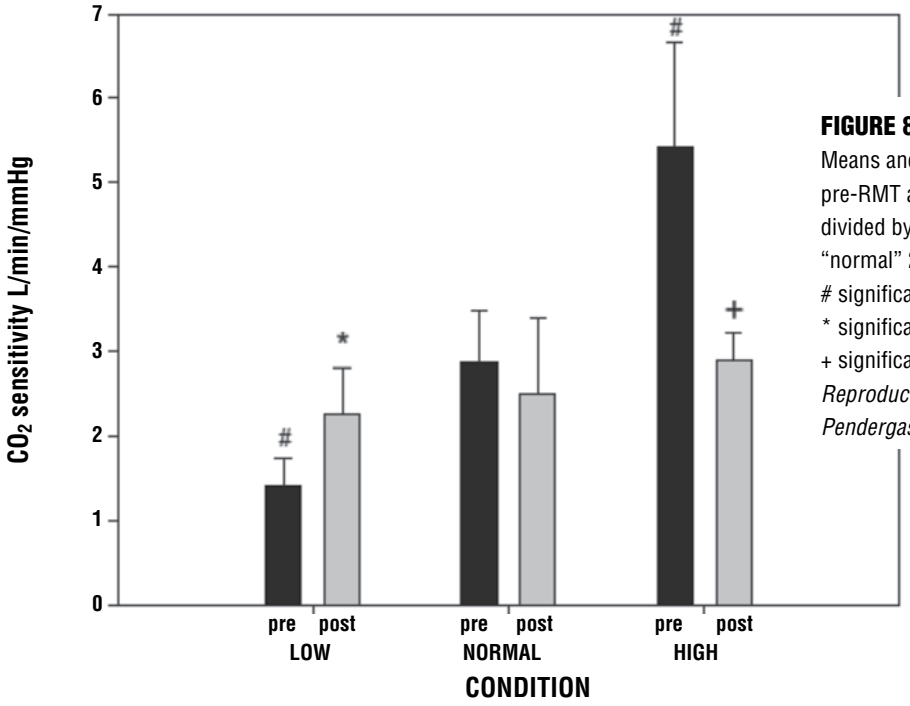


FIGURE 8
Means and standard deviations for pre-RMT and post-RMT CO_2 sensitivity divided by pre-RMT values ("high" > 4, "normal" 2-4, and "low" < 2 l/min/mmHg). # significant difference from "normal," * significant increase post-RMT, + significant reduction. *Reproduced with permission from Pendergast 2006* [68].

task assessments (such as arithmetic) do not fully capture cognitive impairment. A final suggestion is that discrepancies in reported effects of hypercapnia may be the result of differences in PCO_2 measurement [3]. In particular, inspired PCO_2 levels may not accurately reflect alveolar or, more importantly, arterial PCO_2 such that studies examining inspired PCO_2 may underestimate the effects of true hypercapnia.

Prediction of hypercapnia in diving

Given the potentially lethal sequelae of hypercapnia while diving, some attempts have been made to predict carbon dioxide retention at depth. Ventilatory response to elevated CO_2 (hypercapnic ventilatory response, or HCVR) varies among individuals and is often attenuated in scuba (self-contained underwater breathing apparatus) divers [67, 116, 117]. Lanphier, et al. explored HCVR as a predictor of carbon dioxide retention by comparing surface HCVR to end-tidal PCO_2 at depth. The study found that there was an association between a reduced HCVR at the surface and elevated $P_{ET}CO_2$ with exercise at depth. However, the association varied greatly between individuals and was found to be neither statistically significant nor a useful means of prediction across all subjects [116]. Later work by Cherry, et al. using arterial PCO_2 did find a statistically significant association between HCVR at sea level and elevated P_aCO_2 with exercise at depth. Again, the association was not a good individual predictor due to high inter-individual variability [27]. Peacher, et al. describe one example of this variability; one subject with a remarkably low HCVR had below-average levels of P_aCO_2 [29].

While it is an inaccurate tool for predicting individual risk, HCVR is correlated with carbon dioxide retention in some divers. For these individuals, a low HCVR at baseline may be a modifiable risk factor for hypercapnia, as HCVR can be altered by respiratory muscle training (RMT). In a study by Pendergast, et al. [68], subjects underwent baseline HCVR testing followed by four weeks of RMT during which they breathed against a spring-loaded valve for 30 minutes a day three to five times a week. At the end of this training period, HCVR following RMT was approximately equal for all subjects regardless of their baseline sensitivity (Figure 8). Subjects with normal pre-training carbon dioxide sensitivity experienced no change in sensitivity follow-

ing RMT. Low sensitivity subjects, however, showed an increase in sensitivity. For these subjects, RMT may be useful in preventing diving-related carbon dioxide retention.

