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## HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

### Pulmonary gas exchange in diving

R. E. Moon,<sup>1</sup> A. D. Cherry,<sup>1</sup> B. W. Stolp,<sup>1</sup> and E. M. Camporesi<sup>2</sup>

<sup>1</sup>Department of Anesthesiology, Department of Medicine, and Center for Hyperbaric Medicine and Environmental Physiology, Duke University Medical Center, Durham, North Carolina; and <sup>2</sup>Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, Florida

**Moon RE, Cherry AD, Stolp BW, Camporesi EM.** Pulmonary gas exchange in diving. *J Appl Physiol* 106: 668–677, 2009. First published November 13, 2008; doi:10.1152/jappphysiol.91104.2008.—Diving-related pulmonary effects are due mostly to increased gas density, immersion-related increase in pulmonary blood volume, and (usually) a higher inspired  $PO_2$ . Higher gas density produces an increase in airways resistance and work of breathing, and a reduced maximum breathing capacity. An additional mechanical load is due to immersion, which can impose a static transrespiratory pressure load as well as a decrease in pulmonary compliance. The combination of resistive and elastic loads is largely responsible for the reduction in ventilation during underwater exercise. Additionally, there is a density-related increase in dead space/tidal volume ratio ( $V_D/V_T$ ), possibly due to impairment of intrapulmonary gas phase diffusion and distribution of ventilation. The net result of relative hypoventilation and increased  $V_D/V_T$  is hypercapnia. The effect of high inspired  $PO_2$  and inert gas narcosis on respiratory drive appear to be minimal. Exchange of oxygen by the lung is not impaired, at least up to a gas density of 25 g/l. There are few effects of pressure per se, other than a reduction in the P50 of hemoglobin, probably due to either a conformational change or an effect of inert gas binding.

respiratory dead space; ventilation-perfusion ratio; respiratory mechanics

DESPITE HAVING EVOLVED in and adapted to an atmosphere with gas density close to 1 g/l, the performance of the human lung in the diving environment is remarkable. Adequate ventilation and gas exchange have been achieved at an ambient pressure up to 71 atmospheres absolute (ATA) [701 m of sea water (msw); 2,310 ft of sea water (fsw)] with an ambient  $PO_2$  of 0.39 ATA (49), and with a  $PO_2$  of 0.2 ATA up to a gas density of 25 g/l (50). Adequate exchange of oxygen and carbon dioxide while diving requires the ability to maintain ventilation in the face of significantly increased resistive and elastic loads. Resistance is increased primarily by the increase in breathing gas density. Elastic load is enhanced primarily by changes in transrespiratory pressure ( $P_{TR}$ ). Inertial mechanical load is also increased, although this has a minimal effect on the diver. Added challenges include blunted respiratory drive due to elevated partial pressures of inert gas and oxygen, and possibly impaired diffusion within the alveolus (7). While in most dives the breathing gas is hyperoxic, thus precluding hypoxemia, hypercapnia is common. Hyperoxia, particularly in the venous blood, can induce a small reduction in  $CO_2$  solubility, and hence an increase in venous  $PCO_2$  via the Haldane effect (27, 122). Arterial  $PCO_2$  ( $Pa_{CO_2}$ ) is not affected by the Haldane

effect because of regulation of breathing via the chemoreceptors, although hypercapnia does occur for other reasons as discussed below.

Studies of pulmonary gas exchange under hyperbaric conditions designed to simulate diving have been performed since the 1950s. Measurements have included ventilation, oxygen consumption, carbon dioxide elimination, and both end-tidal and arterial gas tensions (51, 53). Ensuing experiments demonstrated hypercapnia at rest (91), but to a greater extent during exercise (11, 25, 40–42, 52, 74, 89–91, 107, 118). The increase in  $Pa_{CO_2}$  is due to two phenomena: 1) relative hypoventilation (6, 37, 40, 50, 55, 74, 91, 103, 104, 107, 126), and 2) elevated dead space, as discussed below.

A recently described phenomenon is a change in breathing pattern in endurance underwater swimming [oxygen uptake ( $\dot{V}O_2$ ) of 1.5–2 l/min, depth of 4 ft]. Fifteen minutes after the start of constant exercise an abrupt 20–25% increase in ventilation has been observed (130). When the study was repeated at a depth of 55 ft (2.7 ATA) breathing air ( $PO_2$  0.56 ATA), there was a similar increase, although it occurred more gradually (85). The investigators interpreted these data as consistent with respiratory compensation for metabolic acidosis, and possibly respiratory muscle fatigue. The effects of this on blood gases, pH, pulmonary hemodynamics, and gas exchange are unknown.

Address for reprint requests and other correspondence: R. E. Moon, Dept. of Anesthesiology, Dept. of Medicine, and Center for Hyperbaric Medicine & Environmental Physiology, Duke Univ. Medical Center, Durham, NC 27710 (e-mail: richard.moon@duke.edu).

## RESPIRATORY MECHANICS

Traditional measures of respiratory load include resistive, elastic, and inertial components. Diving induces an increase in all three components. The primary effect of diving on resistance is mediated by the proportional increase in breathing gas density with the depth of immersion. This occurs because breathing underwater can only occur if breathing gas is delivered to the diver at a pressure within a few cmH<sub>2</sub>O of the ambient pressure at the diver's depth. For turbulent gas flow, which is present throughout most of the conducting airways, flow resistance is proportional to density. During diving the external breathing apparatus adds an additional resistive load. Additionally, there is an increase of the total inertia of the respiratory system due to increased mass of the breathing gas.

