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

Predictors of increased $PaCO_2$ during immersed prone exercise at 4.7 ATA


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Respiratory drive could be affected by the high $Po_2$ at depth. Hyperoxia attenuates the ventilatory response to hypercapnia (17, 34, 44) and has been noted to decrease ventilation during exercise at 1 ATA (1, 11, 20, 24, 33, 46, 65), although its effect on minute ventilation ($Ve$) or $PcO_2$ during diving has not been fully investigated. It has also been suggested that nitrogen narcosis may depress respiratory drive during diving, but the consensus is that nitrogen narcosis does not contribute to hypoventilation and hypercapnia at depth (28).

The ventilatory response to CO$_2$ [hypercapnic ventilatory response (HCVR)] varies among individuals and at one time was proposed as a predictor of $PcO_2$ during underwater exercise. Studies have shown a correlation between low HCVR and hypercapnia in exercise studies at the surface and at depth (25, 36). In most studies at 1 ATA, an attenuated response has been observed in SCUBA divers (14, 37, 55), breath-hold divers (10, 57), and endurance athletes (35, 41); in one study, such an effect was not observed (15). Higher arterial $PcO_2$ ($PaCO_2$) has been observed in divers than in nondivers during exercise at 1 ATA, with no difference between diver and control groups at depth (23). HCVR is generally lower in divers than in nondivers (10, 14, 37, 55, 57), and at 1 ATA it appears that HCVR may be somewhat predictive of $PcO_2$ during exercise. However, the seemingly logical conclusion that a low HCVR should predispose to hypercapnia at depth has not been validated (25, 29).

In addition to the effects of hyperoxia and HCVR on hypercapnia, the mechanical consequences of increased ambient pressure may also contribute. A potential cause of hypoventilation and increased $PaCO_2$, in diving is increased work of breathing (WOB) due to higher gas density at depth, decreased pulmonary compliance, and hydrostatic loading that occurs with submersion. It is thought that, in the setting of increased respiratory load, $Va$ is a compromise between normocapnia and the increased WOB that would be required to maintain it (30).

Internal respiratory resistance is increased at higher gas density (32) to the point that flow limitation, which impacts exercise tolerance, develops in the lungs at depth (66). Denser gas increases $PaCO_2$ in subjects at rest (67) and during exercise at the surface (18). In a study of subjects at rest (49), although...
increased pressure caused \( \text{PaCO}_2 \) to rise, gas density had only a small effect. However, at depth during exercise, it has been suggested that the increase in \( \text{PaCO}_2 \) is mediated by gas density and that pressure alone does not have an effect (22, 26, 39, 50, 51).

Internal respiratory load is also affected by lung compliance and airway caliber. Submersion decreases lung compliance by the redistribution of blood into the thorax and subsequent engorgement of the pulmonary capillaries (2, 38) and can be augmented by a negative transrespiratory pressure (\( P_r \), also known as static lung load). Additionally, expiratory reserve volume is increased at depth (19, 56, 60). This has the effect of increasing internal respiratory load by raising the elastic lung load (8), requiring higher negative inspiratory pressures (42). The overall result is an increased WOB with submersion, which augments the increase in \( \text{PaCO}_2 \) normally seen during the transition from rest to exercise (59).

WOB is also elevated with the addition of negative (38) or positive (8) \( P_r \). However, several studies have shown that the increased WOB caused by changes in \( P_r \) between +10 and −20 cm H\(_2\)O during exercise can cause dyspnea without an effect on end-tidal \( \text{PCO}_2 \) (\( \text{PETCO}_2 \)) (21, 40, 59).

Finally, in addition to the increase in internal respiratory resistance due to various effects of increased ambient pressure, a variable amount of external resistance is present in all underwater breathing apparatus. Breathing resistance decreases the HCVR (5), increases subjective dyspnea scores (60), and raises \( \text{PCO}_2 \) in subjects performing various levels of exercise at the surface (58, 69) and at a range of depths (60–62).

In summary, increased depth and respiratory resistance have been shown to increase \( \text{PCO}_2 \). However, although there are compelling reasons that hyperoxia, HCVR, and \( P_r \) may predict \( \text{PCO}_2 \), the evidence has been inconsistent. The present study was designed to examine and quantify factors contributing to hypercapnia, specifically inspired \( \text{PO}_2 \), \( P_r \), and external breathing resistance, during exercise in submersed human subjects at depth. Previous studies have investigated individually the effect of nitrogen narcosis, HCVR, increased pressure/gas density, respiratory resistance, and \( P_r \) as independent factors, but none have examined multiple factors in a single experimental model. In addition, we are not aware of any studies that have compared varying degrees of hyperoxia at depth. In all but a few studies of contributors to hypercapnia at depth (24, 49–51), \( \text{PETCO}_2 \) has been used as an estimate of \( \text{PaCO}_2 \), and, under resting conditions, \( \text{PETCO}_2 \) is a good approximation. However, \( \text{PETCO}_2 \) is higher than \( \text{PaCO}_2 \) during exercise (27, 39) and lower in conditions under which there is a large component of V\(_A\)/perfusion (Q) mismatch (alveolar dead space) (27, 64), such as with obstructive lung disease and, possibly, with diving. Thus, during exercise at depth, \( \text{PETCO}_2 \) may over- or underestimate \( \text{PaCO}_2 \). Only one study has correlated \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) in diving in dry conditions at 2.8 ATA (39). In view of the uncertainty of the relationship between \( \text{PETCO}_2 \) and \( \text{PaCO}_2 \) at greater depths, the present study was designed with direct measurement of arterial blood gas tensions. Finally, most of the investigations at depth have been done under dry hyperbaric conditions. However, submersion increases WOB (2, 38) and alters hemodynamics (12, 43). To simulate more closely the conditions under which divers actually work, in this study the subjects exercised during immersion in a prone position.