CONCLUSION

Hypercapnia remains a potential and unpredictable risk for divers. It is often studied using end-tidal PCO_2 as a surrogate measure for arterial PCO_2. Despite the widespread use of $P_{ET}CO_2$ in the diving literature, very few studies have examined the relationship between end-tidal and arterial PCO_2 in diving. The available data suggest that end-tidal PCO_2 is a reasonable representative of arterial PCO_2 on average but with large variability within and between subjects. Arterial PCO_2 remains the gold standard for assessing hypercapnia in diving.

In terms of the mechanism of hypercapnia, CO_2 retention often occurs in diving due to alveolar hypoventilation. Conditions of the dive environment lead to reduced alveolar ventilation through an increase in respiratory load and work of breathing, a decrease in hypercapnic ventilatory response and an increase in dead space. While elevated gas density during compressed-air breathing is the main mechanism in these respiratory changes, there is also an effect of PO_2; elevated inspired PO_2 is associated with reduced respiratory chemosensitivity and increased physiologic dead space. Additionally, hyperoxia increases mixed venous PCO_2 due to the Haldane effect. This change in P_vCO_2 could conceivably contribute to carbon dioxide retention in diving, but remains to be explored.

Once carbon dioxide retention occurs, hypercapnia can lead to life-threatening physical and mental changes for divers. Physical symptoms include shortness of breath, sweating, heart palpitations, muscle twitching, tingling, headache and vomiting. Hypercapnia can also exacerbate nitrogen narcosis and oxygen toxicity and will uniformly lead to unconsciousness at high levels. At intermediate levels, hypercapnia may have some additional cognitive and psychomotor effects that are not yet clearly defined. Future research should utilize tests that require multitasking in order to clarify the cognitive impact of hypercapnia at intermediate levels.

New research on HCVR suggests that respiratory muscle training may improve ventilatory response for individuals with a low HCVR at baseline. The effects of RMT on P_aCO_2 in diving have not yet been studied. Through its effects on HCVR, respiratory muscle training may be able to reduce the risk of carbon dioxide retention at depth and could prevent injuries from hypercapnia in the future. Whether this finding can be exploited in practice needs investigation. ■

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Conflict of interest statement

Authors declare no conflicts of interest exist with this submission.

REFERENCES

1. Haldane J. Respiration. New Haven, CT: Yale University Press; 1922. 427.

2. Barlow H, MacIntosh F. Shallow water black-out. Hampstead, NW3, London: National Institute for Medical Research, 1944 Contract No.: UPS 48.

3. Hesser C, Fagraeus L, Adolfson J. Roles of nitrogen, oxygen and carbon dioxide in compressed-air narcosis. Undersea Biomed Res. 1978;5(4):391-400.

4. Hesser C, Adolfson J, Fagraeus L. Role of CO_2 in compressed-air narcosis. Aerosp Med. 1971;42(2):163-168.

5. Leake C, Waters R, editors. The anesthetic properties of carbon dioxide. The Scientific Proceedings of the American Society for Pharmacology and Experimental Therapeutics; 1928; Ann Arbor, Michigan: J Pharmacol Exp Ther.

6. O'Reilly RJ. The clinical recognition of carbon dioxide Intoxication. CHEST Journal. 1960; 37(2): 185. doi: 10.1378/chest.37.2.185.

7. Maresh C, Armstrong L, Kavouras S, et al. Physiological and psychological effects associated with high carbon dioxide levels in healthy men. Aviat Space Environ Med. 1997; 68: 41-45.

8. Alexander W, Duff P, Haldane J, Ives G, Renton D. After-effects of exposure of men to carbon dioxide. The Lancet. 1939: 419-420.

9. Colasanti A, Salamon E, Schruers K, van Diest R, van Duinen M, Griez EJ. Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. Neuropsychopharmacology. 2008; 33(13): 3103-3110. doi: 10.1038/npp.2008.31. PubMed PMID: 18354390.2016: jap 00534 2016. doi: 10.1152/japplphysiol.00534.2016. PubMed PMID: 27633739.