**Internal resistance.** Although gas viscosity is unchanged at increased pressure (at least within the pressure range to which humans have been exposed), gas density is increased in direct proportion to ambient pressure. Breathing gas density has a major effect on airways resistance. This can be readily measured by a reduction in forced expiratory volume in 1 s (FEV<sub>1</sub>), peak expiratory flow, and maximum voluntary ventilation (MVV) (50, 65, 99, 114). The increase in airways resistance purely due to turbulent flow can be augmented further by expiratory flow limitation due to airway collapse (126). Peak expiratory flow or MVV at any gas density ( $\rho$ ) can be approximated by the following formula (125, 128):

$$A = A_0(\rho/\rho_0)^{-k} \quad (1)$$

where  $A$  is either MVV or peak expiratory flow at a gas density  $\rho$ ;  $A_0$  is MVV (or peak expiratory flow) at 1 ATA;  $\rho_0$  is gas density at 1 ATA;  $\rho$  is the gas density; and  $k$  is a constant with the value 0.4–0.5. A similar equation has been verified for the relationship between airway conductance and gas density (4).

**External resistance.** In addition to internal respiratory resistance, some amount of external resistance is present in all

underwater breathing apparatus. Resistance varies with different apparatus, and resistance levels frequently differ between the inspired and expired breathing circuits. High breathing resistance increases subjective dyspnea scores (91, 117) and raises P<sub>CO<sub>2</sub></sub> levels in subjects performing various levels of exercise at the surface (102, 132) and at a range of depths (117–119).

**Compliance.** During water immersion there is a redistribution of 500–800 ml of blood from the legs into the large veins and pulmonary vessels. There is also a negative transthoracic pressure when the diver is in the head-up position (e.g., during head-out immersion), due to the pressure difference between the mouth and the centroid of the lung (see Fig. 1). As a consequence of this pressure difference, there is a reduction in lung volume and its subsets, for example residual volume, vital capacity, and expiratory reserve volume (ERV) (2). This occurs to a greater extent in cold water than in warm, presumably due to active peripheral vasoconstriction and hence greater volume of blood redistributed from the periphery into the pulmonary vessels (46).

Although chest wall compliance does not change significantly, most investigators have reported a concomitant reduction in lung compliance, particularly at low lung volumes, possibly due to the vascular engorgement (16). Others have attributed the compliance change and attendant increase in elastic work solely to the difference in hydrostatic pressure between the lung and the mouth, which is neutralized by supplying breathing gas at a pressure close to lung centroid pressure (105, 106).

ERV during exercise in a dry hyperbaric chamber at depth tends to be increased as subjects breathe at higher lung volumes (37, 98, 117). Similarly, the reduction in ERV during immersion tends to be attenuated at increasing depth as subjects breathe at higher lung volumes, probably in an attempt to increase airway diameter, thus reducing the increase in airways

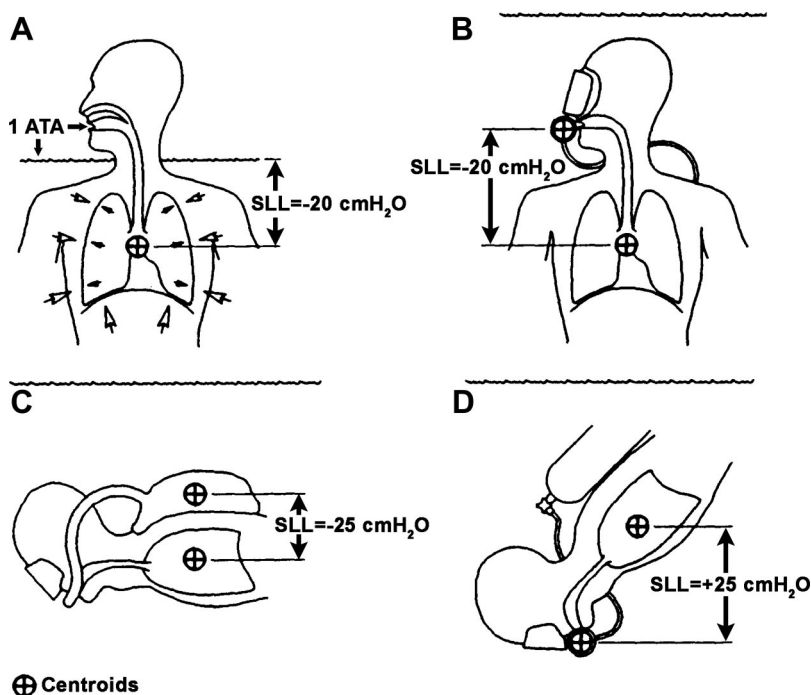


Fig. 1. Transrespiratory pressure ( $P_{TR}$ ) [static lung load (SLL)]. A: a person immersed to the neck (negative  $P_{TR}$ ). 1 ATA, 1 atm absolute. B and D: an open-circuit diver for whom the breathing regulator delivers gas at the hydrostatic pressure of the mouth. C: a closed-circuit rebreather diver, for whom the reservoir (counterlung) is at a lower hydrostatic pressure than the lung centroid (negative  $P_{TR}$ ). In the head-up position  $P_{TR}$  is negative; in the head-down position  $P_{TR}$  is positive, analogous to the clinical application, continuous positive airway pressure (CPAP). [Reproduced from Lundgren (60) with permission. Copyright Informa Healthcare Books.]

resistance (37, 98, 106, 117). The increase in ERV has the effect of increasing internal respiratory load by raising the elastic lung load (14), which allows more passive expiration but results in a requirement for higher negative inspiratory pressures (76). The increased elastic load induced by immersion augments the gas density-related decrease in MVV (129).

