Exercise carbon dioxide (CO_2) retention with inhaled CO_2 and breathing resistance

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ABSTRACT

Combined effects on respiratory minute ventilation ($\dot{V}_E$) — and thus, on end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) — of breathing resistance and elevated inspired carbon dioxide (CO_2) had not been determined during heavy exercise. In this Institutional Review Board-approved, dry, sea-level study, 12 subjects in each of three phases exercised to exhaustion at 85% peak oxygen uptake while $\dot{V}_E$ and $P_{ET}CO_2$ were measured. Participants inhaled 0%, 1%, 2% or 3% CO_2 in air, or 0% or 2% CO_2 in oxygen, with or without breathing resistance, mimicking the U.S. Navy's MK 16 rebreather underwater breathing apparatus (UBA). Compared to air baseline (0% inspired CO_2 in air without resistance):

1. Oxygen decreased baseline $\dot{V}_E$ ($p<0.01$);
2. Inspired CO_2 increased $\dot{V}_E$ and $P_{ET}CO_2$ ($p<0.01$);
3. Resistance decreased $\dot{V}_E$ ($p<0.01$);
4. Inspired CO_2 with resistance elevated $P_{ET}CO_2$ ($p<0.01$). In air, $\dot{V}_E$ did not change from that with resistance alone. In oxygen, $\dot{V}_E$ returned to oxygen baseline.

End-exercise $P_{ET}CO_2$ exceeded 60 Torr (8.0 kPa) in three tests. Subjects identified hypercapnia poorly. Results support dual optimization of arterial carbon dioxide partial pressure and respiratory effort. Because elevated CO_2 may not increase $\dot{V}_E$ if breathing resistance and $\dot{V}_E$ are high, rebreather UBA safety requires very low inspired CO_2.

INTRODUCTION

Working divers frequently retain carbon dioxide (CO_2) [1]. For those breathing gas with elevated partial pressure of oxygen, hypercapnia may be particularly dangerous: even mild hypercapnia may provoke central nervous system oxygen toxicity at oxygen partial pressures (PO_2) that are otherwise considered safe [2]. Divers using rebreather underwater breathing apparatus (UBAs) generally breathe gases with high PO_2. Furthermore, rebreather UBAs, which remove (scrub) metabolically produced CO_2 from exhaled gas before the gas is breathed again, supply elevated inspired CO_2 when their scrubbers are mostly expended. Equally important, they often provide considerable inspiratory and expiratory breathing resistance.Thus, divers using rebreather UBAs may be faced with combined effects of inspired CO_2 and external breathing resistance. The implications of this combination for CO_2 retention at exercise have previously been explored only partly.

In divers under pressure, internal mechanical factors tend to induce hypercapnia independent of external breathing resistance and inspired CO_2 [1]. Respiratory minute ventilation ($\dot{V}_E$) is reduced at depth relative to that at the surface because of the increased gas density: Internal work of breathing increases, as does expiratory flow limitation, which increases end expiratory volume and thus augments elastic load. $\dot{V}_E$ is also reduced by immersion because translocation of blood increases lung stiffness. Additionally, hydrostatic loading is generally unavoidable for immersed divers. The reduction of $\dot{V}_E$ caused by depth and immersion are additive even during moderate exercise [3]. Further, even moderate depth (18.3 meters of sea water [msw], or 2.8 atmospheres absolute [atm abs]) has been shown to reduce the efficiency of $\dot{V}_E$ at removing CO_2 by increasing physiologic dead space relative to that at the surface [4]. Thus, immersed divers tend to retain CO_2 for multiple reasons. Conditions which cause CO_2 retention on the surface can be expected to add at depth to those other causes.

In air at ambient pressure, subjects who inhale CO_2 while resting or performing mild to moderate exercise increase $\dot{V}_E$ relative to that at the same workload without CO_2 [5-11]. However, external breathing resistance at

rest and during mild to moderate exercise diminishes the increase in $\dot{V}_E$ when CO_2 is inhaled and thus causes relative retention of CO_2 [12-14]. Subjects do not increase $\dot{V}_E$ if they inhale CO_2 while performing maximal exercise [5, 9, 11], or, for those of advanced age, while exercising above their ventilatory thresholds [11].