10. Freiberger JJ, Derrick B, Natoli MJ, et al. Assessment of the interaction of hyperbaric N_2, CO_2 and O_2 on psychomotor performance in divers. J Appl Physiol (1985). 2016: jap 00534 2016. doi: 10.1152/japplphysiol.00534.2016. PubMed PMID: 27633739.

11. Gill M, Natoli MJ, Vacchiano C, et al. Effects of elevated oxygen and carbon dioxide partial pressures on respiratory function and cognitive performance. J Appl Physiol (1985). 2014; 117(4): 406-412. doi: 10.1152/japplphysiol.00995.2013. PubMed PMID: 24947022.

12. Inouye A, Kawabata G, Nagaya T, Shigematsu Y. Effect of high carbon dioxide concentration on mental performance and some sensory functions. Jpn J Physiol. 1955;109-121.

13. Manzey D, Lorenz B. Effects of chronically elevated CO_2 on mental performance during 26 days of confinement. Aviat Space Environ Med. 1998; 69: 506-514.

14. Mitchell S, Cronje F, Meintjes W, Britz H. Fatal respiratory failure during a "technical" rebreather dive at extreme pressure. Aviat Space Environ Med. 2007; 78:81-86.

15. Sayers J, Smith R, Holland R, Ketinge W. Effects of carbon dioxide on mental performance. J Appl Physiol. 1987; 63(1): 25-30.

16. Warkander DE, Norfleet WT, Nagasawa GK, Lundgren CE. CO2 retention with minimal symptoms but severe dysfunction during wet simulated dives to 6.8 atm abs. Undersea Biomed Res. 1990; 17(6): 515-23. PubMed PMID: 2288042.

17. Arieli R, Arieli Y, Daskalovic Y, Eynan M, Abramovich A. CNS oxygen toxicity in closed-circuit diving: signs and symptoms before loss of consciousness. Aviat Space Environ Med. 2006; 77(11): 1153-1157. PubMed PMID: 17086769.

18. Arieli R, Ertracht O. Latency to CNS oxygen toxicity in rats as a function of PCO(2) and PO(2). Eur J Appl Physiol Occup Physiol. 1999; 80(6): 598-603. PubMed PMID: 10541928.

19. Behnke AR, Forbes HS, Motley EP. Circulatory and visual effects of oxygen at 3 atmospheres pressure. Am J Physiol. 1936; 114(2):436-442. PubMed PMID: WOS:000202432400019.

20. Lanphier E. Pulmonary Function. In: Bennett PB, Elliott DH, editors. The physiology and medicine of diving and compressed air work. Second ed. Baltimore: The Williams & Wilkins Company; 1975. 102-154.

21. Deng C, Pollock NW, Gant N, et al. The five-minute prebreathe in evaluating carbon dioxide absorption in a closed-circuit rebreather: a randomized single-blind study. Diving Hyperb Med. 2015; 45(1): 16-24. PubMed PMID: 25964034.

22. Shykoff BE, Warkander DE. Exercise carbon dioxide (CO_2) retention with inhaled CO_2 and breathing resistance. Undersea Hyperb Med. 2012; 39(4): 815-828. PubMed PMID: 22908838.

23. Haran F, Lovelace A. Effects of inspired CO_2 and breathing resistance on neurocognitive and postural stability in US Navy divers. Navy Experimental Diving Unit, 2015 Feb 2015. Report No.: NEDU TR 15-05.

24. Henning RA, Sauter SL, Lanphier EH, Reddan WG. Behavioral effects of increased CO2 load in divers. Undersea Biomed Res. 1990; 17(2): 109-120. PubMed PMID: 2108518.

25. Vercruyssen M, Kamon E, Hancock PA. Effects of carbon dioxide inhalation on psychomotor and mental performance during exercise and recovery. Int J Occup Saf Ergon. 2007; 13(1): 15-27. PubMed PMID: 17362655.

26. Doolette DJ, Mitchell SJ. Hyperbaric conditions. Compr Physiol. 2011; 1(1): 163-201. doi: 10.1002/cphy.c091004. PubMed PMID: 23737169.

27. Cherry AD, Forkner IF, Frederick HJ, et al. Predictors of increased P_aCO_2 during immersed prone exercise at 4.7 ATA. J Appl Physiol (1985). 2009; 106(1): 316-325. doi: 10.1152/japplphysiol.00885.2007. PubMed PMID: 18787095.