**Transrespiratory pressure (static lung load).** In an immersed diver, a static positive or negative pressure may be exerted across the respiratory system [ $P_{TR}$ , or static lung load (SLL)] due to the difference between the pressure of the gas delivered to the mouth and the external hydrostatic pressure at the centroid of the lung (see Fig. 1). Positive or negative  $P_{TR}$  alters the equilibrium volume, and measurements in humans have revealed increased or decreased ERV, respectively (107). During negative  $P_{TR}$ , ERV is not determined simply by the relaxation volume of the thorax but is defended to some degree with active inspiratory muscle activity, thus causing additional inspiratory muscle work (106).  $P_{TR}$  is a major determinant of exercise performance in divers. Positive  $P_{TR}$  during immersed heavy exercise is associated with a reduction in dyspnea. Conversely, negative  $P_{TR}$  is poorly tolerated by divers, as it seems to increase dyspnea (107). One possible mechanism for the ameliorative effect of positive  $P_{TR}$  on dyspnea is the benefit of an increased lung volume (decreased airways resistance), which is offset by an increase in elastic work of breathing.  $P_{TR}$  could exert its beneficial effect by reducing the inspiratory elastic work necessary to maintain lung volume at a level that would minimize airways resistance.

**Inertance.** Inertance of the respiratory system and the breathing system is the property related to the mass of the chest wall and the gas flowing within the airways and breathing apparatus. There is also a small component due to the mass of the water surrounding the chest. Respiratory system inertance at 1 ATA, typically  $0.01 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^2$ , increases in direct proportion to gas density (67, 81). Inertial impedance tends to offset elastic impedance. In a cyclic breathing pattern inertial impedance is less than elastic impedance at frequencies less than resonant frequency of the system, which at 1 ATA is typically 6 Hz; inertial impedance exceeds elastic impedance at frequencies greater than the resonant frequency. If breathing gas density increases 10-fold, the resonant frequency decreases to  $\sim 2$  Hz. Thus, given the normally slower breathing frequency exhibited by exercising divers (36, 74, 91), inertial impedance has only a limited role in determining respiratory effort. In an exercising diver breathing a gas with density 10 g/l, assuming a peak acceleration of  $30 \text{ l/s}^2$ , the transrespiratory pressure due to inertance would be  $\sim 3 \text{ cmH}_2\text{O}$ . On the other hand, if the inertance of a breathing circuit is deliberately increased such that the resonant frequency is reduced to within the normal breathing range, elastic work and inertial work can offset each other and reduce peak-to-peak (inspiratory-to-expiratory) pressure. Using a tunable closed-circuit breathing apparatus, Fothergill et al. (28) demonstrated that divers took advantage of this by adjusting their respiratory rate to equal the resonant frequency of the system.

On the other hand, during experimental measurements of ventilation using traditional open-circuit techniques in dense gas environments, gas inertance can produce artifacts. At high flow rate the gas can continue to flow from the inspired source through the valve system to the expired collection bag following end expiration and end inspiration (39). Such "blowby"

will result in an artifactual increase in measured ventilation. This can be a problem particularly at high ventilation rates.

#### GAS MIXING AND DIFFUSION

The process by which inspired gas mixes with gas resident in the alveoli at end expiration is determined by several processes (23). Convective mixing occurs in large conducting airways in which there is turbulent flow. Taylor dispersion occurs during laminar flow in small tubes where there is a parabolic distribution of flow, with the flow rate at the center of the tube being greater than at the periphery. This velocity gradient generates a radial concentration gradient; radial diffusion along such a gradient facilitates mixing between inspired and resident gases. Diffusion occurs in distal gas exchange units. Mixing is further augmented by cardiogenic oscillations (97).

An increase in density of the breathing gas could affect all of the factors listed above. An increase in density should expand the distribution of turbulent flow to more distal airways, thus enhancing convective mixing and improving the efficiency of gas exchange. High gas density has been predicted to enhance cardiogenic mixing (97). On the other hand a high gas density would diminish the effect of Taylor dispersion (and worsen gas exchange) by concomitantly reducing the number of airways with laminar flow. Increased density reduces gas phase diffusivity (113).

Diffusion depends not only on diffusivity, but also on concentration gradients, time for diffusion, and the shape of the space in which the gas is contained (112). A relevant principle is acinar diffusional screening. This refers to oxygen diffusion along the acinar airway, where it is absorbed preferentially by the more proximal alveolar surfaces along the path. Oxygen molecules may not reach the more distal alveoli, which are therefore functionally "screened" (92). In effect this process reduces the available gas exchange area for diffusion of oxygen and carbon dioxide. The screening effect would be more evident at high gas density (120) and would furthermore affect carbon dioxide to a greater degree than oxygen (92).

An observation that appeared to demonstrate gas phase diffusion impairment was the behavior of goats inside a hyperbaric chamber in a helium-oxygen atmosphere at 39.7 ATA. After increasing the pressure to 49.8 ATA by adding helium (density increase from 7.44 to 10.74 g/l), the animals displayed behavioral disturbances and progressive paralysis (9). This quickly resolved when the ambient  $\text{Po}_2$  was raised from 154 to 191 mmHg. This observation, which was attributed to diffusion-related hypoxia, provided a major rationale for maintaining a high  $\text{Po}_2$  in operational and experimental deep-dive exposures. Since then, studies in humans have refuted this hypothesis by demonstrating adequate blood oxygenation at even higher densities (50, 91).

