

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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Cherry AD, Forkner IF, Frederick HJ, Natoli MJ, Schinazi EA, Longphre JP, Conard JL, White WD, Freiburger JJ, Stolp BW, Pollock NW, Doar PO, Boso AE, Alford EL, Walker AJ, Ma AC, Rhodes MA, Moon RE. Predictors of increased PaCO_2 during immersed prone exercise at 4.7 ATA. *J Appl Physiol* 106: 316–325, 2009. First published September 11, 2008; doi:10.1152/jappphysiol.00885.2007.—During diving, arterial PCO_2 (PaCO_2) levels can increase and contribute to psychomotor impairment and unconsciousness. This study was designed to investigate the effects of the hypercapnic ventilatory response (HCVR), exercise, inspired PO_2 , and externally applied transrespiratory pressure (P_{tr}) on PaCO_2 during immersed prone exercise in subjects breathing oxygen-nitrogen mixes at 4.7 ATA. Twenty-five subjects were studied at rest and during 6 min of exercise while dry and submersed at 1 ATA and during exercise submersed at 4.7 ATA. At 4.7 ATA, subsets of the 25 subjects (9–10 for each condition) exercised as P_{tr} was varied between +10, 0, and –10 cmH_2O ; breathing gas PO_2 was 0.7, 1.0, and 1.3 ATA; and inspiratory and expiratory breathing resistances were varied using 14.9-, 11.6-, and 10.2-mm-diameter-aperture disks. During exercise, PaCO_2 (Torr) increased from 31.5 ± 4.1 (mean $\pm$ SD for all subjects) dry to 34.2 ± 4.8 ($P = 0.02$) submersed, to 46.1 ± 5.9 ($P < 0.001$) at 4.7 ATA during air breathing and to 49.9 ± 5.4 ($P < 0.001$ vs. 1 ATA) during breathing with high external resistance. There was no significant effect of inspired PO_2 or P_{tr} on PaCO_2 or minute ventilation ($\dot{V}_E$). $\dot{V}_E$ (l/min) decreased from 89.2 ± 22.9 dry to 76.3 ± 20.5 ($P = 0.02$) submersed, to 61.6 ± 13.9 ($P < 0.001$) at 4.7 ATA during air breathing and to 49.2 ± 7.3 ($P < 0.001$) during breathing with resistance. We conclude that the major contributors to increased PaCO_2 during exercise at 4.7 ATA are increased depth and external respiratory resistance. HCVR and maximal O_2 consumption were also weakly predictive. The effects of P_{tr} , inspired PO_2 , and O_2 consumption during short-term exercise were not significant.

transrespiratory pressure; respiratory resistance; hyperoxia; carbon dioxide response; diving

HYPERCAPNIA CAN BE PROBLEMATIC or dangerous for working and recreational divers. It occurs even at rest (51), but it is more pronounced during exercise (6, 22, 23, 25, 50, 51) and is due to reduced alveolar ventilation ($\dot{V}_A$) caused by increased dead space (39, 51) and reduced total ventilation (21, 40, 50, 59). Several contributing factors have been identified and investigated.

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 ($\dot{V}_E$) 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, $\dot{V}_A$ 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

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increased pressure caused PaCO_2 to rise, gas density had only a small effect. However, at depth during exercise, it has been suggested that the increase in 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_{tr} , 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 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_{tr} . However, several studies have shown that the increased WOB caused by changes in P_{tr} between +10 and -20 cmH₂O during exercise can cause dyspnea without an effect on end-tidal PCO_2 (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 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 PCO_2 . However, although there are compelling reasons that hyperoxia, HCVR, and P_{tr} may predict PCO_2 , the evidence has been inconsistent. The present study was designed to examine and quantify factors contributing to hypercapnia, specifically inspired PO_2 , P_{tr} , 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_{tr} 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), PETCO_2 has been used as an estimate of PaCO_2 , and, under resting conditions, PETCO_2 is a good approximation. However, PETCO_2 is higher than PaCO_2 during exercise (27, 39) and lower in conditions under which there is a large component of $\dot{V}_A$ -perfusion ($\dot{Q}$) mismatch (alveolar dead space) (27, 64), such as with obstructive lung disease and, possibly, with diving. Thus, during exercise at depth, PETCO_2 may over- or underestimate PaCO_2 . Only one study has correlated PETCO_2 and PaCO_2 in diving in dry conditions at 2.8 ATA (39). In view of the uncertainty of the relationship between PETCO_2 and 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 $\dot{V}_{\text{O}_{2\text{max}}}$
I	Inhaled external breathing resistance
IE	Inhaled and exhaled external breathing resistance
Mod	Exercise trials at 60% of $\dot{V}_{\text{O}_{2\text{max}}}$
OMPS	Oronasal mask pressure swing (OMPS), the difference between inspired and expired oronasal mask pressures
PaO_2 , PaCO_2	Arterial PO_2 , PCO_2
P_{tr}	Transrespiratory pressure
$\text{P}\bar{\text{V}}_{\text{O}_2}$, $\text{P}\bar{\text{V}}_{\text{CO}_2}$	Mixed venous PO_2 , PCO_2
SO_2	Hemoglobin- O_2 saturation
V_T	Tidal volume
$\dot{V}_E$	Respiratory minute ventilation
$\dot{V}_{\text{O}_2}$	Oxygen consumption rate
$\dot{V}_{\text{O}_{2\text{max}}}$	Maximum oxygen consumption rate
$\dot{V}_{\text{CO}_2}$	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 O_2 consumption ($\dot{V}_{\text{O}_{2\text{max}}}$)] 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). $\dot{V}_{\text{O}_{2\text{max}}} < 30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, 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. $\dot{V}_{\text{O}_{2\text{max}}}$ measurements also allowed determination of the appropriate work rate to produce an effort of 60% or 80% of $\dot{V}_{\text{O}_{2\text{max}}}$. Three volunteers with $\dot{V}_{\text{O}_{2\text{max}}} < 30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ were excluded from the study.

The HCVR was determined at 1 ATA for each subject using measurements of PETCO_2 and $\dot{V}_E$ 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 $\sim 500 \text{ ml}$ connected the mouthpiece to the bag. The bag initially contained 7 liters of 5% CO_2 -balance 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 O_2 for the balance gas was logical. After 2 min of moderate hyperventilation to reduce PETCO_2 to 20 Torr during room air breathing, subjects rebreathed from the bag until PETCO_2 reached 65 Torr (usually within 4 min). HCVR

was calculated as the slope of $\dot{V}_E$ vs. P_{ETCO_2} between 55 and 65 Torr. Because HCVR has been shown to have good intraindividual 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) $l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, 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 P_{tr} . 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 m^3 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 ($30.0 \pm 0.7^\circ\text{C}$) 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% O_2 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 $\frac{3}{8}$ -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 $\sim 50 \text{ cmH}_2\text{O} \pm P_{tr}$) such that gas delivered to the

subject was at the desired P_{tr} . 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 $\sim 5\%$ at depth. This error, however, would not affect $\dot{V}_{\text{O}_2}$ consumption ($\dot{V}_{\text{O}_2}$) or CO_2 elimination ($\dot{V}_{\text{CO}_2}$) 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 (V_T) 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 $\sim 50 \text{ cm}$ in thermoneutral water at the surface (after a 1-h break), and 3) submersed $\sim 50 \text{ cm}$ 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 $\geq 10 \text{ min}$ 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% O_2 , or 0.21 ATA PO_2). Ten subjects performed three exercise trials at 60% of $\dot{V}_{\text{O}_{2\text{max}}}$ (Mod) at depth while breathing gas mixtures of 0.7 ATA PO_2 (15.2% O_2), 1.0 ATA PO_2 (21.0% O_2), and 1.3 ATA PO_2 (28.0% O_2) were delivered in random order. Ten subjects performed three exercise trials during Mod at depth, with P_{tr} of -10 , 0 , and $+10 \text{ cmH}_2\text{O}$ set in random order. Nine subjects performed two exercise trials at 80% of $\dot{V}_{\text{O}_{2\text{max}}}$ (Hi) at depth with gas mixtures of 0.7 and 1.3 ATA PO_2 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 $\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$, 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.