28. Wester TE, Cherry AD, Pollock NW, et al. Effects of head and body cooling on hemodynamics during immersed prone exercise at 1 ATA. J Appl Physiol (1985). 2009; 106(2): 691-700. doi: 10.1152/japplphysiol.91237.2008. PubMed PMID: 19023017.

29. Peacher DF, Pecorella SR, Freiberger JJ, et al. Effects of hyperoxia on ventilation and pulmonary hemodynamics during immersed prone exercise at 4.7 ATA: possible implications for immersion pulmonary edema. J Appl Physiol (1985). 2010; 109(1): 68-78. doi: 10.1152/japplphysiol.01431.2009. PubMed PMID: 20431020; PubMed Central PMCID: PMCPMC3774425.

30. Fraser JA, Peacher DF, Freiberger JJ, et al. Risk factors for immersion pulmonary edema: hyperoxia does not attenuate pulmonary hypertension associated with cold water-immersed prone exercise at 4.7 ATA. J Appl Physiol (1985). 2011; 110(3): 610-618. doi: 10.1152/japplphysiol.01088.2010. PubMed PMID: 21148341.

31. Liu Z, Vargas F, Stansbury D, Sasse SA, Light RW. Comparison of the end-tidal arterial PCO2 gradient during exercise in normal subjects and in patients with severe COPD. Chest. 1995; 107(5): 1218-1224. PubMed PMID: 7750309.

32. Losa-Reyna J, Torres-Peralta R, Henriquez JJ, Calbet JA. Arterial to end-tidal Pco2 difference during exercise in normoxia and severe acute hypoxia: importance of blood temperature correction. Physiol Rep. 2015; 3(10). doi: 10.14814/phy2.12512. PubMed PMID: 26508736; PubMed Central PMCID: PMCPMC4632943.

33. Gonzalez Henriquez JJ, Losa-Reyna J, Torres-Peralta R, Radegran G, Koskolou M, Calbet JA. A new equation to estimate temperature-corrected P_aCO_2 from $P_{ET}CO_2$ during exercise in normoxia and hypoxia. Scand J Med Sci Sports. 2015. doi: 10.1111/sms.12545. PubMed PMID: 26314285.

34. Mummery HJ, Stolp BW, de LDG, et al. Effects of age and exercise on physiological dead space during simulated dives at 2.8 ATA. J Appl Physiol (1985). 2003; 94(2): 507-517. doi: 10.1152/japplphysiol.00367.2002. PubMed PMID: 12391136.

35. Hlastala MP, Berger AJ. Physiology of respiration. 2nd ed. Oxford; New York: Oxford University Press; 2001. ix, 275.

36. Salzano JV, Camporesi EM, Stolp BW, Moon RE. Physiological responses to exercise at 47 and 66 ATA. J Appl Physiol Respir Environ Exerc Physiol. 1984; 57(4): 1055-1068. PubMed PMID: 6438026.

37. Carylyle RF, Nichols G, Paciorek JA, Rowles PM, Spencer N. Changes in morphology and carbonic anhydrase content of red blood cells from men subjected to simulated dives [proceedings]. J Physiol. 1979; 292: 34P-5P. PubMed PMID: 114625.

38. Linnarsson D, Ostlund A, Lind F, Hesser CM. Hyperbaric bradycardia and hypoventilation in exercising men: effects of ambient pressure and breathing gas. J Appl Physiol (1985). 1999; 87(4): 1428-1432. PubMed PMID: 10517774.

39. Cherniack NS. What causes hypercapnia? Won't breathe, can't breathe or something in between? Respiration. 2008; 75(3): 251-252. doi: 10.1159/000114654. PubMed PMID: 18367850.

40. Poon CS, Tin C, Song G. Submissive hypercapnia: Why COPD patients are more prone to CO2 retention than heart failure patients. Respir Physiol Neurobiol. 2015; 216: 86-93. doi: 10.1016/j.resp.2015.03.001. PubMed PMID: 25891787; PubMed Central PMCID: PMCPMC4568120.

41. Pendergast DR, Moon RE, Krasney JJ, Held HE, Zamparo P. Human Physiology in an Aquatic Environment. Compr Physiol. 2015; 5(4): 1705-1750. doi: 10.1002/cphy.c140018. PubMed PMID: 26426465.

42. Dahlback GO, Jonsson E, Liner MH. Influence of hydrostatic compression of the chest and intrathoracic blood pooling on static lung mechanics during head-out immersion. Undersea Biomed Res. 1978; 5(1): 71-85. PubMed PMID: 636076.