**Glossary**

- **EWOB**: External work of breathing
- **EWOB/V**: External work of breathing per volume
- **f**: Ventilatory frequency
- **GC**: Gas chromatography
- **HCVR**: Hypercapnic ventilatory response
- **Hi**: Exercise trials at 80% of \( \text{VO}_{2\text{max}} \)
- **IE**: Inhaled external breathing resistance
- **Mod**: Exercise trials at 60% of \( \text{VO}_{2\text{max}} \)
- **OMPS**: Oronasal mask pressure swing (OMPS), the difference between inspired and expired oronasal mask pressures
- **\( \text{Pa}\_\text{O}_2 \), \( \text{Pa}\_\text{CO}_2 \)**: Arterial \( \text{PO}_2 \), \( \text{PCO}_2 \)
- **\( P_r \)**: Transrespiratory pressure
- **\( \text{PV}\_\text{CO}_2 \), \( \text{PV}\_\text{O}_2 \)**: Mixed venous \( \text{PO}_2 \), \( \text{PCO}_2 \)
- **\( \text{Sa}\_\text{O}_2 \)**: Hemoglobin-O\(_2\) saturation
- **\( \text{VT} \)**: Tidal volume
- **\( \text{VE} \)**: Respiratory minute ventilation
- **\( \text{Vo}\_2 \)**: Oxygen consumption rate
- **\( \text{VO}_{2\text{max}} \)**: Maximum oxygen consumption rate
- **\( \text{VCO}_2 \)**: Carbon dioxide elimination rate

**MATERIALS AND METHODS**

**Subjects and experimenter roles.** After institutional approval and informed consent, 25 volunteer subjects were studied. Screening before the experimental day included a medical history, physical examination, 12-lead ECG, posterior-anterior and lateral chest radiographs, and measurement of vital capacity, forced expiratory volume (FEV) in 1 s (FEV\(_1\)), FEV at 25–27% of vital capacity (FEV\(_{25–75}\)), body composition, aerobic capacity, and HCVR.

Aerobic capacity [maximal \( \text{O}_2 \) consumption (\( \text{VO}_{2\text{max}} \))] was tested ≥3 days before an experimental trial day. The graded maximal test was conducted on a cycle ergometer (model 818E, Monark) according to a protocol developed in our laboratory: three 3-min stages (50, 100, and 150 W) followed by 1-min stages (starting at 175 W and increasing in 25-W increments to exhaustion). Expired gas was analyzed by a metabolic cart (ParvoMedics TruMax 2400, Consentius Technologies), and data were recorded as 30-s averages. Maximal effort was confirmed through review of respiratory exchange ratio, heart rate, and rate of perceived exertion (3). \( \text{VO}_{2\text{max}} \) <30 ml·kg\(^{-1}\)-min\(^{-1}\), ratio of FEV\(_1\) to forced vital capacity <0.75, contraindications to diving (ear or sinus infection and inability to auto-inflate the middle ear), and pregnancy were grounds for exclusion from the study. The aerobic fitness minimum threshold was established so that the subject pool might reasonably model US Navy divers. \( \text{VO}_{2\text{max}} \) measurements also allowed determination of the appropriate work rate to produce an effort of 60% or 80% of \( \text{VO}_{2\text{max}} \). Three volunteers with \( \text{VO}_{2\text{max}} \) <30 ml·kg\(^{-1}\)-min\(^{-1}\) were excluded from the study.

The HCVR was determined at 1 ATA for each subject using measurements of \( \text{PETCO}_2 \) and \( \text{Ve} \) while the subjects breathed on a 15-liter bag-in-box rebreather. A 20-cm section of 3.5-cm-diameter tubing (model 9000, Hans Rudolph, Kansas City, MO) with a dead space of ~500 ml connected the mouthpiece to the bag. The bag initially contained 7 liters of 5% \( \text{CO}_2\)-balance \( \text{O}_2 \). Hyperoxia can affect the slope of the HCVR curve (34, 44); since all subjects at depth were breathing hyperoxic gas, the choice of \( \text{O}_2 \) for the balance gas was logical. After 2 min of moderate hyperventilation to reduce \( \text{PETCO}_2 \) to 20 Torr during room air breathing, subjects rebreathed from the bag until \( \text{PETCO}_2 \) reached 65 Torr (usually within 4 min). HCVR
was calculated as the slope of Ve vs. PetCO2 between 55 and 65 Torr. Because HCVR has been shown to have good intradividual reproducibility over 7 days (39), in this study HCVR was measured once several days before the experimental trial day for each subject. Within our own laboratory, a series of five repeated measurements over several days in five subjects has demonstrated good reproducibility on the apparatus used for the subjects in this study [HCVR = 1.90 ± 0.93 (SD) l·min⁻¹·mmHg⁻¹, average coefficient of variation = 0.15, repeated-measures ANOVA F ratio = 1.2, P = 0.35].

For each experiment, one attendant (who remained in the pool with the subject) and two experimenters (who performed blood draws) were inside the hyperbaric chamber with the subject. A fourth experimenter, who worked with the inspired and expired gas bags in a connected hyperbaric chamber (Fig. 1), was separated from the main chamber by a Plexiglas hatch, which allowed the pressure inside the chamber to be adjusted to maintain specified Ptw. Communication with outside personnel was maintained at all times.