Ventilation with the highest conceivable fluid density was achieved in experiments performed by Kylstra and colleagues, who examined oxygen and carbon dioxide diffusion by ventilating the lungs with saline. Studies in anesthetized dogs ventilated with hyperoxygenated saline (inspired  $\text{Po}_2$  3,300–3,640 mmHg) revealed that despite evidence for diffusion limitation of both oxygen and carbon dioxide exchange, adequate arterial  $\text{Po}_2$  and  $\text{Pco}_2$  could be achieved (47). These animal experiments were followed up by a study in patients



undergoing therapeutic lung lavage for alveolar proteinosis and a human volunteer, using a double-lumen endotracheal tube. Saline was cycled in and out of one lung while the contralateral lung was ventilated with oxygen (48). In these humans there was no evidence for incomplete diffusive equilibrium between alveoli and capillary blood. However, unlike the dog experiments the respiratory cycle time exceeded 30 s. The prolonged cycle time presumably permitted equilibrium to occur even in the face of extremely low diffusivity.

In summary, the effects of an increase in gas density are predicted to impair gas phase diffusion but augment convective mixing. Despite at least a theoretical understanding of these processes during static or quasi-static flow within conduits of simple geometry or in simple experimental models, with currently available technology it has been challenging to elucidate their respective contributions to pulmonary gas exchange (22, 77).

#### DISTRIBUTIONS OF VENTILATION, BLOOD FLOW, AND VENTILATION-PERFUSION RATIO

The distribution of ventilation is dependent on cyclic changes in externally applied pressure and regional mechanical properties. Despite the wide range in path length from large airways to gas exchange units within the lung, time constants of different lung units are close enough to one another such that under normal circumstances ventilation of different lung regions is acceptably uniform. Differences in time constants among lung regions would increase heterogeneity of ventilation. This could result from higher breathing gas density and increased turbulence in conducting airways, to a differing degree depending on diameter. In airways in which turbulent flow predominates, increased gas density would cause an increase in flow resistance to a degree dependent on the flow characteristics and airway geometry. Time constants would become more disperse and ventilation of different lung units more asynchronous. Breathing a gas of higher density must therefore result in an increased heterogeneity of ventilation. This is supported by the model of Pedley et al. (79) and the observation by Forkert et al. (26) that, compared with air, dynamic compliance is reduced by an increase in breathing gas density using SF<sub>6</sub>-O<sub>2</sub>.

Gas distribution may also depend on other factors. It is usually assumed that pleural pressure swings are uniform over the entire lung; however, there is evidence to the contrary (23). During resting breathing, regional pressure changes are less in the upper than in the lower chest (17). Regional pressure variations may occur due to gravitational effects, the position of the heart relative to the lung, interactions between the lung and the abdominal contents or between the shapes of the lung and the chest wall, or selective contraction of muscles of ventilation (23, 131). An additional mechanism that may produce asynchrony of ventilation is therefore topical variability of distribution of pleural pressure swings within the thorax, which under increased respiratory load in a dense gas environment could become more exaggerated.

Although evidence against regional differences in ventilation is provided by a study using <sup>133</sup>Xe to image topographic ventilation during SF<sub>6</sub>-O<sub>2</sub> breathing, that technique is limited to visualization of differences between large regions; it cannot detect ventilation changes in small compartments within a region.

Unless inequalities of ventilation are matched by regional changes in perfusion then gas exchange would become less efficient. Intriguingly, although little is known about the effects of dense gas breathing on blood flow distribution per se, several investigators have reported that breathing dense gas is associated with a decrease in the alveolar-arterial PO<sub>2</sub> difference (P<sub>A</sub>O<sub>2</sub> - P<sub>a</sub>O<sub>2</sub>) (10, 25, 33, 89, 127) (see Fig. 2). This suggests more efficient matching of ventilation and perfusion. However, under similar conditions dead space/tidal volume ratio (V<sub>D</sub>/V<sub>T</sub>) is increased (66, 74, 89, 91, 127), an effect that appears independent of PO<sub>2</sub> over a range from 0.2 to 3 ATA.

Reduced diffusivity adversely affects gas exchange of both molecules, while enhanced cardiogenic mixing would effect an improvement. Wood et al. (127) have speculated that increased breathing gas density reduces P<sub>A</sub>O<sub>2</sub> - P<sub>a</sub>O<sub>2</sub> because it promotes intraregional convective mixing and hence reduced ventilation/perfusion (V̇<sub>A</sub>/Q̇) dispersion, which affects V<sub>D</sub>/V<sub>T</sub> to a lesser degree than P<sub>A</sub>O<sub>2</sub> - P<sub>a</sub>O<sub>2</sub>. Wood et al. have proposed that the increase in V<sub>D</sub>/V<sub>T</sub> is predominantly due to impaired molecular diffusion of carbon dioxide. Although oxygen diffusion should be similarly affected, they speculated that this is insufficient to offset the convective mixing effect. While there is no straightforward explanation for these two contradictory observations, preliminary observations using the multiple inert gas technique lend support for impaired distribution of ventilation as the cause of the increased dead space (see Fig. 3).