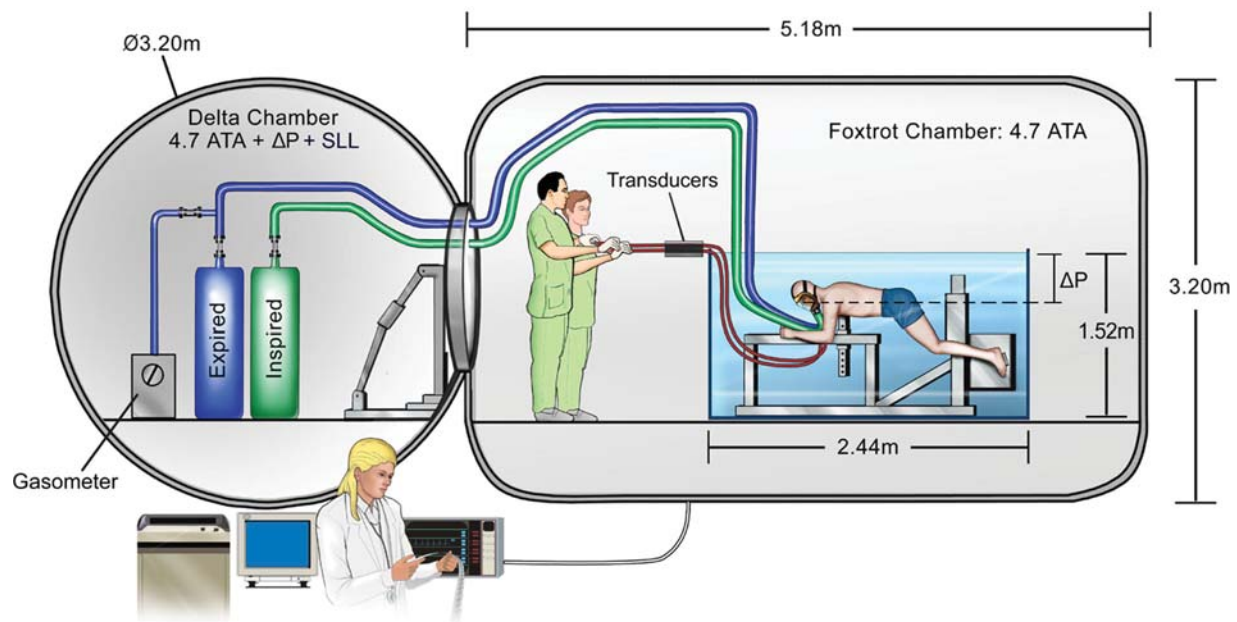


Fig. 1. Schematic representation of experimental setup. Subject exercised in immersed prone position on an ergometer. Two tenders drew blood samples and maintained communication with experimenters. Experimenters outside the chambers monitored the subject's hemodynamic and expired gas data. Delta chamber was pressurized such that gas was delivered to the subject at the desired static lung load (SLL).

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 caudad to the sternal angle during dry exercise and at midchest during submersion. The reference level (pressure centroid) for setting the P_{tr} 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 O_2 supersaturation of the depth samples. PO_2 was measured first for those samples expected to have the highest content. Hemoglobin- O_2 saturation (SO_2) as measured by CO-oximeter and as calculated by blood gas analyzer (16, 54) was recorded for each sample. Measured values of SO_2 were used for samples collected at 1 ATA. For these samples, an excellent correlation was observed between measured and calculated SO_2 . At depth, it was observed that CO-oximeter measurement of SO_2 (performed at the surface after blood gas analysis) was systematically high, presumably because of transient exposure to hyperbaric air ($PO_2 = 0.56$ ATA) after injection of the sample into the blood gas analyzer. Therefore, for depth samples, the calculated values of SO_2 are reported.

Mixed expired O_2 and CO_2 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. $\dot{V}_T$ was calculated using measurements of $\dot{V}_E$ and f and was converted to BTPS. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were determined from standard equations. Fick cardiac output (CO) was calculated as $\dot{V}_{O_2}/(Ca_{O_2} - \bar{C}\bar{v}_{O_2})$, where Ca_{O_2} and $\bar{C}\bar{v}_{O_2}$ are the arterial and mixed venous O_2 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: $EWOB = \int P dV$, 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 Pa_{CO_2} 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 $\dot{V}_{O_2}$, depth, submersion, resistance, P_{tr} , inspired PO_2 , HCVR slope, forced vital capacity, and $\dot{V}_{O_{2max}}$, as well as the two-way interactions of $\dot{V}_{O_2}$ with all the other terms. Nonsignificant effects were removed from the model in a stepwise manner until only significant effects remained. $\dot{V}_{CO_2}$ and the $\dot{V}_{O_2}/\dot{V}_{O_{2max}}$ fraction were also tested in place of $\dot{V}_{O_2}$ as alternative measures of level of exercise. Depth, submersion, resistance, and P_{tr} were treated as categorical yes-no variables. Because depth has been previously shown to increase Pa_{CO_2} , 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 $\alpha = 0.05$, 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 O_2 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 paresthesias (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: PO_2 of 0.7, 1.0, and 1.3 ATA (*condition a*), P_{tr} of -10 , 0 , and $+10$ cmH $_2$ O (*condition b*), PO_2 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*.