43. Lundgren CE. Respiratory function during simulated wet dives. Undersea Biomed Res. 1984; 11(2): 139-147. PubMed PMID: 6485143.

44. Otis AB, Fenn WO, Rahn H. Mechanics of breathing in man. J Appl Physiol. 1950;2(11):592-607. PubMed PMID: 15436363.

45. Moon RE, Cherry AD, Stolp BW, Camporesi EM. Pulmonary gas exchange in diving. J Appl Physiol (1985). 2009; 106(2): 668-677. doi: 10.1152/japplphysiol.91104.2008. PubMed PMID: 19008484.

46. Hong SK, Cerretelli P, Cruz JC, Rahn H. Mechanics of respiration during submersion in water. J Appl Physiol. 1969; 27(4): 535-538. PubMed PMID: 5822562.

47. Agostoni E, Gurtner G, Torri G, Rahn H. Respiratory mechanics during submersion and negative-pressure breathing. J Appl Physiol. 1966; 21(1): 251-258. PubMed PMID: 5903920.

48. McCully KK, Faulkner JA. Length-tension relationship of mammalian diaphragm muscles. J Appl Physiol Respir Environ Exerc Physiol. 1983; 54(6): 1681-1686. PubMed PMID: 6874493.

49. Braun NM, Arora NS, Rochester DF. Force-length relationship of the normal human diaphragm. J Appl Physiol Respir Environ Exerc Physiol. 1982; 53(2): 405-412. PubMed PMID: 7118662.

50. Thalmann ED, Sponholtz DK, Lundgren CE. Effects of immersion and static lung loading on submerged exercise at depth. Undersea Biomed Res. 1979; 6(3): 259-290.

51. Maio DA, Farhi LE. Effect of gas density on mechanics of breathing. J Appl Physiol. 1967;23(5):687-93. PubMed PMID: 6061383.

52. Vorosmarti J, Bradley ME, Anthonisen NR. The effects of increased gas density on pulmonary mechanics. Undersea Biomed Res. 1975; 2(1):1-10. PubMed PMID: 1181702.

53. Spaur WH, Raymond LW, Knott MM, et al. Dyspnea in divers at 49.5 ATA - mechanical, not chemical in origin. Undersea Biomed Res. 1977; 4(2): 183-198. PubMed PMID: WOS:A1977DT77000008.

54. Wright WB, Crothers JC. Effects of immersion and high pressures on pulmonary mechanical functions in man. Aerospace Medical Association 1973 Annual Scientific Meeting; May 1973; Las Vegas, Nevada: Aerospace Medical Association; 1973.

55. Wood WB, Leve LH. Ventilatory dynamics under hyperbaric states. Arch Environ Health. 1963; 7: 47-59. PubMed PMID: 14047562.

56. Wood LD, Bryan AC. Effect of increased ambient pressure on flow-volume curve of the lung. J Appl Physiol. 1969; 27(1): 4-8. PubMed PMID: 5786969.

57. Demedts M, Anthonisen NR. Effects of increased external airway resistance during steady-state exercise. J Appl Physiol. 1973; 35(3): 361-366. PubMed PMID: 4732328.

58. Warkander DE, Norfleet WT, Nagasawa GK, Lundgren CE. Physiologically and subjectively acceptable breathing resistance in divers' breathing gear. Undersea Biomed Res. 1992; 19(6): 427-445. PubMed PMID: 1304670.

59. Mead J. Measurement of inertia of the lungs at increased ambient pressure. J Appl Physiol. 1956; 9(2): 208-212. PubMed PMID: 13376430.

60. Fothergill DM, Joye DD, Carlson NA. Diver respiratory responses to a tunable closed-circuit breathing apparatus. Undersea Hyperb Med. 1997; 24(2): 91-105. PubMed PMID: 9171468.

61. Hickey DD, Norfleet WT, Pasche AJ, Lundgren CE. Respiratory function in the upright, working diver at 6.8 ATA (190 fsw). Undersea Biomed Res. 1987; 14(3): 241-262. PubMed PMID: 3629740.

62. Jarrett AS. Alveolar carbon dioxide tension at increased ambient pressures. J Appl Physiol. 1966; 21(1): 158-162. PubMed PMID: 5903903.