Chamber and conditions. The experiment was conducted in a dry hyperbaric chamber (45) containing a small water-filled pool (4.42 m³ volume). An electronically braked ergometer (Pedalmate, WE Collins, Braintree, MA) was used for all exercise. Subjects were upright for dry exercise, and the ergometer was placed in the pool such that subjects were prone for immersed exercise. Submersion trials were conducted in thermoneutral (30.0 ± 0.7°C) water (9). The actual bottom time (time from leaving the surface to the start of decompression per study ranged from 54 to 86 min. Decompression tables were designed for the study using 100% O2 breathing with intermittent breaks during which the subjects breathed air.

Equipment. Gases were supplied to subjects on a full face mask with an inner oronasal mask (AGA Divator MkII, Amron, Vista, CA, modified at State University of New York, Buffalo) with low-resistance directional breathing valves. A respiratory hose (1%-in. ID, WE Collins) connected the mask to leak-tested inspiratory and expiratory gas bags (model 150L, WE Collins; and model 200L, VacuMed, Ventura, CA) located in a connected hyperbaric chamber. Gases were supplied to subjects at surface pressure during dry trials. For immersion trials, the chamber containing the gas bags was pressurized (to an additional depth of ~50 cmH2O ± Ptw) such that gas delivered to the subject was at the desired Ptw. To examine the possible effect of inertia of gas within the apparatus, we mechanically ventilated the breathing circuit at the surface and at depth. At ventilations similar to those we observed in the study (40–70 l/min), the error was ~5% at depth. This error, however, would not affect O2 consumption (VO2) or CO2 elimination (VCO2) calculations.

Breathing mask pressure was measured using a pressure transducer near the mouth (model MP 45-30, Validyne, Northridge, CA). Fleisch pneumotachographs on the inspiratory and expiratory limbs (58 and 118 mm OD, respectively) were used to record tidal volume (VT) and breathing frequency (f).

Procedure. Each subject was studied at rest and during exercise under the following conditions: 1) dry at the surface (1 ATA), 2) submersed ~50 cm in thermoneutral water at the surface (after a 1-h break), and 3) submersed ~50 cm in water at simulated depth of 36.6 m of seawater (4.7 ATA). Subjects performed a total of two or three bouts of exercise at 4.7 ATA with ≥10 min between each bout. For the remainder of the text, “surface” will be defined as 1 ATA and “depth” as 4.7 ATA.

All subjects breathed air for trials at the surface (21% O2, or 0.21 ATA PO2). Ten subjects performed three exercise trials at 60% of VO2max (Mod) at depth while breathing gas mixtures of 0.7 ATA PO2 (15.2% O2), 1.0 ATA PO2 (21.0% O2), and 1.3 ATA PO2 (28.0% O2) were delivered in random order. Ten subjects performed three exercise trials during Mod at depth, with Ptw of −10, 0, and +10 cmH2O set in random order. Nine subjects performed two exercise trials at 80% of VO2max (Hi) at depth with gas mixtures of 0.7 and 1.3 ATA PO2 delivered in random order. Nine subjects performed three exercise trials during Mod at depth with low, medium, or high inhaled (I) or inhaled-and-exhaled (IE) external respiratory resistance in random order. Resistance was imposed by insertion of 14.9-, 11.6-, and 10.2-mm-diameter-aperture disks into the breathing circuit, with resistances measured at a steady-state flow of air at 2.3 l/s at 4.7 ATA of 4.4, 7.1, and 12.3 cmH2O·l⁻¹·s, respectively. Randomization of surface vs. depth measurements could not be performed because of the risk of decompression illness (DCI) with heavy exercise immediately after diving.

![Fig. 1. Schematic representation of experimental setup. Subject exercised in immersed prone position on an ergometer. Two tenders drew blood samples and maintained communication with experimenters. Experimenters outside the chambers monitored the subject’s hemodynamic and expired gas data. Delta chamber was pressurized such that gas was delivered to the subject at the desired static lung load (SLL).](http://jap.physiology.org/)
Each trial at the surface consisted of 6 min of resting measurements followed by 6 min of exercise measurements. Resting data were not collected at depth because of time constraints. For the resting portion of each trial, expired gas was collected during minutes 3–6. Arterial (from an indwelling catheter in a radial artery) and mixed venous (from an indwelling pulmonary artery catheter) blood samples were collected anaerobically over a 15- to 20-s period during minute 6 of rest.

Expired gas was collected during minute 5 (bag 1) and minute 6 (bag 2) of each exercise period. Arterial and mixed venous blood samples were collected over a 15- to 20-s period during minute 6. Values from minutes 5 and 6 were compared to ensure that the subject was in steady state. Blood gas and expired gas values from minute 6 of exercise were used in all analyses.

Submersed workloads were adjusted to account for increased resistance due to leg movement in water. The average adjustment for all subjects was 45 ± 14 W. For adjustment of work rates, workloads were changed while subjects pedaled at a rate of 60 rpm.

Measurements. At the start of the experiment, sterile technique and 1% lidocaine were used to place a catheter in the radial artery (20 gauge; Arrow, Reading, PA) and a pulmonary artery catheter (model 114F7 triple-lumen monitoring catheter, Edwards Lifesciences, Irvine, CA). The pulmonary artery catheter was inserted via the basilic vein, with radiographic imaging used to ensure that the tip traversed the right heart, without knotting of the catheter, to confirm that the final position of the tip was in the right or left pulmonary artery and that the catheter could be wedged by balloon inflation. The subject’s ECG tracing was recorded throughout the experiment, as were the arterial, central venous, and pulmonary arterial blood pressures. Pressure transducers (Hospira, Lake Forest, IL) were positioned 5 cm caudal to the sternal angle during dry exercise and at midchest during submersion. The reference level (pressure centroid) for setting the Pn and depth of immersion was also midchest. Because the subjects spent only a short time submersed in water in the thermoneutral range during the intermittent exercise periods, core body temperature was assumed to be constant at 37°C.