The further effect of added external breathing resistance on CO_2 retention during heavy exercise with inhaled CO_2 was addressed in this study. Both inspiratory and expiratory resistances were matched to those of a rebreather UBA. Measurements were made dry at 1 atm abs during exercise at 80 to 85% of the maximum rate of oxygen uptake ($\dot{V}O_{2\,max}$).

Two levels of elevated end-tidal CO_2 partial pressure ($P_{ET}CO_2$) were considered to indicate important retention of CO_2: 60 and 51 Torr (8.0 and 6.8 kPa), the higher value because divers' breathing gear is deemed unacceptable if an individual shows $P_{ET}CO_2$ greater than 60 Torr during testing [15], and the lower value because reasoning capacity in a dry laboratory setting was shown to be impeded with $P_{ET}CO_2$ greater than or equal to 51 Torr [16].

Participants were asked after they stopped exercise if they had had symptoms. Although symptoms of interest were those that might relate to hypercapnia, no list was presented to the participants.

The hypotheses were that heavy exercise would tax the respiratory system sufficiently that increases in $\dot{V}_E$ in the face of inspired CO_2 would be blunted, that respiratory resistance would cause a reduction in $\dot{V}_E$ at exercise, and that addition of inspired CO_2 to a resistive breathing circuit at heavy exercise would increase $\dot{V}_E$ towards the level without resistance until participants would be forced to stop exercise. Exercise duration was expected to be limited by respiratory fatigue or by hypercapnia.

MATERIAL AND METHODS

The study was conducted in three phases:

- Phase 1, with CO_2 in inspired air but no added resistance;
- Phase 2, with resistance in inspired air with or without CO_2; and
- Phase 3, with CO_2 in inspired oxygen, with and without resistance.

Protocols were approved by the Navy Experimental Diving Unit (NEDU) Institutional Review Board, and all participants gave written consent.

Twelve active-duty or reserve military subjects, some of whom were Navy divers, completed each phase. Subject characteristics are listed in Table 1 *(above right)*.

TABLE 1 – *Subject characteristics*

	PHASE 1 10 men 2 women 6 divers	PHASE 2 10 men 2 women 7 divers	PHASE 3 12 men 0 women 8 divers
Age (years)	35.5 27-40	38.5 32-47	37.5 20-40
Height (cm)	175 (160–190)	173 (160–185)	183 (169–193)
Body mass (kg)	82 (73–107)	81 (62–107)	87 (70–114)
Ergometer settings (W)	185 (90–210)	160 (100–250)	185 (160–250)

Table 1. Subject characteristics: Median values, with minimum to maximum in parentheses.

Only healthy non-smokers without diabetes, uncontrolled hypertension, or history of adult asthma, and with Framingham risk of cardiovascular event in the next 10 years less than 5% [17] participated. Women were not queried about menstrual phase. Subjects were instructed to refrain from heavy exercise on the morning of an experiment.

A total of 26 individuals completed the study. Seven subjects completed both Phases 1 and 2; three, both Phases 1 and 3; and two, included in the other counts, completed all three phases. Because data were analyzed only within a phase, participation in multiple phases was ignored.

Table 2 *(below)* details the test conditions. Within each phase of the study, conditions were presented to different subjects in different orders, and no subject was told which gas or resistance was used.

TABLE 2 – *Respiratory conditions*

PHASE 1	PHASE 2	PHASE 3
No air No *R*	No air No *R*	No air No *R*
2% CO_2 in air No *R*	Air Moderate *R*	O_2 No *R*
3% CO_2 in air No *R*	Air High *R*	2% CO_2 in O_2 No *R*
	1% CO_2 in air Moderate *R*	O_2 Moderate *R*
	2% CO_2 in air Moderate *R*	2% CO_2 in O_2 Moderate *R*

Table 2. Respiratory conditions for endurance exercise tests, by phase. *R* = resistance

Subjects exercised on a bicycle ergometer: for Phases 1 and 2, and for part of Phase 3, one built at NEDU in which a pedal shaft drives the shaft of a hysteresis brake (Magtrol, HB210, Buffalo, N.Y.) through a gear train. Subjects who used the hysteresis brake were required to maintain a cadence of 60 rpm. For most of Phase 3, a Monarch Ergomedic 839E cycle ergometer (Vansbro, Sweden) was used. No subject changed ergometers during a test phase.