Table 1. *Subject characteristics*

Subj No.	Sex	Age, yr	Height, cm	Weight, kg	Body Fat, %	Maximal O ₂ Uptake, ml·kg ⁻¹ ·min ⁻¹	HCVR, l·min ⁻¹ ·Torr ⁻¹	FVC, liters	Condition
1	M	30.7	173.0	68.4	13.5	51.4	1.16	4.3	a,b,c,d
2	M	30.5	178.0	66.2	9.8	55.3	0.88	5.3	a,b
3	F	29.0	173.0	94.8	19.6	60.5	0.54	5.6	a
4	M	21.5	185.0	73.1	9.2	71.6	1.72	5.8	b
5	M	33.4	193.0	97.5	11.1	72.9	0.64	8.4	b,c
6	M	46.0	173.0	72.8	11.0	49.6	0.66	5.5	a
7	F	25.0	160.0	62.3	17.6	72.1	1.14	5.1	a
8	M	23.7	175.0	77.6	12.1	66.4	0.32	6.3	a,b,c
9	M	23.0	175.0	71.9	8.9	50.3	0.48	5.5	a
10	M	37.0	173.0	86.7	26.7	43.9	0.48	6.0	c
11	M	20.5	185.0	73.7	4.1	48.8	0.99	7.9	a
12	M	22.7	180.0	94.8	24.7	35.0	1.23	5.5	a
13	M	30.1	183.0	77.6	11.8	49.4	0.44	5.6	b
14	M	30.3	180.0	92.5	13.2	67.1	1.61	6.3	b,c,d
15	F	36.9	173.0	69.2	25.0	37.7	0.97	4.8	b,c,d
16	M	25.1	173.0	73.1	13.2	41.8	2.06	5.9	b
17	F	36.3	160.0	75.3	35.1	42.7	1.08	3.9	b
18	M	23.5	183.0	87.9	13.0	59.6	5.04	7.1	c
19	M	26.9	180.0	81.6	13.3	48.9	1.02	6.8	c
20	M	43.6	178.0	92.9	22.8	31.9	1.53	5.6	c,d
21	M	24.4	178.0	75.2	4.2	42.4	1.27	7.0	d
22	M	42.1	175.0	76.6	6.3	55.0	0.87	5.8	d
23	M	40.1	180.0	78.2	18.1	52.3	1.17	5.5	d
24	M	29.8	191.0	99.9	13.0	39.9	1.37	6.8	d
25	M	39.7	173.0	80.8	19.5	38.0	0.24	6.1	d
Mean ± SD		30.9 ± 7.5	177.2 ± 7.6	80.0 ± 10.5	15.1 ± 7.4	51.4 ± 11.9	1.16 ± 0.93	5.9 ± 1.0	

HCVR; hypercapnic ventilatory response; FVC; forced vital capacity. Subjects were studied under one or more of the following conditions during exercise: Po₂ = 0.7, 1.0, and 1.3 ATA (*condition a*), transrespiratory pressure (P_{tr}) = -10, 0, and +10 cmH₂O (*condition b*), Po₂ = 0.7 and 1.3 ATA with heavier exercise (*condition c*), and low, medium, and high breathing resistance (*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.

$\dot{V}_E$ and fractional dead space. At the surface, $\dot{V}_E$ (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 $\dot{V}_E$ to fall still further (31% decrease from dry, $P < 0.01$). The addition of resistance, P_{tr}, or different inspired Po₂ at depth did not result in a significant change in $\dot{V}_E$. A higher work rate at the surface and at depth was associated with an increase in $\dot{V}_E$ ($P < 0.05$ in both cases). $\dot{V}_E$ results appear in Table 2, along with f, PaCO₂, arterial Po₂ (PaO₂), mixed venous PCO₂ (P $\bar{V}_{CO_2}$), mixed venous Po₂ (P $\bar{V}_{O_2}$), $\dot{V}_{CO_2}$, $\dot{V}O_2$, 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 $\dot{V}_E$, and the magnitude of the error increases with gas density. However, the change demonstrated here is a decrease in $\dot{V}_E$ for the transition to depth, so although an inertance error could underestimate a decrease in $\dot{V}_E$, it cannot account for the observed change in $\dot{V}_E$.

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_{tr} (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 cmH₂O P_{tr} ($P < 0.01$ for depth vs. depth and +10 cmH₂O

P_{tr}). 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. I resistance. OMPS was higher during Mod ($P = 0.01$) and Hi ($P < 0.005$). 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.

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

During Mod breathing air without P_{tr} at 4.7 ATA, $\dot{V}_{CO_2}$ was not significantly different from surface values ($P = 0.10$). Hi increased $\dot{V}_{CO_2}$ from Mod values for submersed ($P = 0.04$) conditions. At depth, varying inspired Po₂ did not affect $\dot{V}_{CO_2}$, but positive P_{tr} produced an effect that approached statistical significance ($\dot{V}_{CO_2}$ higher with positive and negative P_{tr}, $P = 0.06$). There was no significant change in $\dot{V}_{CO_2}$ with the addition of breathing resistance.

P $\bar{V}_{CO_2}$, P $\bar{V}_{O_2}$, and Fick CO. P $\bar{V}_{CO_2}$ 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 Po₂ and the addition of P_{tr} or breathing

Table 2. Minute ventilation and other respiratory variable results

Condition	Work Level	Po ₂ , ATA	n	Minute Ventilation, l/min	Arterial Pco ₂ , Torr	Arterial Po ₂ , Torr	Mixed Venous Pco ₂ , Torr	Mixed Venous Po ₂ , Torr	O ₂ Uptake, l/min	CO ₂ Output, l/min	OMPS, cmH ₂ O	Fick CO, l/min
<i>Rest at 1.0 ATA</i>												
Dry		0.2	38	12.4±1.9	34.6±4.0	98.3±18.1	38.7±7.8	36.5±2.6	0.33±0.07	0.26±0.05	1.2±0.4	5.1±1.0
Submersed		0.2	38	10.7±4.8	35.6±3.7	108.5±16.4	40.4±4.5	39.8±4.5	0.32±0.12	0.26±0.10	1.4±0.6	6.1±2.1
<i>Exercise at 1.0 ATA</i>												
Dry	Mod	0.2	29	89.2±22.9	31.5±5.1	101.0±13.1	54.2±7.2	25.0±4.1	2.44±0.28	2.53±0.42	3.7±1.6	16.8±3.5
Submersed	Mod	0.2	29	76.3±20.5	34.2±4.8	105.6±10.1	53.8±7.0	25.8±2.8	2.27±0.44	2.23±0.48	3.4±1.5	17.6±2.9
Dry	Hi	0.2	9	111.4±25.6	29.2±3.1	97.7±14.7	50.1±9.2	24.1±4.2	2.92±0.81	3.10±0.82	4.1±1.3	21.1±3.9
Submersed	Hi	0.2	9	110.9±25.7	30.4±3.1	105.0±14.0	53.4±6.2	24.8±2.7	2.68±0.86	2.79±0.86	4.5±1.3	19.2±4.4
<i>Exercise at 4.7 ATA</i>												
0 cmH ₂ O P _{tr}	Mod	1.0	19	61.6±13.9	46.1±5.9	616.2±52.3	70.6±8.1	31.2±3.5	2.37±0.39	2.09±0.37	4.7±1.6	18.1±2.1
-10 cmH ₂ O P _{tr}	Mod	1.0	8	61.6±8.3	44.7±5.3	611.1±52.6	65.7±15.4	31.7±3.6	2.33±0.56	2.20±0.50	4.9±1.2	15.7±3.1
+10 cmH ₂ O P _{tr}	Mod	1.0	8	65.1±12.4	46.1±2.5	608.3±36.2	71.9±8.7	31.3±4.1	2.44±0.54	2.23±0.47	5.8±1.7	21.7±3.2
0 cmH ₂ O P _{tr}	Mod	0.7	10	62.1±13.2	47.1±4.7	445.4±85.1	69.8±4.8	29.7±2.9	2.15±0.40	2.12±0.36	4.7±1.2	19.8±5.2
0 cmH ₂ O P _{tr}	Mod	1.3	10	61.5±14.4	46.3±4.6	825.6±60.7	72.4±8.5	32.2±3.9		2.08±0.34	4.1±1.0	
0 cmH ₂ O P _{tr}	Hi	0.7	9	76.5±9.3	43.7±6.5	506.0±120.1	71.2±9.5	30.0±4.0	2.77±0.99	2.65±0.63	6.2±2.2	18.3±2.5
0 cmH ₂ O P _{tr}	Hi	1.3	9	73.2±11.4	45.0±5.7	776.1±101.7	73.7±11.7	33.3±3.7		2.55±0.57	6.9±4.6	
14.88 I Resist	Mod	1.0	4	58.7±9.6	45.9±4.2	665.5±69.0	73.9±7.3	32.0±1.4	2.22±0.26	1.91±0.26	22.7±5.0	14.3±3.5
11.6 I Resist	Mod	1.0	5	53.2±8.7	47.8±5.5	605.5±56.6	71.5±7.4	30.4±2.5	2.35±0.47	1.93±0.36	29.6±5.0	18.8±2.9
14.88 IE Resist	Mod	1.0	6	55.1±7.5	48.0±5.9	650.3±21.6	72.3±8.0	31.5±3.0	2.42±0.31	1.95±0.22	27.5±6.7	18.3±2.7
10.23 I Resist	Mod	1.0	4	50.6±8.7	48.4±4.2	644.3±81.3	71.7±0.7	30.0±1.2	2.29±0.09	1.80±0.13	34.8±4.9	16.2±0.4
11.6 IE Resist	Mod	1.0	3	48.7±7.3	49.1±1.5	640.7±20.0	74.4±4.7	31.2±2.6	2.40±0.43	1.96±0.30	49.2±6.5	18.3±4.8
10.23 IE Resist	Mod	1.0	2	44.6±3.7	54.5±4.2	635.5±74.2	76.1±0.5	32.5±3.5	2.48±0.09	1.87±0.06	50.3±4.7	19.7±4.4