63. Kerem D, Daskalovic YI, Arieli R, Shupak A. CO_2 retention during hyperbaric exercise while breathing 40/60 nitrox. Undersea Hyperb Med. 1995; 22(4): 339-346. PubMed PMID: 8574121.

64. Anthonisen NR, Utz G, Kryger MH, Urbanetti JS. Exercise tolerance at 4 and 6 ATA. Undersea Biomed Res. 1976; 3(2): 95-112. PubMed PMID: 951829.

65. Cain CC, Otis AB. Some physiological effects resulting from added resistance to respiration. J Aviat Med. 1949; 20(3): 149-160. PubMed PMID: 18150937.

66. Poon CS. Effects of inspiratory elastic load on respiratory control in hypercapnia and exercise. J Appl Physiol (1985). 1989; 66(5): 2400-2406. PubMed PMID: 2501282.

67. Froeb HF. Ventilatory response of SCUBA divers to CO_2 inhalations. J Appl Physiol. 1961; 16: 8-10. PubMed PMID: 13702178.

68. Pendergast DR, Lindholm P, Wylegala J, Warkander D, Lundgren CE. Effects of respiratory muscle training on respiratory CO_2 sensitivity in SCUBA divers. Undersea Hyperb Med. 2006; 33(6): 447-453. PubMed PMID: 17274314.

69. Lambertsen CJ, Owen SG, Wendel H, et al. Respiratory and cerebral circulatory control during exercise at .21 and 2.0 atmospheres inspired p02. J Appl Physiol. 1959; 14: 966-982. PubMed PMID: 14413614.

70. Campbell EJ. Respiratory failure: the relation between oxygen concentrations of inspired air and arterial blood. Lancet. 1960; 2(7140): 10-11. PubMed PMID: 13807248.

71. Rialp G, Raurich JM, Llompart-Pou JA, Ayestaran I. Role of respiratory drive in hyperoxia-induced hypercapnia in ready-to-wean subjects with COPD. Respir Care. 2015; 60(3): 328-334. doi: 10.4187/respcare.03270. PubMed PMID: 25492961.

72. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1980; 122(2): 191-199. PubMed PMID: 6774639.

73. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis. 1980; 122(5): 747-754. PubMed PMID: 6778278.

74. Kraan J, Rispens P. Contribution of the Haldane effect to the increase in arterial carbon dioxide tension in hypoxaemic subjects treated with oxygen. Adv Exp Med Biol. 1985; 191: 543-551. PubMed PMID: 3938604.

75. Sassoon CS, Hassell KT, Mahutte CK. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. Am Rev Respir Dis. 1987; 135(4): 907-911. PubMed PMID: 3565937.

76. Gelfand R, Lambertsen CJ. Dynamic respiratory response to abrupt change of inspired CO_2 at normal and high PO_2. J Appl Physiol. 1973; 35(6): 903-913. PubMed PMID: 4765831.

77. Dahan A, Degoede J, Berkenbosch AAD, Olievier ICW. The influence of oxygen on the ventilatory response to carbon dioxide in man. J Physiol-London. 1990;428:485-99. PubMed PMID: WOS:A1990DY38300027.

78. Miyamura M, Folgering HT, Binkhorst RA, Smolders FDJ, Kreuzer F. Ventilatory response to CO_2 at rest and during positive and negative work in normoxia and hyperoxia. Pflug Arch Eur J Phy. 1976; 364(1): 7-15. doi: Doi 10.1007/Bf01062905. PubMed PMID: WOS:A1976BX15800002.

79. Loeschcke HH, Mitchell RA, Katsaros B, Perkins JF, Konig A. Interaction of intracranial chemosensitivity with peripheral afferents to the respiratory centers. Ann N Y Acad Sci. 1963; 109: 651-660. PubMed PMID: 13931281.

80. Blain GM, Smith CA, Henderson KS, Dempsey JA. Peripheral chemoreceptors determine the respiratory sensitivity of central chemoreceptors to CO(2). J Physiol. 2010; 588(Pt 13): 2455-2471. doi: 10.1113/jphysiol.2010.187211. PubMed PMID: 20421288; PubMed Central PMCID: PMCPMC2915520.

81. Guyenet PG, Bayliss DA, Mulkey DK, Stornetta RL, Moreira TS, Takakura AT. The retrotrapezoid nucleus and central chemoreception. Adv Exp Med Biol. 2008; 605: 327-332. doi: 10.1007/978-0-387-73693-8_57. PubMed PMID: 18085294.