Samples of arterial and mixed venous blood (4–5 ml) were drawn anaerobically into prewetted heparinized glass syringes, which were capped and kept on ice until analysis (<30 min). Because of time constraints at depth, blood samples were placed in iced hermetically sealed polyvinylchloride canisters (to maintain pressurization until analysis) and removed through the air lock for analysis by a blood gas analyzer (Synthesis 15, Instrumentation Laboratory, Lexington, MA) and CO-oximeter (model 682, Instrumentation Laboratory) in a separate chamber pressurized to 18.3 m of seawater (2.82 ATA) to prevent reading error due to O2 supersaturation of the depth samples. PO2 was measured first for those samples expected to have the highest content. Hemoglobin-O2 saturation (SO2) as measured by CO-oximeter and as calculated by blood gas analyzer (16, 54) was recorded for each sample. Measured values of SO2 were used for samples collected at 1 ATA. For these samples, an excellent correlation was observed between measured and calculated SO2. At depth, it was observed that CO-oximeter measurement of SO2 (performed at the surface after blood gas analysis) was systematically high, presumably because of transient exposure to hyperbaric air (PO2 ≈ 0.56 ATA) after injection of the sample into the blood gas analyzer. Therefore, for depth samples, the calculated values of SO2 are reported.

Mixed expired O2 and CO2 concentrations were measured using a mass spectrometer (model 1100 medical gas analyzer, Perkin-Elmer, Pomona, CA) connected to Labview (version 6.1, National Instruments, Austin, TX) with a data acquisition board (PCI 6014, National Instruments). Each value was confirmed using gas chromatography (GC; model 3800, Varian, Palo Alto, CA). Gas samples for GC were drawn into gas-tight glass syringes with vented plungers, which were prewetted with 10% lactic acid. Mass spectrometer and GC results were highly correlated for all subjects and conditions. Mass spectrometer data are presented here. After gas samples were obtained, expired gas volumes were measured using a calibrated gasometer (model DTM 325-4, American Meter, Nebraska City, NE), to which GC and mass spectrometer sample volumes were added.

Calculations. VT was calculated using measurements of V̇t and f and was converted to VT. VO2 and V̇CO2 were determined from standard equations. Fick cardiac output (CO) was calculated as VO2/ (CaO2 – CvO2), where CaO2 and CvO2 are the arterial and mixed venous O2 contents, respectively. External WOB (EWOB, J) was calculated using data from the oronasal mask pressure transducer and the pneumotachographs on the inspired and expired breathing circuits by the following formula: EWOB = ∫PdV, where P is mouthpiece pressure and dV is change in volume. Inspired and expired EWOB per volume (J/l) were averaged to obtain the mean EWOB per volume (EWOB/V) over a full breath cycle. The mean of several breath cycles per condition is reported in RESULTS.

Statistics. Effects on PaCO2 were analyzed using a repeated-measures general linear model (SAS Mixed procedure), which accounted for the correlation of multiple measures from the same subject. For evaluation of simultaneous effects, the starting model included VO2, depth, submersion, resistance, Pn, inspired PO2, HCVR slope, forced vital capacity, and VO2max, as well as the two-way interactions of VO2 with all the other terms. Nonsignificant effects were removed from the model in a stepwise manner until only significant effects remained. VO2 and the VO2/VO2max fraction were also tested in place of VO2 as alternative measures of level of exercise. Depth, submersion, resistance, and Pn were treated as categorical yes-no variables. Because depth has been previously shown to increase PaCO2, the model was also run without depth as a variable. Results of both models, with and without the depth variable, are reported for comparison. All effects were treated as fixed, and a compound-symmetrical covariance structure was specified after examination of best fit. Physiological responses were measured under various sets of conditions and on various sets of subjects, so that the measurements included repeated (dependent) and one-time observations. The differences in physiological measurements under varying specific conditions were compared with a one-way repeated-measures ANOVA on a subset of measures limited to the conditions of interest. The significance level was set at α = 0.05, and no attempt was made to adjust for multiple comparisons in this exploratory investigation of the data.

RESULTS

Subjects. In addition to the 25 subjects who completed the study, 2 did not finish, 1 subject had a malfunctioning arterial line, and 1 subject developed severe leg cramps, which prevented him from completing the exercise runs. There was one incident of otic barotrauma and DCI, consisting of right thumb numbness, with mild opponens pollicis weakness that responded to treatment with a US Navy Treatment Table 6. After this incident, decompression tables were modified by the addition of more O2 time (25 min) at 60 ft. There were a total of 223 person-dives in the study, which gives a DCI rate of 0.45%. One subject had transient, evanescent paresthesia (niggles) of the right hand, which resolved without treatment. Two subjects had phlebothrombosis in the arm of the catheter insertion, which became asymptomatic within a few days.

Subject characteristics appear in Table 1. Mean values did not vary significantly by condition: PO2 of 0.7, 1.0, and 1.3 ATA (condition a), PO2 of −10, 0, and +10 cmH2O (condition b), P02 of 0.7 and 1.3 ATA with heavier exercise (condition c), and low, medium, and high breathing resistance (condition d). However, HCVR slope was highly variable across all subjects, and group mean values reflect this finding. HCVR slopes were 1.63 ± 1.29 for condition a, 0.64 ± 0.35 for condition b, 1.13 ± 0.43 for condition c, and 0.95 ± 0.36 for condition d.
Mean work rate and $\dot{V}_{O_2}$ (30.5 ± 5.5 ml·kg$^{-1}$·min$^{-1}$) were similar over all conditions, with the exception of condition c, for which the work rate was intentionally increased. None of the subjects were smokers.