Values are means ± SD; n, number of measurements for each condition, in some cases including >1 measurement for a handful of subjects. P_{tr}, transrespiratory pressure; OMPS, oronasal mask pressure swing (inspired and expired pressure difference); Fick CO, Fick cardiac output. O₂ uptake and Fick CO are not reported for 1.3 ATA Po₂ because of possible contamination of gas samples.

resistance did not affect P_VCO₂. There was no significant difference in P_VCO₂ between Mod and Hi. There was no change in Fick CO with the transition to depth.

The effect of submersion, exercise, and pressure on P_VO₂ was essentially the opposite of the effect on P_VCO₂. The

transition from rest to exercise lowered P_VO₂ in dry ($P < 0.0001$) and submersed ($P < 0.0001$) conditions. However, P_VO₂ increased with pressure during Mod with submersion ($P < 0.0001$). The corresponding venous O₂ saturation in-

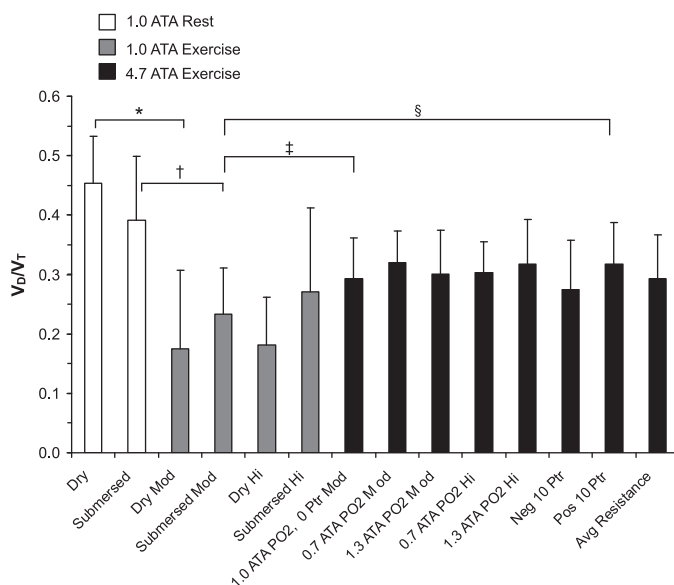


Fig. 2. Fractional dead space [i.e., ratio of dead space to tidal volume (V_d/V_t)] during rest and exercise for different conditions. Mod, 60% of maximal O₂ consumption ($\dot{V}_{O_{2max}}$); Hi, 80% of $\dot{V}_{O_{2max}}$. Values are means ± SD. * $P < 0.05$, dry rest vs. dry Mod at surface. † $P < 0.05$, 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 (P_{tr}).

Table 3. Dead space and tidal volume results

Condition	Work Level	Po ₂ , ATA	n	Vd/Vt	Vt, liters	f, min ⁻¹
<i>Rest at 1.0 ATA</i>						
Dry		0.2	38	0.45±0.08	1.0±0.3	14.6±2.7
Submersed		0.2	38	0.39±0.11	1.1±0.6	11.7±3.3
<i>Exercise at 1.0 ATA</i>						
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
<i>Exercise at 4.7 ATA</i>						
0 cmH ₂ O P _{tr}	Mod	1.0	19	0.29±0.07	2.4±0.5	27.0±8.0
-10 cmH ₂ O P _{tr}	Mod	1.0	8	0.27±0.08	2.4±0.5	27.3±6.5
+10 cmH ₂ O P _{tr}	Mod	1.0	8	0.32±0.07	2.3±0.4	27.9±7.0
0 cmH ₂ O P _{tr}	Mod	0.7	10	0.32±0.05	2.4±0.5	26.9±5.5
0 cmH ₂ O P _{tr}	Mod	1.3	10	0.30±0.07	2.5±0.4	26.7±5.8
0 cmH ₂ O P _{tr}	Hi	0.7	9	0.30±0.05	2.4±0.5	32.4±7.1
0 cmH ₂ O P _{tr}	Hi	1.3	9	0.32±0.08	2.4±0.5	30.0±6.6
14.88 I Resist	Mod	1.0	4	0.34±0.05	2.5±0.6	26.4±9.4
11.6 I Resist	Mod	1.0	5	0.27±0.11	2.8±1.9	18.4±6.5
14.88 IE Resist	Mod	1.0	6	0.31±0.08	3.1±0.6	25.3±10.5
10.23 I Resist	Mod	1.0	4	0.26±0.08	2.7±0.6	17.7±4.6
11.6 IE Resist	Mod	1.0	3	0.30±0.07	3.2±0.5	20.1±7.8
10.23 IE Resist	Mod	1.0	2	0.29±0.02	3.2±0.4	15.0±0.8