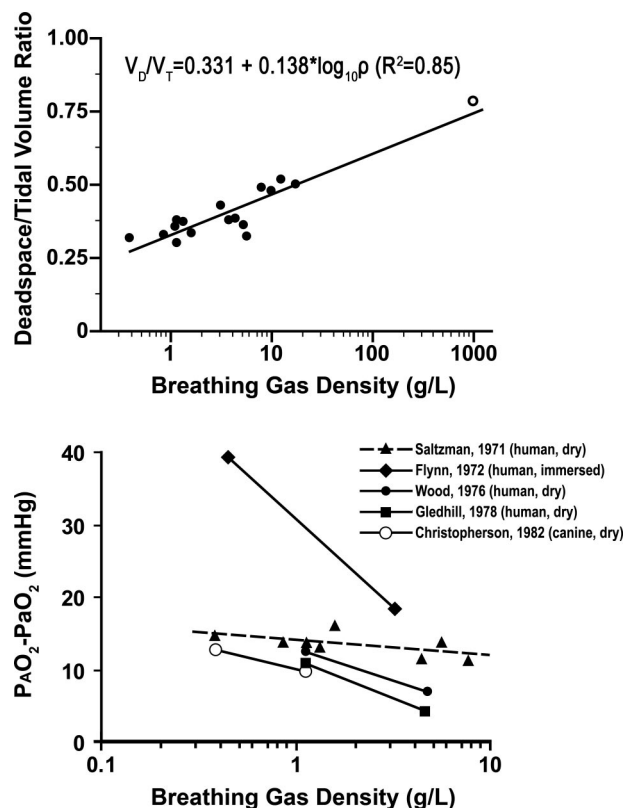


Fig. 2. *Top*: effect of gas density ( $\rho$ ) on dead space. V<sub>D</sub>/V<sub>T</sub>, dead space/tidal volume ratio. Data from Saltzman et al. (89), Wood et al. (127), Salzano et al. (91), McMahon et al. (66), and Mummery et al. (74). ●, Human data; ○ is from a liquid-breathing experiment in dogs (47). *Bottom*: alveolar-arterial PO<sub>2</sub> difference (P<sub>A</sub>O<sub>2</sub> - P<sub>a</sub>O<sub>2</sub>) as a function of breathing gas density. Data from Saltzman et al. (▲; 89), Flynn et al. (◆; 25), Wood et al. (●; 127), Gledhill et al. (■; 33), and Christopherson and Hlastala (○; 10).

*Effects of immersion on ventilation and perfusion.* The engorgement of the pulmonary vessels and reduction in lung volume tend to be associated with several effects that could affect gas exchange. Several investigators have observed an increase in closing volume (CV) (5, 19, 83), consistent with some gas trapping. Also in support of gas trapping is the observation that during immersion residual volume by body plethysmography exceeds that measured by inert gas dilution (87). When CV exceeds ERV in upright immersion, there is an inversion of the normal cephalo-caudad distribution of blood flow, such that blood flow per gas exchange unit is higher at the apex than at the base of the lung (83). However, varied effects have been observed on pulmonary gas exchange. During immersion, one study indicated an increase in  $P_{A_{O_2}} - P_{a_{O_2}}$  (13), while one other observed a transient decrease, and after a few minutes of immersion, a return to baseline (20). In the presence of mild pulmonary pathology, immersion may have an additional effect: loss of an observable phase IV of the single-breath inert gas washout curve, which is traditionally interpreted as signaling the onset of airway closure (54), which, in a group of mild asthmatic subjects, was interpreted by the investigators as evidence of airway closure throughout the entire vital capacity maneuver.

It has been hypothesized that if CV impinges on tidal volume (i.e., CV exceeds ERV),  $P_{a_{O_2}}$  should decrease. This was confirmed by Cohen et al. (13) and Prefaut et al. (84), but not by Derion et al. (20). In the latter study, shunt measured by multiple inert gas elimination was slightly increased in older subjects (ages 40–54 yr) but not in younger subjects (ages

20–29 yr).  $P_{a_{O_2}}$  did not decrease in the older subjects, possibly because of a large increase in  $V_T$ , which could have reduced the fraction of  $V_T$  within CV. However, when the observations from two studies were combined, there was a clear increase in  $P_{A_{O_2}} - P_{a_{O_2}}$  as CV approached  $ERV + V_T$  (see Fig. 4).

*Pulmonary-blood transfer of oxygen.* Altered affinity of hemoglobin for oxygen has been observed at high pressures. Increased hemoglobin-oxygen affinity has been observed in studies in vitro (32, 43, 44, 86) and in a human in vivo study during a saturation dive to 69 ATA (101) (Fig. 5). During the latter study, erythrocyte 2,3-DPG levels were slightly decreased from control (mean  $\pm$  SD, control:  $15.9 \pm 3.5$ ; hyperbaric exposure:  $13.7 \pm 2.6$   $\mu$ mol/g Hb); however, the change was insufficient to explain the decrease in the  $P_{O_2}$  at 50% hemoglobin saturation (P50) (100). These small changes in P50 appear to be due to conformational changes in hemoglobin induced by high pressure and, to a small extent with gases actually breathed by divers, binding by inert gas. It is unlikely that these small changes in hemoglobin P50 have any significant effect on pulmonary gas exchange or exercise capacity (115).

#### VENTILATORY DRIVE

Hypercapnic ventilatory response (HVR) varies among individuals and has been proposed as a predictor of  $P_{CO_2}$  during underwater exercise. In one case study (71), a diver with an extremely low HVR was studied during exercise at 4 atmospheres absolute (ATA) and demonstrated hypoventilation and hypercapnia to an extent far greater than that seen in most normal volunteers. Other studies have indeed shown a correlation between low HVR and hypercapnia in exercise studies at the surface and at depth (52, 70). Overall, however, HVR is a poor predictor of  $P_{CO_2}$  at depth (8, 62). In a study of military divers, only 60% of subjects with hypercapnia at depth also had a low HVR (52).