82. Pedersen ME, Fatemian M, Robbins PA. Identification of fast and slow ventilatory responses to carbon dioxide under hypoxic and hyperoxic conditions in humans. J Physiol. 1999;521 Pt 1:273-87. PubMed PMID: 10562351; PubMed Central PMCID: PMCPMC2269657.

83. Gardner WN. The pattern of breathing following step changes of alveolar partial pressures of carbon dioxide and oxygen in man. J Physiol. 1980; 300: 55-73. PubMed PMID: 6770086; PubMed Central PMCID: PMCPMC1279344.

84. Miller JP, Cunningham DJ, Lloyd BB, Young JM. The transient respiratory effects in man of sudden changes in alveolar CO_2 in hypoxia and in high oxygen. Respir Physiol. 1974; 20(1): 17-31. PubMed PMID: 4821653.

85. Gelfand R, Lambertsen CJ, Peterson RE. Human respiratory control at high ambient pressures and inspired gas densities. J Appl Physiol Respir Environ Exerc Physiol. 1980; 48(3): 528-539. PubMed PMID: 6768702.

86. Otis AB, McKerrow CB, Bartlett RA, et al. Mechanical factors in distribution of pulmonary ventilation. J Appl Physiol. 1956; 8(4): 427-443. PubMed PMID: 13286206.

87. Forkert L, Wood LD, Cherniack RM. Effect of gas density on dynamic pulmonary compliance. J Appl Physiol. 1975; 39(6): 906-910. PubMed PMID: 1213970.

88. Daly WJ, Bondurant S. Direct measurement of respiratory pleural pressure changes in normal man. J Appl Physiol. 1963; 18(3): 513-518. PubMed PMID: WOS:A19633718B00008.

89. Arieli R. Cyclic perfusion of the lung by dense gas breathing may reduce the (A-a)DO2. J Basic Clin Physiol Pharmacol. 1992; 3(3): 207-221. PubMed PMID: 1298340.

90. Arieli R, Farhi LE. Gas exchange in tidally ventilated and non-steadily perfused lung model. Respir Physiol. 1985; 60(3): 295-309. PubMed PMID: 4035107.

91. Saltzman HA, Salzano JV, Blenkarn GD, Kylstra JA. Effects of pressure on ventilation and gas exchange in man. J Appl Physiol. 1971; 30(4): 443-449. PubMed PMID: 5572758.

92. Verbanck S, Paiva M. Could lobar flow sequencing account for convection-dependent ventilation heterogeneity in normal humans? J Appl Physiol. 2016; 121(2): 589-591. doi: 10.1152/japplphysiol.01049.2015. PubMed PMID: 27013609.

93. McMahon TJ, Moon RE, Luschinger BP, et al. Nitric oxide in the human respiratory cycle. Nat Med. 2002; 8(7): 711-717. doi: 10.1038/nm718. PubMed PMID: 12042776.

94. Luft UC, Mostyn EM, Loeppky JA, Venters MD. Contribution of the Haldane effect to the rise of arterial Pco2 in hypoxic patients breathing oxygen. Crit Care Med. 1981; 9(1): 32-37. PubMed PMID: 6780265.

95. Forkner IF, Piantadosi CA, Scafetta N, Moon RE. Hyperoxia-induced tissue hypoxia: a danger? Anesthesiology. 2007; 106(5): 1051-1055. doi: 10.1097/01.anes.0000265167.14383.44. PubMed PMID: 17457139.

96. Sapoval B, Filoche M, Weibel ER. Smaller is better-but not too small: A physical scale for the design of the mammalian pulmonary acinus. P Natl Acad Sci USA. 2002; 99(16): 10411-10416. doi: 10.1073/pnas.122352499. PubMed PMID: WOS:000177343200037.

97. Weibel ER, Sapoval B, Filoche M. Design of peripheral airways for efficient gas exchange. Resp Physiol Neurobi. 2005; 148(1-2): 3-21. doi: 10.1016/j.resp.2005.03.005. PubMed PMID: WOS:000231710100002.

98. Kylstra JA, Paganelli CV, Lanphier EH. Pulmonary gas exchange in dogs ventilated with hyperbarically oxygenated liquid. J Appl Physiol. 1966; 21(1): 177-184. PubMed PMID: 5904532.