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

Table 4. *EWOB/V for resistor plate combinations*

Resist	EWOB/V, J/l	
	Inspired	Average
Surface, no resist	0.048 ± 0.003	
Depth, no resist	0.052 ± 0.003	
Aperture diameter for restrictors, mm		
14.9 (I)	1.55 ± 0.44	1.05 ± 0.56
11.6 (I)	1.66 ± 0.39	1.42 ± 0.40
14.9 (IE)	2.30 ± 0.53	1.28 ± 0.26
10.2 (I)	2.47 ± 0.75	1.72 ± 0.84
11.6 (IE)	2.70 ± 0.69	2.09 ± 0.34
10.2 (IE)	2.22 ± 0.15	2.15 ± 0.39

Values are means ± SD. Inspired external work of breathing per volume (EWOB/V) was calculated for submersed exercise at the surface and at depth without and with added resistance. Average EWOB/V is mean EWOB over an entire breath for exercise at depth with resistance only. I, inspired resistance only; IE, inspired and expired resistance.

creased from $35.6 \pm 6.4\%$ at 1 ATA submersed to $44.9 \pm 6.9\%$ at 4.7 ATA. $\dot{V}\bar{V}_{O_2}$ increased from 0.7 ATA PO_2 to 1.3 ATA PO_2 for Mod ($P = 0.01$) and Hi ($P < 0.0001$). Addition of respiratory resistance or P_{tr} did not affect $\dot{V}\bar{V}_{O_2}$.

HCVR slope and $\dot{V}O_{2max}$. A plot of Pa_{CO_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 Pa_{CO_2} vs. $\dot{V}O_{2max}$ and HCVR slope vs. $\dot{V}O_{2max}$ show no correlation between the variables ($P = 0.16$ and 0.79 , respectively).

Pa_{CO_2} . From rest to Mod, Pa_{CO_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). Pa_{CO_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 Pa_{CO_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 Pa_{CO_2} of added resistance ($P = 0.06$). There was also no significant difference between Pa_{CO_2} values during Mod for the different inspired PO_2 or P_{tr} and the Pa_{CO_2} at 4.7 ATA during air breathing with 0 cmH₂O P_{tr} .

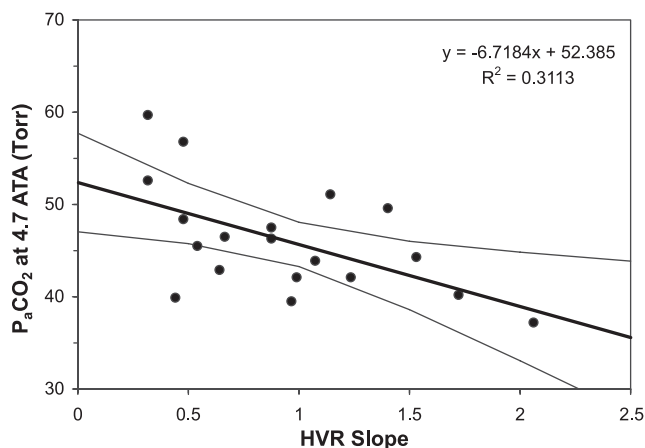


Fig. 3. Arterial PCO_2 (Pa_{CO_2}) during exercise at depth vs. hypercapnic ventilatory response (HCVR) slope with line of best fit (solid line) at 4.7 ATA during Mod with 0 cmH₂O P_{tr} and 1.0 ATA PO_2 . Dashed lines, 95% confidence intervals. $P = 0.01$.

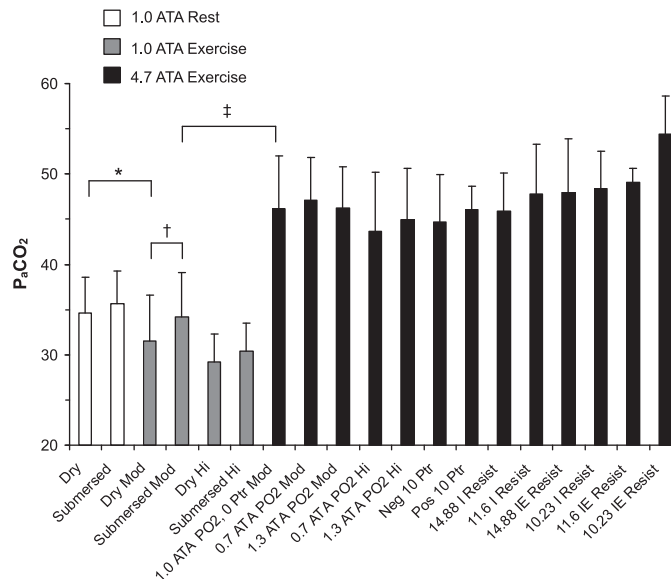


Fig. 4. Pa_{CO_2} for each condition. I, inhaled; IE, inhaled and exhaled. Values are means ± SD. * $P < 0.05$, dry rest vs. dry Mod at surface. † $P < 0.05$, dry Mod vs. submersed Mod at surface. ‡ $P < 0.05$, submersed Mod at surface vs. submersed Mod at depth.

Predictors of Pa_{CO_2} . The final predictive model found significant simultaneous independent effects on Pa_{CO_2} of depth, resistance, HCVR slope, and $\dot{V}O_{2max}$, with no significant effect of $\dot{V}O_2$. Since depth is already known to raise Pa_{CO_2} , the model was also used without depth as a variable, incorporating only data points from depth measurements. Resistance, HCVR slope, and $\dot{V}O_{2max}$ were still found to be significant. When used as alternative measures of exercise, $\dot{V}CO_2$ and the $\dot{V}O_2/\dot{V}O_{2max}$ fraction similarly showed no significant effect. None of the two-way interactions with $\dot{V}O_2$ were significant, nor was the interaction of $\dot{V}O_2$ with $\dot{V}O_{2max}$. P_{tr} and inspired PO_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 Pa_{CO_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 Pa_{CO_2} as predicted by the final statistical model based on inputs of depth, resistance, HCVR slope, and $\dot{V}O_{2max}$ plotted against measured values for Pa_{CO_2} , as well as the predicted Pa_{CO_2} for the model without depth as an input.

Table 5. *Independent predictors of arterial Pco_2*

Variable	Coefficient	F	P
Depth	13.14 ± 0.65	416	<0.0001
Resistance	4.29 ± 1.10	15.42	0.006
HCVR slope, $l \cdot \min^{-1} \cdot \text{Torr}^{-1}$	-1.78 ± 0.73	5.93	0.02
Maximal O_2 uptake, $ml \cdot \min^{-1} \cdot kg^{-1}$	0.14 ± 0.05	7.46	0.01
Resistance	5.08 ± 1.1	20.07	0.02
HCVR slope, $l \cdot \min^{-1} \cdot \text{Torr}^{-1}$	-2.04 ± 0.77	7.01	0.02
Maximal O_2 uptake, $ml \cdot \min^{-1} \cdot kg^{-1}$	0.17 ± 0.06	8.89	0.01

Coefficients are means ± SE. Depth and resistance were treated as categorical variables (0,1).