VE and fractional dead space. At the surface, $V_E$ (l/min) decreased when subjects went from the dry to the submersed state during Mod (14% decrease, $P = 0.02$) and rest (23% decrease, $P = 0.02$). Exposure to 4.7 ATA during submersion during Mod caused $V_E$ to fall still further (31% decrease from dry, $P < 0.01$). The addition of resistance, $P_{ir}$, or different inspired $P_{O_2}$ at depth did not result in a significant change in $V_E$. A higher work rate at the surface and at depth was associated with an increase in $V_E$ ($P < 0.05$ in both cases). $V_E$ results appear in Table 2, along with $f$, $P_{aCO_2}$, arterial $P_{O_2}$ ($P_{A_0}$), mixed venous $P_{CO_2}$ ($P_{vCO_2}$), mixed venous $P_{O_2}$ ($P_{vO_2}$), $V_{CO_2}$, $V_{O_2}$, oronasal mask pressure swing (OMPS), the difference between the inspired and expired oronasal mask pressures), and Fick CO. The error due to inertia-induced flow of gas at depth is ~5%. Inertance error tends to overestimate $V_E$, and the magnitude of the error increases with gas density. However, the change demonstrated here is a decrease in $V_E$ for the transition to depth, so although an inertance error could underestimate a decrease in $V_E$, it cannot account for the observed change in $V_E$.

There was a slight increase in fractional dead space [i.e., the ratio of dead space to $V_T$ ($V_d/V_T$)] during Mod with added depth and with the addition of positive $P_{ir}$ (Fig. 2). Values increased from 0.23 ± 0.08 at 1 ATA submersed to 0.29 ± 0.07 ($P < 0.01$) at 4.7 ATA submersed and to 0.32 ± 0.07 with +10 cmH$_2$O $P_{ir}$ ($P < 0.01$ for depth vs. depth and +10 cmH$_2$O $P_{ir}$). Table 3 gives average values for $V_d/V_T$ and $V_T$ for each condition.

Oronasal mask pressure and EWOB. OMPS increased dramatically with the addition of resistance to the breathing circuit. Average EWOB/V (mean for expiration and inspiration) is reported in Table 4. Inspired EWOB/V is also listed to allow comparison of conditions without added resistance. EWOB/V and OMPS increased as resistor plate orifice diameter decreased and with IE vs. IR resistance. OMPS was higher during Mod ($P = 0.01$) and Hi ($P < 0.0005$). There was a significant increase in EWOB/V from 14.9 mm I to 11.6 mm IE and 10.2 mm IE ($P = 0.01$), but the differences between the other resistances were too small to reach statistical significance.

$V_{O_2}$ and $V_{CO_2}$. There was no significant change in $V_{O_2}$ for the transition from submersed at 1 ATA to 4.7 ATA, nor was there an effect of $P_{ir}$ or added breathing resistance ($P = 0.33$ for high resistance).

During Mod breathing air without $P_{ir}$ at 4.7 ATA, $V_{CO_2}$ was not significantly different from surface values ($P = 0.10$). Hi increased $V_{CO_2}$ from Mod values for submersed ($P = 0.04$) conditions. At depth, varying inspired $P_{O_2}$ did not affect $V_{CO_2}$, but positive $P_{ir}$ produced an effect that approached statistical significance ($V_{CO_2}$ higher with positive and negative $P_{ir}$, $P = 0.06$). There was no significant change in $V_{CO_2}$ with the addition of breathing resistance.

$P_{vCO_2}$, $P_{vO_2}$, and Fick CO. $P_{vCO_2}$ increased from rest to exercise in dry ($P < 0.0001$) and submersed ($P < 0.0001$) conditions and was markedly elevated at depth ($P < 0.0001$). Changes in inspired $P_{O_2}$ and the addition of $P_{ir}$ or breathing resistance
PREDICTORS OF HYPERCAPNIA IN IMMERSED EXERCISE AT DEPTH

Table 2. Minute ventilation and other respiratory variable results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Work Level</th>
<th>PO2, ATA</th>
<th>n</th>
<th>Minute Ventilation, l/min</th>
<th>Arterial PO2, Torr</th>
<th>Arterial PO2, Torr</th>
<th>Mixed Venous PO2, Torr</th>
<th>Mixed Venous PO2, Torr</th>
<th>O2 Uptake, l/min</th>
<th>CO2 Output, l/min</th>
<th>OMPS, cmH2O</th>
<th>Fick CO2, l/min</th>
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</thead>
<tbody>
<tr>
<td>Dry</td>
<td>Mod</td>
<td>0.2</td>
<td>29</td>
<td>89.2 ± 22.9</td>
<td>31.5 ± 5.1</td>
<td>101.0 ± 13.1</td>
<td>54.2 ± 7.2</td>
<td>25.0 ± 4.1</td>
<td>2.44 ± 0.28</td>
<td>2.53 ± 0.42</td>
<td>3.7 ± 1.6</td>
<td>16.8 ± 3.5</td>
</tr>
<tr>
<td>Submersed</td>
<td>Mod</td>
<td>0.2</td>
<td>29</td>
<td>76.3 ± 20.5</td>
<td>34.2 ± 4.8</td>
<td>105.6 ± 10.1</td>
<td>53.8 ± 7.0</td>
<td>25.8 ± 2.8</td>
<td>2.27 ± 0.44</td>
<td>2.23 ± 0.48</td>
<td>3.4 ± 1.5</td>
<td>17.6 ± 2.9</td>
</tr>
<tr>
<td>Dry</td>
<td>Hi</td>
<td>0.2</td>
<td>9</td>
<td>111.4 ± 25.6</td>
<td>29.2 ± 3.1</td>
<td>97.7 ± 14.7</td>
<td>50.1 ± 9.2</td>
<td>24.1 ± 4.2</td>
<td>2.92 ± 0.81</td>
<td>3.10 ± 0.82</td>
<td>4.1 ± 1.3</td>
<td>21.1 ± 3.9</td>
</tr>
<tr>
<td>Submersed</td>
<td>Hi</td>
<td>0.2</td>
<td>9</td>
<td>110.9 ± 25.7</td>
<td>30.4 ± 3.1</td>
<td>105.0 ± 14.0</td>
<td>53.4 ± 6.2</td>
<td>24.8 ± 2.7</td>
<td>2.68 ± 0.86</td>
<td>2.79 ± 0.86</td>
<td>4.5 ± 1.3</td>
<td>19.2 ± 4.4</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of measurements for each condition, in some cases including >1 measurement for a handful of subjects. PO2, transrespiratory pressure; OMPS, oronasal mask pressure swing (inspired and expired pressure difference); Fick CO2, Fick cardiac output. O2 uptake and Fick CO2 are not reported for 1.3 ATA PO2 because of possible contamination of gas samples.