99. Case EM, Haldane JB. Human physiology under high pressure: I. effects of nitrogen, carbon dioxide, and cold. J Hyg (Lond). 1941; 41(3): 225-249. PubMed PMID: 20475589; PubMed Central PMCID: PMCPMC2199778.

100. Jerusalem E, Starling EH. On the significance of carbon dioxide for the heart beat. J Physiol. 1910; 40(4): 279-294. PubMed PMID: 16993008; PubMed Central PMCID: PMCPMC1533681.

101. Price HL. Effects of carbon dioxide on the cardiovascular system. Anesthesiology. 1960; 21: 652-663. PubMed PMID: 13737968.

102. Sechzer PH, Egbert LD, Linde HW, Cooper DY, Dripps RD, Price HL. Effect of carbon dioxide inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. J Appl Physiol. 1960; 15: 454-458. PubMed PMID: 14444401.

103. Vatner SF, Rutherford JD. Control of the myocardial contractile state by carotid chemo- and baroreceptor and pulmonary inflation reflexes in conscious dogs. J Clin Invest. 1978; 61(6): 1593-1601. doi: 10.1172/JCI109079. PubMed PMID: 659617; PubMed Central PMCID: PMCPMC372685.

104. Foex P, Ryder WA, Bennett MJ. Carbon dioxide and coronary blood flow: direct effects or consequences of altered dynamics of the systemic circulation. Bull Eur Physiopathol Respir. 1980; 16(2): 185-194.

105. Kazmaier S, Weyland A, Buhre W, et al. Effects of respiratory alkalosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. Anesthesiology. 1998; 89(4): 831-837. PubMed PMID: 9777999.

106. Markwalder J, Starling EH. A note on some factors which determine the blood-flow through the coronary circulation. J Physiol-London. 1913; 47(4/5): 275-85. PubMed PMID: WOS:000201345000001.

107. Case RB, Greenberg H. The response of canine coronary vascular resistance to local alterations in coronary arterial P CO2. Circ Res. 1976; 39(4): 558-566. PubMed PMID: 963840.

108. Feinberg H, Gerola A, Katz LN. Effect of changes in blood CO2 level on coronary flow and myocardial O2 consumption. Am J Physiol. 1960; 199: 349-354. PubMed PMID: 13698638.

109. Gurevicius J, Salem MR, Metwally AA, Silver JM, Crystal GJ. Contribution of nitric oxide to coronary vasodilation during hypercapnic acidosis. Am J Physiol. 1995; 268(1 Pt 2): H39-47. PubMed PMID: 7530920.

110. Powers ER, Bannerman KS, Fitz-James I, Cannon PJ. Effect of elevations of coronary artery partial pressure of carbon dioxide (PCO2) on coronary blood flow. J Am Coll Cardiol. 1986; 8(5): 1175-1181. PubMed PMID: 3093553.

111. Kitakaze M, Takashima S, Funaya H, et al. Temporary acidosis during reperfusion limits myocardial infarct size in dogs. Am J Physiol. 1997; 272 (5 Pt 2): H2071-2078. PubMed PMID: 9176271.

112. Nomura F, Aoki M, Forbess JM, Mayer JE, Jr. Effects of hypercarbic acidotic reperfusion on recovery of myocardial function after cardioplegic ischemia in neonatal lambs. Circulation. 1994; 90(5 Pt 2): II321-327. PubMed PMID: 7955274.

113. Reivich M. Arterial PCO2 and cerebral hemodynamics. Am J Physiol. 1964; 206: 25-35. PubMed PMID: 14117646.

114. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest. 1948; 27(4): 484-492. doi: 10.1172/JCI101995. PubMed PMID: 16695569; PubMed Central PMCID: PMCPMC439519.

115. Kane MJ, Conway AR, Miura TK, Colflesh GJ. Working memory, attention control, and the N-back task: a question of construct validity. J Exp Psychol Learn Mem Cogn. 2007; 33(3): 615-622. doi: 10.1037/0278-7393.33.3.615. PubMed PMID: 17470009.

116. Lanphier E. Nitrogen-oxygen mixture physiology. Phase 4: Carbon dioxide sensitivity as a potential means of personnel selection. Phase 6: Carbon dioxide regulation under diving conditions. Washington, DC: Navy Experimental Diving Unit, 1958; 7-58.

117. Morrison JB, Florio JT, Butt WS. Effects of CO2 insensitivity and respiratory pattern on respiration in divers. Undersea Biomed Res. 1981; 8(4): 209-217. PubMed PMID: 6798730.

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