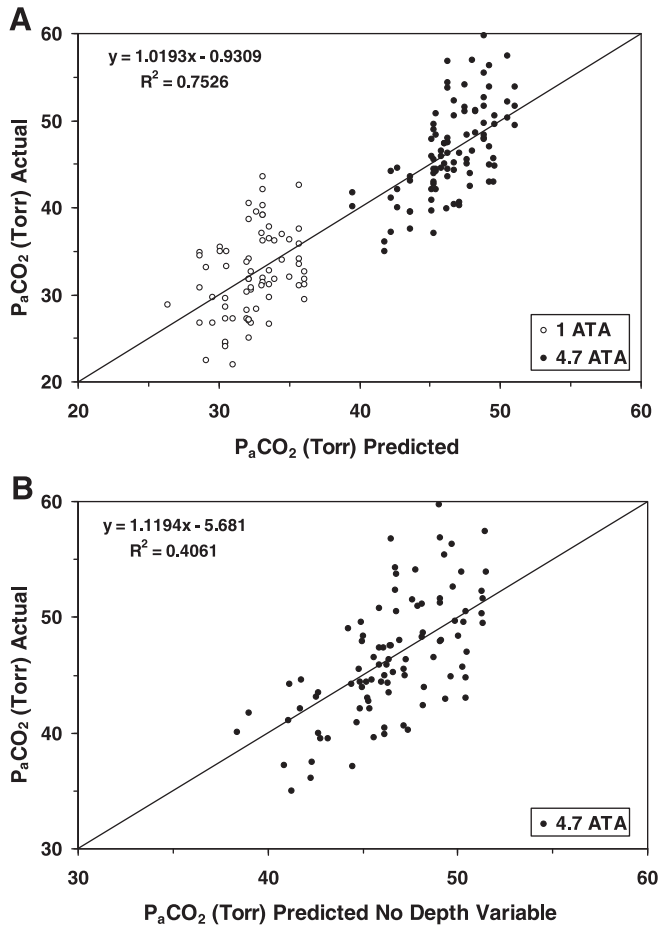


Fig. 5. A: predicted $P_a\text{CO}_2$ vs. measured $P_a\text{CO}_2$. Predicted $P_a\text{CO}_2$ is given by the final statistical model based on inputs of depth (categorical), resistance (categorical), HCVR slope ($\text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$), and $\dot{V}_{O_{2\max}}$ ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). B: predicted $P_a\text{CO}_2$ vs. measured $P_a\text{CO}_2$ as predicted by a separate statistical model based only on depth measurements. Diagonal lines, lines of identity.

DISCUSSION

$\dot{V}_E$ and dead space. The drop in $\dot{V}_E$ from 1 ATA dry to 1 ATA submersed to 4.7 ATA submersed paralleled the rise in $P_a\text{CO}_2$. Despite the increased EWOB associated with the addition of breathing resistance, a significantly smaller $\dot{V}_E$ was not observed as smaller-bore resistor plates were added. The slight rise in $\dot{V}_E$ with positive P_{tr} was also not significant. The average rise in V_D/V_T for surface vs. depth during exercise was 6%. This increase in V_D/V_T would require an increase in $\dot{V}_E$ of 6.4 l/min at depth, but instead $\dot{V}_E$ decreased by 14.7 l/min. Thus it is a combination of decreased $\dot{V}_E$ and increased V_D/V_T that caused the alveolar hypoventilation and the resulting increase in $P_a\text{CO}_2$.

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/V 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/V, since it has been used in previous studies of external breathing resistance (60).

$\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were increased, as expected, for the transition from rest to exercise. A decreased $\dot{V}_{O_2}$ 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.

P_{aO_2} , $P\bar{V}_{O_2}$, and $P\bar{V}_{CO_2}$. The marked elevation of $P\bar{V}_{CO_2}$ during exercise at depth can be partially attributed to concurrent increases in $P_a\text{CO}_2$ and $P\bar{V}_{O_2}$, since depth had no significant effect on $\dot{V}_{CO_2}$ or cardiac output. The change in $P\bar{V}_{O_2}$ resulted in a 9.3% increase in venous O_2 saturation. This would, via the Haldane effect, raise the PCO_2 of the venous blood and, presumably, the tissues (48). The slight increase in $P\bar{V}_{O_2}$ and $P\bar{V}_{CO_2}$ for changes in inspired PO_2 from 0.7 to 1.3 ATA supports this mechanism.

Predictors of increased $P_a\text{CO}_2$. During exercise, the increased pressure or gas density at depth had by far the greatest effect on $P_a\text{CO}_2$, with a calculated change in $P_a\text{CO}_2$ 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 $P_a\text{CO}_2$. 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 $P_a\text{CO}_2$, with a predicted change in $P_a\text{CO}_2$ of 4.3 ± 1.1 Torr from 1 to 4.7 ATA. Other studies have also found that added resistance raises P_{ETCO_2} (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 $P_a\text{CO}_2$.

HCVR and $\dot{V}_{O_{2\max}}$ were continuous variables. Under the conditions tested, the change in $P_a\text{CO}_2$ for $\dot{V}_{O_{2\max}}$ was predicted to be 0.14 ± 0.05 Torr $\cdot \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. This is an extremely small effect with a relatively large error, but when multiplied by the $\dot{V}_{O_{2\max}}$ range for all subjects in the study ($41 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), it predicts a change in $P_a\text{CO}_2$ of ~ 6 Torr if all other conditions are held constant. Nevertheless, a plot of $P_a\text{CO}_2$ during exercise at depth vs. $\dot{V}_{O_{2\max}}$ indicates significant individual variability ($R^2 = 0.11$, 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 $P_a\text{CO}_2$ during exercise at depth vs. HCVR (Fig. 3) reinforces the conclusion that, despite a correlation ($R^2 = 0.33$, $P = 0.01$), 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 $P_a\text{CO}_2$ during endurance events. One might expect subjects with higher $\dot{V}_{O_{2\max}}$ to have a decreased HCVR slope, but there was no correlation between $\dot{V}_{O_{2\max}}$ and HCVR slope in the subjects in the present study ($R^2 = 0.0033$, P = not

significant). Additionally, although HCVR may be lower in endurance athletes, this diminished HCVR at rest does not necessarily translate into a decreased HCVR during exercise (31).

The average HCVR in this study was lower than normal values reported by others (52). This may be partly due to differences in equipment and rate of rise of P_{CO_2} during the 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).