resistance did not affect PVen. There was no significant difference in PInCO2, between Mod and Hi. There was no change in Fick CO2 with the transition to depth.

The effect of submersion, exercise, and pressure on PVen was essentially the opposite of the effect on PInCO2. The transition from rest to exercise lowered PVen in dry (P < 0.0001) and submersed (P < 0.0001) conditions. However, PVen increased with pressure during Mod with submersion (P < 0.0001). The corresponding venous O2 saturation in-

Table 3. Dead space and tidal volume results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Work Level</th>
<th>PO2, ATA</th>
<th>n</th>
<th>Vd/Vt</th>
<th>VT, liters</th>
<th>f, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>Mod</td>
<td>0.2</td>
<td>29</td>
<td>0.45 ± 0.08</td>
<td>1.0 ± 0.3</td>
<td>14.6 ± 2.7</td>
</tr>
<tr>
<td>Submersed</td>
<td>Mod</td>
<td>0.2</td>
<td>38</td>
<td>0.39 ± 0.11</td>
<td>1.1 ± 0.6</td>
<td>11.7 ± 3.3</td>
</tr>
</tbody>
</table>

| Dry       | Mod        | 0.2      | 29 | 0.17 ± 0.13 | 2.8 ± 0.5 | 34.0 ± 10.8 |
| Submersed | Mod        | 0.2      | 29 | 0.23 ± 0.08 | 2.6 ± 0.6 | 30.6 ± 9.3  |
| Dry       | Hi         | 0.2      | 9  | 0.18 ± 0.08 | 2.9 ± 0.6 | 39.6 ± 11.5 |
| Submersed | Hi         | 0.2      | 9  | 0.27 ± 0.14 | 2.9 ± 0.7 | 39.6 ± 11.4 |

Values are means ± SD. Vd, dead space; VT, tidal volume; f, ventilatory frequency.

Fig. 2. Fractional dead space [i.e., ratio of dead space to tidal volume (Vd/Vt)] during rest and exercise for different conditions. Mod, 60% of maximal O2 consumption (Vo2max); Hi, 80% of Vo2max. Values are means ± SD. *P < 0.05, dry rest vs. dry Mod at surface; †P < 0.05, submersed rest vs. submersed Mod at surface. ‡P < 0.05, submersed Mod at surface vs. submersed Mod at depth. §P < 0.05, submersed Mod at surface vs. submersed Mod at depth with +10 cmH2O transrespiratory pressure (Pp).
increased from 35.6 ± 6.4% at 1 ATA submersed to 44.9 ± 6.9% at 4.7 ATA. \( P_{\text{CO}_2} \) increased from 0.7 ATA \( P_{\text{O}_2} \) to 1.3 ATA \( P_{\text{O}_2} \) for Mod (\( P = 0.01 \)) and Hi (\( P < 0.0001 \)). Addition of respiratory resistance or \( P_{\text{tr}} \) did not affect \( P_{\text{CO}_2} \).

**HCVR slope and \( V_{\text{O}_2\text{max}} \).** A plot of \( P_{\text{ACO}_2} \) during exercise at depth vs. HCVR measured at the surface (Fig. 3) shows some correlation between the two (slope = \(-6.72, R^2 = 0.31, P = 0.01 \)). Plots of \( P_{\text{ACO}_2} \) vs. \( V_{\text{O}_2\text{max}} \) and HCVR slope vs. \( V_{\text{O}_2\text{max}} \) show no correlation between the variables (\( P = 0.16 \) and 0.79, respectively).

\( P_{\text{ACO}_2} \). From rest to Mod, \( P_{\text{ACO}_2} \) dropped significantly for the dry condition (\( P < 0.01 \)) but remained at the same level for the submersed condition (\( P = 0.13 \); Fig. 4). \( P_{\text{ACO}_2} \) (Torr) increased during Mod in the transition from dry to submersed (\( P = 0.02 \)) and still further on exposure to 4.7 ATA (\( P < 0.0001 \)). The most extreme \( P_{\text{ACO}_2} \) of 57.4 Torr was attained by a subject during Mod at depth with the 10.2-mm IE resistance disk. However, there was no significant overall effect on \( P_{\text{ACO}_2} \) of added resistance (\( P = 0.06 \)). There was also no significant difference between \( P_{\text{ACO}_2} \) values during Mod for the different inspired \( P_{\text{O}_2} \) or \( P_{\text{tr}} \) and the \( P_{\text{ACO}_2} \) at 4.7 ATA during air breathing with 0 cmH\(_2\)O \( P_{\text{tr}} \).