This poor predictive value may be due to intrasubject HVR variability on different days (88) and in different conditions. It can also be affected by respiratory muscle training, which tends to decrease the HVR of both low and high responders toward the mean (80): muscle training attenuates the HVR of individuals with high values and increases it in low responders. HVR tends to be decreased in scuba divers (24, 71, 93) although not all studies have confirmed this (29). Kerem et al. (42) observed higher end-tidal  $P_{CO_2}$  ( $P_{ETCO_2}$ ) in divers compared with nondivers during exercise at 1 ATA, but there was no difference between the diver and control groups when breathing 40%  $O_2$  and 60%  $N_2$  at 4 ATA (42). Unfortunately, it is difficult to compare surface vs. depth  $P_{CO_2}$  during exercise using end-tidal measurements, since  $P_{ETCO_2}$  overestimates  $P_{a_{CO_2}}$  at the surface (56, 74) but more accurately reflects  $P_{a_{CO_2}}$  under hyperbaric conditions (74).

*Effect of hyperoxia.* Respiratory drive could be affected by a high partial pressure of oxygen, which for a fixed  $O_2$  fraction increases linearly with depth. Hyperoxia therefore occurs in divers even when diving with a breathing gas that is normoxic at the surface. Still higher  $P_{O_2}$  is produced by enriched oxygen breathing gas mixtures that are intentionally used in an effort to reduce inert gas load. Hyperoxia attenuates the ventilatory response to hypercapnia (15, 30, 69, 78) and has been noted to decrease ventilation during exercise (1, 21, 38, 51, 68, 82,

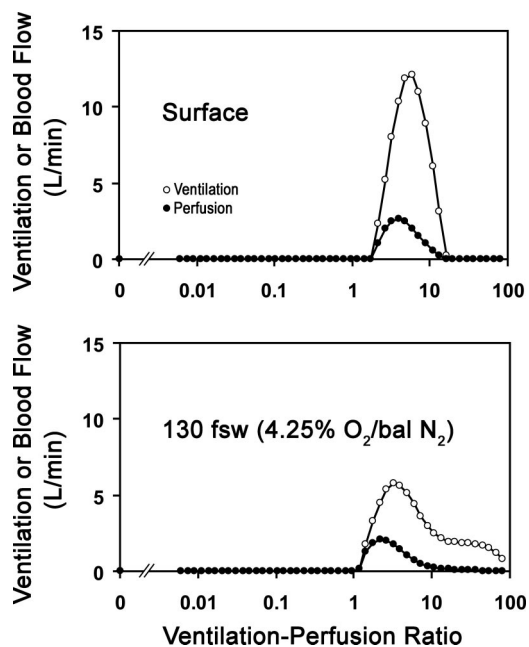


Fig. 3. Ventilation/perfusion distribution using the multiple inert gas (MIG) elimination technique in a human volunteer during upright dry exercise at 1 ATA (top) and a pressure equivalent to 130 feet of sea water (fsw) (4.94 ATA, bottom), breathing 4.25%  $O_2$ /balance (bal)  $N_2$  measured in a dry hyperbaric chamber. Minute ventilations were, respectively, 94 and 62 l/min. Bohr dead space was higher at depth (0.29 vs. 0.21 liter); dead space measured using the MIG technique (116) was 0.15 and 0.03 liter, respectively. The data are consistent with the higher Bohr dead space at pressure being due to increased dispersion of ventilation (log SD of the ventilation distribution 0.55 and 1.12 at 1 and 4.94 ATA, respectively).

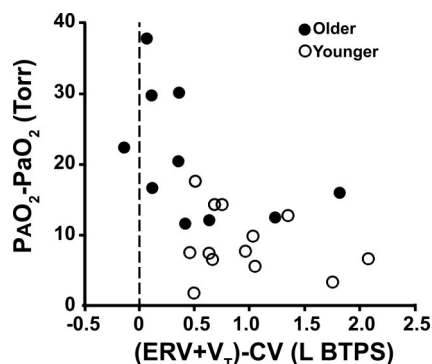


Fig. 4. Effect of closing volume (CV) on oxygen exchange as assessed by alveolar-arterial gradient. ERV, expiratory reserve volume. Data are from Derion et al. (20) and Prefaut et al. (84). [Redrawn from Derion and Guy (19), copyright 1994, with permission from Elsevier.]

124). Mild hypercapnia ( $P_{aCO_2} = 44$  mmHg) has been observed during heavy exercise while breathing 100%  $O_2$  at 2 ATA (11). Few hyperbaric studies exist in which exercise was tested as a function of  $PO_2$  at constant breathing gas density. One such study demonstrated attenuation of the ventilatory response to heavy bicycle exercise in the dry at 2 ATA (103). Arterial blood samples were obtained 7–9 min following completion of 5 min of exercise up to  $1,800$   $Kp \cdot \text{min}^{-1}$ , and demonstrated slightly higher pH and lower base deficits in hyperoxia. Therefore it was not possible to confirm a direct effect of hyperoxia on respiratory drive. Another study failed to find an effect of  $PO_2$  on arterial  $P_{CO_2}$  between 0.7 and 1.3 ATA during immersed prone exercise at 4.7 ATA (8). Factors besides respiratory drive attenuation that may contribute to the reduction in exercise ventilation include peripheral chemoreceptor inhibition and attenuation of the acidemia that occurs during heavy exercise (51).