P_{tr} , PO_2 , and $\dot{V}O_2$ during exercise did not have an effect on Pa_{CO_2} in the present study. Since P_{tr} has been shown to increase WOB, it might be expected that a higher level of P_{tr} than that applied in the present study may have a more significant effect on Pa_{CO_2} . However, P_{tr} outside the range of ± 20 cmH₂O is extremely uncomfortable for subjects during moderate-to-heavy exercise (59) and is unlikely to be tolerated by working divers. In the present study, the analysis of the effect of PO_2 and $\dot{V}O_2$ was confounded by depth, with lower PO_2 (0.2 ATA) and resting $\dot{V}O_2$ tested only at the surface, and only higher PO_2 (0.7–1.3 ATA) and $\dot{V}O_2$ tested at depth. Thus it was not possible for the model to distinguish changes in Pa_{CO_2} for any PO_2 levels, except at 0.7–1.3 ATA and for the range of $\dot{V}O_2$ levels at exercise. We cannot exclude hyperoxia as a factor contributing to changes in Pa_{CO_2} at depth. However, increasing PO_2 from 0.7 to 1.3 ATA had no effect. This is a reassuring result for divers using enriched O_2 breathing mixtures, at least to the depth of this study. In the case of P_{tr} , no studies have shown an increase in Pa_{CO_2} 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 Pa_{CO_2} . Higher levels of breathing resistance and ambient pressures will likely increase Pa_{CO_2} 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 $\dot{V}O_{2max}$, as continuous variables, are difficult to compare with the categorical variables but appear to have a smaller impact on Pa_{CO_2} , 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 $\dot{V}O_2$, P_{tr} , and inspired PO_2 variations could augment the effect of those factors on Pa_{CO_2} . Given the low average HCVR in the study, it is possible that conclusions may not apply to those with higher CO_2 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 $\dot{V}O_{2max}$ 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 Pa_{CO_2} 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 Pa_{CO_2} , indicate that Pa_{CO_2} 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 Pa_{CO_2} is primarily attributed to the decrease in $\dot{V}_E$ 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 $\dot{V}O_{2max}$ values, whereas inspired PO_2 , P_{tr} , and small variations in $\dot{V}O_2$ did not have a significant effect. A predictive model based on inputs of depth, external breathing resistance, HCVR, and $\dot{V}O_{2max}$ shows generally good agreement between the predicted and the measured values.

GRANTS

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REFERENCES

- Adams RP, Welch HG. Oxygen uptake, acid-base status, and performance with varied inspired oxygen fractions. *J Appl Physiol* 49: 863–868, 1980.
- Begin R, Epstein M, Sackner MA, Levinson R, Dougherty R, Duncan D. Effects of water immersion to the neck on pulmonary circulation and tissue volume in man. *J Appl Physiol* 40: 293–299, 1976.
- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982.
- Byrne-Quinn E, Weil JV, Sodal IE, Filley GF, Grover RF. Ventilatory control in the athlete. *J Appl Physiol* 30: 91–98, 1971.
- Cherniack RM, Snidal DP. The effect of obstruction to breathing on the ventilatory response to CO_2 . *J Clin Invest* 35: 1286–1290, 1956.
- Chuang ML, Ting H, Otsuka T, Sun XG, Chiu FY, Beaver WL, Hansen JE, Lewis DA, Wasserman K. Aerobically generated CO_2 stored during early exercise. *J Appl Physiol* 87: 1048–1058, 1999.
- Clark TJ, Godfrey S. The effect of CO_2 on ventilation and breath-holding during exercise and while breathing through an added resistance. *J Physiol* 201: 551–566, 1969.
- Collett PW, Engel LA. Influence of lung volume on oxygen cost of resistive breathing. *J Appl Physiol* 61: 16–24, 1986.
- Craig AB Jr, Dvorak M. Thermal regulation of man exercising during water immersion. *J Appl Physiol* 25: 28–35, 1968.
- Davis FM, Graves MP, Guy HJ, Prisk GK, Tanner TE. Carbon dioxide response and breath-hold times in underwater hockey players. *Undersea Biomed Res* 14: 527–534, 1987.
- Eklblom B, Huot R, Stein EM, Thorstensson AT. Effect of changes in arterial oxygen content on circulation and physical performance. *J Appl Physiol* 39: 71–75, 1975.
- Epstein M. Renal effects of head-out water immersion in humans: a 15-year update. *Physiol Rev* 72: 563–621, 1992.
- Fagraeus L, Karlsson J, Linnarsson D, Saltin B. Oxygen uptake during maximal work at lowered and raised ambient air pressures. *Acta Physiol Scand* 87: 411–421, 1973.
- Florio JT, Morrison JB, Butt WS. Breathing pattern and ventilatory response to carbon dioxide in divers. *J Appl Physiol* 46: 1076–1080, 1979.
- Froeh HF. Ventilatory response of scuba divers to CO_2 inhalations. *J Appl Physiol* 16: 8–10, 1961.
- Gabel RA. Algorithms for calculating and correcting blood-gas and acid-base variables. *Respir Physiol* 42: 211–232, 1980.
- Gelfand R, Lambertsen CJ. Dynamic respiratory response to abrupt change of inspired CO_2 at normal and high PO_2 . *J Appl Physiol* 35: 903–913, 1973.