![Fig. 3. Arterial \( P_{\text{CO}_2} \) (\( P_{\text{ACO}_2} \)) during exercise at depth vs. hypercapnic ventilatory response (HCVR) slope with line of best fit (solid line) at 4.7 ATA during Mod with 0 cmH\(_2\)O \( P_{\text{tr}} \) and 1.0 ATA \( P_{\text{O}_2} \). Dashed lines, 95% confidence intervals. \( P = 0.01 \).](image)

![Fig. 4. \( P_{\text{CO}_2} \) for each condition. I, inhaled; IE, inhaled and exhaled. Values are means ± SD. * \( P < 0.05 \), dry rest vs. dry Mod at surface. † \( P < 0.05 \), dry Mod vs. submersed Mod at surface. ‡ \( P < 0.05 \), submersed Mod at surface vs. submersed Mod at depth.](image)

**Predictors of \( P_{\text{ACO}_2} \).** The final predictive model found significant simultaneous independent effects on \( P_{\text{ACO}_2} \) of depth, resistance, HCVR slope, and \( V_{\text{O}_2\text{max}} \), with no significant effect of \( V_{\text{CO}_2} \). Since depth is already known to raise \( P_{\text{ACO}_2} \), the model was also used without depth as a variable, incorporating only data points from depth measurements. Resistance, HCVR slope, and \( V_{\text{O}_2\text{max}} \) were still found to be significant. When used as alternative measures of exercise, \( V_{\text{CO}_2} \) and the \( V_{\text{O}_2}/V_{\text{O}_2\text{max}} \) fraction similarly showed no significant effect. None of the two-way interactions with \( V_{\text{O}_2} \) were significant, nor was the interaction of \( V_{\text{O}_2} \) with \( V_{\text{O}_2\text{max}} \). \( P_{\text{tr}} \) and inspired \( P_{\text{O}_2} \) were removed from the final model, as were the two-way interaction terms. The coefficients in the solution for fixed effects, which give the change in \( P_{\text{ACO}_2} \) (Torr) for a change of one unit for a given variable (with all other terms remaining fixed), are shown in Table 5, along with their \( F \) and \( P \) values with and without depth as a variable. Figure 5 shows \( P_{\text{ACO}_2} \) as predicted by the final statistical model based on inputs of depth, resistance, HCVR slope, and \( V_{\text{O}_2\text{max}} \) plotted against measured values for \( P_{\text{ACO}_2} \), as well as the predicted \( P_{\text{ACO}_2} \) for the model without depth as an input.

![Table 5. Independent predictors of arterial \( P_{\text{CO}_2} \)](image)
6.4 l/min at depth, but instead V˙E decreased by 14.7 l/min.

... final statistical model based on inputs of depth (categorical), resistance (categorical), HCVR slope (l·min⁻¹·mmHg⁻¹), and VO₂max (ml·kg⁻¹·min⁻¹). Diagonal lines, lines of identity.

**DISCUSSION**

**Ve and dead space.** The drop in Ve from 1 ATA dry to 1 ATA submersed to 4.7 ATA submersed paralleled the rise in PaCO₂. Despite the increased EWOB associated with the addition of breathing resistance, a significantly smaller Ve was not observed as smaller-bore resistor plates were added. The slight rise in Ve with positive Pe was also not significant. The average rise in Vd/Vt for surface vs. depth during exercise was 6%. This increase in Vd/Vt would require an increase in Ve of 6.4 l/min at depth, but instead Ve decreased by 14.7 l/min. Thus it is a combination of decreased Ve and increased Vd/Vt that caused the alveolar hypoventilation and the resulting increase in PaCO₂.

**Oronasal mask pressure and EWOB.** It is unknown whether breathing patterns tend to minimize EWOB, oronasal mask pressure, or some combination of the two. We supposed that it would be rare to see extremes of one to minimize the other; therefore, we assumed that OMPS and EWOB/N would be equally representative of external breathing resistance. This notion is supported by their concurrent increase with increasing gas density and with the addition of resistor plates. Internal and external WOB increase with increases in gas density, but only EWOB was measured in this study. Thus EWOB was not included in the model as a continuous variable but, rather, as a categorical variable. External power of breathing (measured in W) could have been used, but we chose EWOB/N, since it has been used in previous studies of external breathing resistance (60).

VO₂ and VCO₂. VO₂ and VCO₂ were increased, as expected, for the transition from rest to exercise. A decreased VO₂ in hyperoxia at 1 ATA (63, 65) and at depth (13, 59) has been found in other studies, but an effect was not observed in the present study.

PaO₂, PTVO₂, and PTVCO₂. The marked elevation of PTVCO₂ during exercise at depth can be partially attributed to concurrent increases in PaCO₂ and PTVO₂, since depth had no significant effect on VCO₂ or cardiac output. The change in PTVO₂ resulted in a 9.3% increase in venous O₂ saturation. This would, via the Haldane effect, raise the PCO₂ of the venous blood and, presumably, the tissues (48). The slight increase in PTVO₂ and PTVCO₂ for changes in inspired PO₂ from 0.7 to 1.3 ATA supports this mechanism.

**Predictors of increased PaCO₂.** During exercise, the increased pressure or gas density at depth had by far the greatest effect on PaCO₂, with a calculated change in PaCO₂ of 13.1 ± 0.7 Torr from 1 to 4.7 ATA, which is consistent with other studies of hypercapnia in divers (22, 23, 25, 50, 51). The present study was not designed to separate the individual effects of increased gas density and increased pressure on PaCO₂. However, several previous studies show that increased gas density has the greatest effect (18, 26, 67), primarily because of increased inspiratory resistance and expiratory flow limitation due to increased gas density (66).