Paradoxically, in some studies, after a few minutes of hyperoxia at 1 ATA, hyperventilation has been observed (18). A possible explanation has been proposed, based on observations of increased firing rates of solitary complex neurons in brain slices exposed to hyperbaric hyperoxia (73). However, despite increased ventilation and reduced  $P_{ETCO_2}$ ,  $P_{aCO_2}$  in human hyperoxia studies is generally normal (27, 35). The

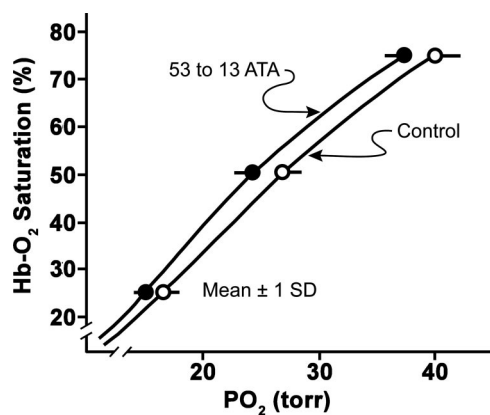


Fig. 5. Hemoglobin-oxygen (Hb- $O_2$ ) dissociation curve measured at pressure during a saturation dive (mean  $\pm$  SD of all measurements in 3 divers over the pressure range indicated). Control curve was obtained at 1 ATA;  $P < 0.05$ . [Redrawn from Stolp et al. (101), copyright 1984, with permission from Undersea and Hyperbaric Medical Society.]

observations in brain slices (73), in which tissue  $PO_2$  is higher than could occur in human divers, may reflect toxic effects of oxygen.

**Effect of narcosis.** It has been suggested that when breathing nitrogen-oxygen mixtures, nitrogen narcosis could also contribute to hypercapnia during diving. While HVR is attenuated at increased ambient pressure, studies using nonnarcotic gases support increased gas density vs. nitrogen narcosis as the mechanism (8, 31, 61).

**Effect of mechanical load and ventilation.** A major contributor to hypoventilation and increased  $P_{aCO_2}$  seen in diving is increased work of breathing as discussed above. Investigators have traditionally argued that in the setting of increased respiratory load, ventilatory effort (and hence the alveolar ventilation) represents a compromise between the drive to maintain normocapnia and the greater work of breathing that would be required to achieve it (63). Several studies have supported a major effect of increased gas density on exercise ventilation. A human study by Linnarsson et al. (55) in a dry hyperbaric chamber measured exercise ventilation while breathing four different gases (air and  $SF_6-O_2$  at 1–1.3 ATA;  $He-O_2$ , and  $N_2-O_2$  at 5.5 ATA). These combinations created two different gas densities (1.1 and 6.0 g/l) at each ambient pressure.  $PO_2$  was 0.2 ATA under all conditions. There was a significant density-related decrease in exercise ventilation (Fig. 6). In explaining the hypoventilation during exercise in divers, this experiment excluded ambient pressure and supported the major role of increased gas density, although a narcosis effect could not be excluded. A recent study demonstrated that external resistive load increased  $P_{aCO_2}$  during prone immersed exercise at 4.7 ATA (8).

During the transition from rest to exercise at the surface, carbon dioxide levels can increase by a small but significant amount in normal subjects (12). It is thought that this effect is due to a low ventilatory response to low levels of exercise. With submersion, this effect is slightly more pronounced (107) and is generally explained by the increased work of breathing during immersion, as discussed above. Submersion causes reduced lung compliance due to a redistribution of blood into

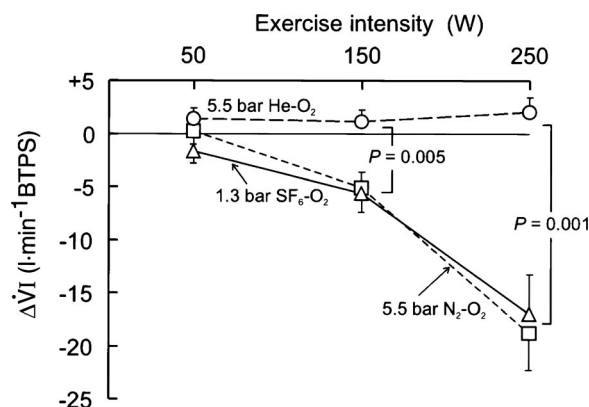


Fig. 6. Differences in exercise ventilation ( $\Delta\dot{V}_i$ ) between 1-bar air (control) and 3 gas + pressure conditions with normal (5.5-bar  $He-O_2$ ) or 5.5 times increased gas density (1.3-bar  $SF_6-O_2$ , 5.5-bar  $N_2-O_2$ ). Values are means  $\pm$  SE. Effect of gas density on ventilatory response to exercise. Air at 1 ATA and heliox at 5.5 have density 1.1 g/l;  $SF_6-O_2$  at 1.3 ATA and  $N_2-O_2$  at 5.5 ATA have density 6 g/l. All gas mixtures were normoxic ( $PO_2 = 0.2$  ATA). [Reproduced from Linnarsson et al. (55).]



the thorax and engorgement of the pulmonary capillaries (16, 72), which can be augmented by a negative  $P_{TR}$ .

Work of breathing is also elevated with the addition of negative (72) or positive (14)  $P_{TR}$ . The increased work of breathing with negative  $P_{TR}$  can be attributed to an increase in internal respiratory resistance due to compression of the extrathoracic airways (2). Positive  $P_{TR}$  causes subjects to have a higher expiratory reserve volume and increased elastic recoil of the lungs (14). However, several studies have shown that the increased work of breathing caused by changes in  $P_{TR}$  between +10 and -20 cmH<sub>2</sub>O during exercise can cause dyspnea but does not translate into higher  $P_{ETCO_2}$  (40, 75, 107), although in these studies it is possible that  $P_{aCO_2}$  was underestimated by  $P_{ETCO_2}$ . It is also possible that positive  $P_{TR}$  could increase dead space by increasing the caliber of the large airways, and thus increase  $P_{aCO_2}$ , although there is not yet any evidence to support this hypothesis.