18. Gledhill N, Froese AB, Buick FJ, Bryan AC. $\dot{V}_A/\dot{Q}$ inhomogeneity and $AaDO_2$ in man during exercise: effect of SF_6 breathing. *J Appl Physiol* 45: 512–515, 1978.
19. Hesser CM, Linnarsson D, Fagraeus L. Pulmonary mechanisms and work of breathing at maximal ventilation and raised air pressure. *J Appl Physiol* 50: 747–753, 1981.
20. Hickam JB, Pryor WW, Page EB, Atwell RJ. Respiratory regulation during exercise in unconditioned subjects. *J Clin Invest* 30: 503–516, 1951.
21. Hickey DD, Norfleet WT, Pasche AJ, Lundgren CE. Respiratory function in the upright, working diver at 6.8 ATA (190 fsw). *Undersea Biomed Res* 14: 241–262, 1987.
22. Jarrett AS. Alveolar carbon dioxide tension at increased ambient pressures. *J Appl Physiol* 21: 158–162, 1966.
23. Kerem D, Daskalovic YI, Arieli R, Shupak A. CO_2 retention during hyperbaric exercise while breathing 40/60 nitrox. *Undersea Hyperb Med* 22: 339–346, 1995.
24. Lambertsen CJ, Owen SG, Wendel H, Stroud MW, Lurie AA, Lochner W, Clark GF. Respiratory and cerebral circulatory control during exercise at .21 and 2.0 atmospheres inspired PO_2 . *J Appl Physiol* 14: 966–982, 1959.
25. 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*. Panama City, FL: US Navy Experimental Diving Unit, 1958. (Publ. No. 7-58.)
26. 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* 87: 1428–1432, 1999.
27. Liu Z, Vargas F, Stansbury D, Sasse SA, Light RW. Comparison of the end-tidal arterial PCO_2 gradient during exercise in normal subjects and in patients with severe COPD. *Chest* 107: 1218–1224, 1995.
28. Lundgren CEG, Miller JN. Enhancement of inert gas narcosis by carbon dioxide. In: *Lung Biology in Health and Disease: The Lung at Depth*. New York: Dekker, 1999, vol. xvii.
29. Lundgren CEG, Miller JN. Identification of CO_2 retainers. In: *Lung Biology in Health and Disease: The Lung at Depth*. New York: Dekker, 1999, vol. xvii.
30. Lundgren CEG, Miller JN. Increased Work of Breathing. In: *Lung Biology in Health and Disease: The Lung at Depth*. New York: Dekker, 1999, vol. xvii.
31. McConnell AK, Semple ES. Ventilatory sensitivity to carbon dioxide: the influence of exercise and athleticism. *Med Sci Sports Exerc* 28: 685–691, 1996.
32. Miller RD, Fleisher LA. Airway resistance. In: *Miller's Anesthesia*. Philadelphia: Elsevier Churchill Livingstone, 2005.
33. Miyamoto Y, Niizeki K. Ventilatory responses during incremental exercise in men under hyperoxic conditions. *Jpn J Physiol* 45: 59–68, 1995.
34. Miyamura M, Folgering HT, Binkhorst RA, Smolders FD. Ventilatory response to CO_2 at rest and during positive and negative work in normoxia and hyperoxia. *Pflügers Arch* 364: 7–15, 1976.
35. Miyamura M, Ishida K. Adaptive changes in hypercapnic ventilatory response during training and detraining. *Eur J Appl Physiol Occup Physiol* 60: 353–359, 1990.
36. Morrison JB, Florio JT, Butt WS. The effect of insensitivity to carbon dioxide on the respiratory response to exercise at 4 ATA. *R Naval Physiol Lab Rep* 2/76 January 1976.
37. Morrison JB, Florio JT, Butt WS. Effects of CO_2 insensitivity and respiratory pattern on respiration in divers. *Undersea Biomed Res* 8: 209–217, 1981.
38. Morrison JB, Taylor NA. Measurement of static and dynamic pulmonary work during pressure breathing. *Undersea Biomed Res* 17: 453–467, 1990.
39. Mummery HJ, Stolp BW, de LDG, Doar PO, Natoli MJ, Boso AE, Archibald JD, Hobbs GW, El-Moalem HE, Moon RE. Effects of age and exercise on physiological dead space during simulated dives at 2.8 ATA. *J Appl Physiol* 94: 507–517, 2003.
40. Norfleet WT, Hickey DD, Lundgren CE. A comparison of respiratory function in divers breathing with a mouthpiece or a full face mask. *Undersea Biomed Res* 14: 503–526, 1987.
41. Ohkuwa T, Fujitsuka N, Utsuno T, Miyamura M. Ventilatory response to hypercapnia in sprint and long-distance swimmers. *Eur J Appl Physiol Occup Physiol* 43: 235–241, 1980.
42. Otis AB, Fenn WO, Rahn H. Mechanics of breathing in man. *J Appl Physiol* 2: 592–607, 1950.
43. Park KS, Choi JK, Park YS. Cardiovascular regulation during water immersion. *Appl Human Sci* 18: 233–241, 1999.
44. Pedersen MEF, Fatemian M, Robbins PA. Identification of fast and slow ventilatory responses to carbon dioxide under hypoxic and hyperoxic conditions in humans. *J Physiol* 521: 273–287, 1999.
45. 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* 33: 447–453, 2006.
46. Pirnay F, Marechal R, Dujardin R, Lamy M, Deroanne R, Petit JM. Exercise during hyperoxia and hyperbaric oxygenation. *Int Z Angew Physiol* 31: 259–268, 1973.
47. Rebuck AS, Read J. Patterns of ventilatory response to carbon dioxide during recovery from severe asthma. *Clin Sci* 41: 13–21, 1971.
48. Sahlin K, Alvestrand A, Brandt R, Hultman E. Intracellular pH and bicarbonate concentration in human muscle during recovery from exercise. *J Appl Physiol* 45: 474–480, 1978.
49. Saltzman HA, Salzano JV, Blenkarn GD, Kylstra JA. Effects of pressure on ventilation and gas exchange in man. *J Appl Physiol* 30: 443–449, 1971.
50. Salzano J, Rausch DC, Saltzman HA. Cardiorespiratory responses to exercise at a simulated seawater depth of 1,000 feet. *J Appl Physiol* 28: 34–41, 1970.
51. Salzano JV, Camporesi EM, Stolp BW, Moon RE. Physiological responses to exercise at 47 and 66 ATA. *J Appl Physiol* 57: 1055–1068, 1984.
52. Saunders NA, Heilpern S, Rebuck AS. Relation between personality and ventilatory response to carbon dioxide in normal subjects: a role in asthma? *Br Med J* 1: 719–721, 1972.
53. Scoggin CH, Doekel RD, Kryger MH, Zwillich CW, Weil JV. Familial aspects of decreased hypoxic drive in endurance athletes. *J Appl Physiol* 44: 464–468, 1978.
54. Severinghaus JW. Simple, accurate equations for human blood O_2 dissociation computations. *J Appl Physiol* 46: 599–602, 1979.
55. Sherman D, Eilender E, Shefer A, Kerem D. Ventilatory and occlusion-pressure responses to hypercapnia in divers and non-divers. *Undersea Biomed Res* 7: 61–74, 1980.
56. Smith RM, Hong SK, Dressendorfer RH, Dwyer HJ, Hayashi E, Yelverton C. Hana Kai II: a 17-day dry saturation dive at 18.6 ATA. IV. Cardiopulmonary functions. *Undersea Biomed Res* 4: 267–281, 1977.
57. Song SH, Kang DH, Kang BS, Hong SK. Lung volumes and ventilatory responses to high CO_2 and low O_2 in the ama. *J Appl Physiol* 18: 466–470, 1963.
58. Tabakin BS, Hanson JS. Response to ventilatory obstruction during steady-state exercise. *J Appl Physiol* 15: 579–582, 1960.
59. Thalmann ED, Sponholtz DK, Lundgren CE. Effects of immersion and static lung loading on submerged exercise at depth. *Undersea Biomed Res* 6: 259–290, 1979.
60. Warkander DE, Nagasawa GK, Lundgren CE. Effects of inspiratory and expiratory resistance in divers' breathing apparatus. *Undersea Hyperb Med* 28: 63–73, 2001.
61. Warkander DE, Norfleet WT, Nagasawa GK, Lundgren CE. CO_2 retention with minimal symptoms but severe dysfunction during wet simulated dives to 6.8 atm abs. *Undersea Biomed Res* 17: 515–523, 1990.
62. Warkander DE, Norfleet WT, Nagasawa GK, Lundgren CE. Physiologically and subjectively acceptable breathing resistance in divers' breathing gear. *Undersea Biomed Res* 19: 427–445, 1992.
63. Welch HG, Pedersen PK. Measurement of metabolic rate in hyperoxia. *J Appl Physiol* 51: 725–731, 1981.
64. Williams JS, Babb TG. Differences between estimates and measured $Paco_2$ during rest and exercise in older subjects. *J Appl Physiol* 83: 312–316, 1997.
65. Wilson BA, Welch HG, Liles JN. Effects of hyperoxic gas mixtures on energy metabolism during prolonged work. *J Appl Physiol* 39: 267–271, 1975.
66. Wood LD, Bryan AC. Exercise ventilatory mechanics at increased ambient pressure. *J Appl Physiol* 44: 231–237, 1978.
67. Wood LD, Bryan AC, Bau SK, Weng TR, Levison H. Effect of increased gas density on pulmonary gas exchange in man. *J Appl Physiol* 41: 206–210, 1976.
68. Wylegala JA, Pendergast DR, Gosselin LE, Warkander DE, Lundgren CE. Respiratory muscle training improves swimming endurance in divers. *Eur J Appl Physiol* 99: 393–404, 2007.
69. Zechman F, Hall FG, Hull WE. Effects of graded resistance to tracheal air flow in man. *J Appl Physiol* 10: 356–362, 1957.