The addition of breathing resistance had a smaller effect on PaCO₂, with a predicted change in PaCO₂ of 4.3 ± 1.1 Torr from 1 to 4.7 ATA. Other studies have also found that added resistance raises PETCO₂ (58, 60–62, 69). It is expected that higher levels of resistance would produce larger changes, which may augment the impact of pressure/gas density on PaCO₂.

HCVR and VO₂max were continuous variables. Under the conditions tested, the change in PaCO₂ for VO₂max was predicted to be 0.14 ± 0.05 Torr·ml·kg⁻¹·min⁻¹. This is an extremely small effect with a relatively large error, but when multiplied by the VO₂max range for all subjects in the study (41 ml·kg⁻¹·min⁻¹), it predicts a change in PaCO₂ of ~6 Torr if all other conditions are held constant. Nevertheless, a plot of PaCO₂ during exercise at depth vs. VO₂max indicates significant individual variability (R² = 0.11, P = not significant).

The HCVR effect (~1.78 ± 0.73 Torr) was also relatively small. The negative correlation but large scatter in the plot of PaCO₂ during exercise at depth vs. HCVR (Fig. 3) reinforces the conclusion that, despite a correlation (R² = 0.33, P = 0.01), HCVR slope at rest is a poor predictor of hypercapnia during exercise at depth (25, 29).

It has been reported that trained endurance athletes have lower HCVR slopes than sprinters (7, 31, 35) and “tend” to have lower HCVR slopes than untrained individuals (41, 47, 53). This blunted response may serve to reduce the energy cost of respiratory work required to maintain a physiologically normal PaCO₂ during endurance events. One might expect subjects with higher VO₂max to have a decreased HCVR slope, but there was no correlation between VO₂max and HCVR slope in the subjects in the present study (R² = 0.0033, P = not
PO2 from 0.7 to 1.3 ATA had no effect. This is a reassuring divers. In the present study, the analysis of the effect of PO2 and extremely uncomfortable for subjects during moderate-to-exercise (4), or that many were divers (14, 37, 55).

PaCO2 in the present study. Since P tr, has been shown to increase with positive or negative Ptr. However, it is fair to conclude that, under conditions but, more likely, reflected true low HCVR due to measurement but, more likely, reflected true low HCVR due to subject self-selection (52), a relatively high level of group fitness (4), or that many were divers (14, 37, 55).

V˙O2 was confounded by depth, with lower PO2 (0.2 ATA) and V˙O2 tested at depth. Thus it was not possible for the model to distinguish changes in PaCO2 for any PO2 levels, except at 0.7–1.3 ATA and for the range of V˙O2 levels at exercise. We cannot exclude hyperoxia as a factor contributing to changes in PaCO2 at depth. However, increasing PO2 from 0.7 to 1.3 ATA had no effect. This is a reassuring result for divers using enriched O2 breathing mixtures, at least to the depth of this study. In the case of P tr, no studies have shown an increase in PaCO2 with positive or negative P tr.

Limitations of the study. Because depth and resistance were treated as categorical variables, this model does not allow inference regarding the quantitative effect of depths other than 4.7 ATA or specific resistance levels on PaCO2. Higher levels of breathing resistance and ambient pressures will likely increase breathing resistance and ambient pressures will likely increase PaCO2 values to some degree, but the magnitude of those effects cannot be accurately predicted from the above-described results. Moreover, numbers of subjects tested were insufficient to demonstrate statistical significance between different levels of breathing resistance. However, it is fair to conclude that, under the conditions tested, the relative importance of those effects was 1) depth and 2) added breathing resistance. HCVR slope and V˙O2max as continuous variables, are difficult to compare with the categorical variables but appear to have a smaller impact on PaCO2, with HCVR slope having the smaller effect. It should not be inferred that depth would be more influential than resistance for other depth and resistance combinations, and it is possible that the application of more extreme V˙O2, P tr, and inspired PO2 variations could augment the effect of those factors on PaCO2. Given the low average HCVR in the study, it is possible that conclusions may not apply to those with higher CO2 sensitivity. In addition, recently published observations have shown a profound change in ventilatory pattern due to respiratory muscle fatigue in divers swimming at 70% of V˙O2max after 15 min and that the ventilatory pattern and time to the change in pattern can be influenced by prior respiratory muscle training (68). Thus it is possible that, over a longer course of exercise, the addition of P tr and external respiratory resistance would more significantly affect the ventilatory pattern and PaCO2 by hastening the development of respiratory muscle fatigue. Because of dive time limitations, not all interventions at depth were performed on each of the 25 subjects; this factor limited, to some extent, the ability to produce a complete global model. The statistical treatment of the data did take into account the combination of paired and unpaired data points. To investigate these effects fully on so many different variables, a study exceeding the scope of the present study would be required.

Summary. The results of this study, the first of its kind with direct measurement of PaCO2, indicate that PaCO2 was increased during moderate and heavy short-term immersed exercise at 4.7 ATA. The hypercapnia was not extreme enough to affect consciousness or exercise performance in any of the subjects. The rise in PaCO2 is primarily attributed to the decrease in Ve and slight increase in dead space. The two main factors contributing to the hypercapnia were the increased gas density/pressure at depth and the presence of external respiratory resistance. Minor contributors included HCVR and V˙O2max values, whereas inspired PO2, P tr, and small variations in V˙O2 did not have a significant effect. A predictive model based on inputs of depth, external breathing resistance, HCVR, and V˙O2max shows generally good agreement between the predicted and the measured values.

GRANTS

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REFERENCES