All but a few studies examining contributors to hypercapnia at depth (8, 51, 74, 89–91) have used  $P_{ETCO_2}$  as an estimate of  $P_{aCO_2}$ , which under resting conditions is a good approximation. During exercise the approximation is not as good:  $P_{ETCO_2}$  is higher than  $P_{aCO_2}$  during exercise at 1 ATA (56) and lower in conditions under which there is increased dead space, as may be the case with diving. Only one study has directly correlated the two in diving, in the dry at 2.8 ATA (74), demonstrating a reasonable correlation.

**Pressure.** Theoretically, there could also be some effect of extremely high pressure on the control of breathing. A study in subjects at rest (89) found that while increased pressure caused  $P_{aCO_2}$  to rise, gas density had only a small effect. However, that study investigated only resting conditions. Studies of hyperbaric exercise have tended to exclude pressure having any significant influence on ventilation (55).

#### PATHOLOGICAL EFFECTS OF DIVING

**Impaired gas exchange after saturation dives.** During saturation dives, divers remain in a hyperbaric environment for many days or weeks. Physical activity is limited, thus engendering loss of cardiorespiratory fitness, and the ambient  $P_{O_2}$  is higher than normal (typically 0.4–0.5 ATA), thus exposing the divers to oxygen tensions that could be mildly toxic to the lung. Additionally, venous gas embolism may occur during decompression, which can last several days. Observations by Thorsen et al. suggest that saturation dives may have persistent cardiorespiratory effects on divers. After deep saturation dives to 37 ATA, maximal  $\dot{V}_{O_2}$  ( $\dot{V}_{O_{2max}}$ ) and carbon monoxide transfer factor are reduced and respiratory dead space is increased (108). While the reduction in  $\dot{V}_{O_{2max}}$  may in part reflect deconditioning due to many days of reduced aerobic exercise in the confined environment of a diving chamber, other explanations were proposed for the gas exchange impairment. The first was a cumulative effect of venous gas embolism on the lung. In support of this hypothesis was the observation that the fractional reduction in  $\dot{V}_{O_{2max}}$  after the dive correlated with the cumulative venous bubble score as detected by ultrasound (108). The second proposed explanation was mild pulmonary oxygen toxicity, due to an inspired  $P_{O_2}$  of 0.4–0.5 ATA during the 18–28 days in which the divers were continuously under pressure. This second hypothesis is supported by a study in which volunteers were exposed in a hyperbaric chamber to a

lower pressure (2.5 ATA) but with duration and inspired  $P_{O_2}$  similar to the deep dives, but with no detectable venous gas emboli. After this exposure there was a similar reduction in  $\dot{V}_{O_{2max}}$  and carbon monoxide transfer factor. A control dive of similar duration but at a lower pressure (1.5 ATA) and  $P_{O_2}$  (0.2 ATA) produced no effect on carbon monoxide transfer factor (110). Logistic regression analysis of possible risk factors after a series of saturation dives implicated both hyperoxia and venous gas embolism as factors contributing to impairment in pulmonary gas exchange (109). These data suggest that hyperoxia, albeit at levels traditionally considered nontoxic, is a major contributor to pulmonary gas impairment after long saturation dives.

**Immersion pulmonary edema.** Immersion pulmonary edema (IPE) is a condition in which cough, hemoptysis, dyspnea, and hypoxemia develop after surface swimming or diving, often in young, healthy individuals (34, 45, 57, 64, 96, 123), including exceptionally fit military divers (59, 64, 95, 121). It occurs predominantly in males. The condition usually resolves spontaneously or with  $\beta_2$ -adrenergic agonist or diuretic therapy, but it can be fatal (96). Risk factors may include cold water (45, 123), exertion (34, 94, 95, 121), fluid loading (121), negative  $P_{TR}$  (111) or low vital capacity (95). The cause is unknown, although hydrostatic pulmonary edema is a strong possibility. Pulmonary artery wedge pressure in IPE at the time of evaluation has been reported as normal (34), although thus far there have been no measurements in IPE during the acute event. Post-event echocardiography is usually normal (34, 45, 57, 96). Bronchoalveolar lavage studies have revealed no evidence of inflammation. Capillary stress failure due to high pulmonary capillary flow/pressure has been implicated (45, 58). Proposed mechanisms involve the additive effects of immersion-induced increase in pulmonary blood volume and pulmonary artery hypertension due to exertion, and cold water (46).

#### CONCLUSION

Despite the diving-related increase in resistance to bulk flow and impairment of gas phase diffusion, it is surprising that the human lung is at all capable of supporting oxygenation and carbon dioxide elimination at gas densities severalfold higher than normal. Nevertheless, there remain several open questions. Ventilation/perfusion relationships during dense gas breathing have not yet been elucidated. Recent studies at 1 ATA suggest that the normal exercise-induced rise in cardiac output can be attenuated by external breathing resistance (3). However, studies to examine the effect on cardiac output of increased pulmonary resistive load are lacking. Although both physiological and safety-related measurements rely mostly on the analysis of end-tidal gas, only one study has been published comparing  $P_{ETCO_2}$  and arterial  $P_{CO_2}$  during exercise, breathing air at 2.8 ATA (density 3.2 g/l) (74). There have been no reported studies at higher densities or  $P_{O_2}$ . The effect of  $P_{O_2}$  on regulation of ventilation and arterial  $P_{CO_2}$  has been incompletely studied during exercise, with the controls in most studies consisting of exercise runs at a different density (1 ATA), thus precluding the elimination of gas density as a confounder. Finally, indirect evidence of metabolic acidosis and respiratory muscle fatigue during endurance exercise pose questions related to the effects on cardiovascular performance and gas exchange. Intriguing recent evidence that respiratory



muscle training may affect ventilatory control and endurance in divers needs further study.

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