Testing was conducted at ambient room temperature with a fan available if subjects wanted it. Peak exercise capacity and $\dot{V}O_{2\,max}$ for each subject were determined initially using graded incremental exercise (three-minute increments) from 25 Watts (W), in increments of 50 W (25 W when we deemed that a subject was nearing peak power capacity) to voluntary termination. The endurance load was selected from those data as the power setting most closely corresponding to 80% to 85% of the subject's peak $\dot{V}O_2$. In general, 85% was chosen if the subject completed most of a three-minute increment at his or her peak load, and 80% was selected if the duration at the peak load was short.

Endurance testing began with a two-minute warm-up at 50 W followed by a rapid transition to the endurance setting, and it continued until the subject stopped cycling or could not maintain cadence. Exercise endurance time was recorded, as were the reason the subject gave for stopping exercise and any symptoms reported from the exercise period. To prevent subjects from setting specific goals for themselves, they were not permitted to see the time. They were permitted to listen to music. No individual performed more than one test on any day.

Breathing gas – that is, air, O_2 or one of those gases mixed with CO_2 – was available for the subjects to breathe at ambient pressure from a volume tank, a 120-L spirometer (Collins; Braintree, Mass.). For Phase 3, O_2 or premixed CO_2 in O_2 filled the reservoir, but for Phases 1 and 2, CO_2 was added to air on the fly [18]. Air flow from a pressurized source was set manually to maintain a sufficient buffer volume to accommodate the subject's $\dot{V}_E$, and measured with a mass flow meter (Model FMA1843, Omega Engineering, Stamford Conn.). From the instantaneously measured air flow, a control box built for the study determined the CO_2 flow needed for the selected inspired fraction of CO_2 and provided that signal to a mass flow controller (Model 8272-0414, Matheson Gas Products, Montgomeryville, Pa.), which fed CO_2 into the inlet line to the spirometer. A two-channel CO_2 analyzer (Rosemount MLT, Rosemount Analytical Inc., Solon, Ohio), monitored the composition of the gas entering the spirometer and of that leaving the spirometer to the subject (F_ICO_2, the fractional concentration of inspired CO_2). F_ICO_2 could be fine-tuned by adjusting the selected gas fraction. Deviation from target F_ICO_2 was less than 0.05%.

Subjects breathed from the reservoir through wide-bore tubing and a T-piece (28.6 mm i.d.) containing a system of one-way valves attached to an oronasal mask (Hans Rudolph, Kansas City, Mo.). The inspiratory resistance element, when used, was inserted inside the inspiratory end of the T-piece. To reduce moisture condensation on the expiratory resistance, that element, when used, was attached to the downstream end of the non-elastic expiratory hose.

The resistance elements for Phases 2 and 3 were constructed to match characteristics of the U.S. Navy MK 16 UBA at 50 feet of sea water (fsw) (154 kPa). The resistances were designed to represent conditions for a diver working and breathing hard enough to reach the maximally acceptable work of breathing per tidal volume (WOB/V_T) with his apparatus. Maximum tolerable external WOB/V_T for diving gear at the surface is 2.99 kPa [19]. In unmanned MK 16 tests conducted specifically for this study, the average ratio of expiratory to inspiratory WOB/V_T was 1.9 [standard deviation (SD) = 0.3]. The WOB/V_T was therefore partitioned into approximately 1 kPa on inspiration and 2 kPa on expiration.

The pressure-flow data from those unmanned tests of the MK 16 indicated that the resistive component of expiratory pressure was nearly linear with flow, and that of inspiratory pressure was quadratic with flow. For our experiment, orifices provided turbulent, inspiratory pressure drops and layers of jersey knit cloth stretched over the downstream end of the expiratory hose gave laminar expiratory resistance. High resistance was designed to provide WOB/V_T = 3 kPa if $\dot{V}_E$ equaled the median value measured in Phase 1 with air alone. Moderate resistance was designed for that WOB/V_T if $\dot{V}_E$ equaled the median value measured with 2% CO_2 in air. Respiratory measurements were made using the Cosmed k4b2 (Cosmed USA, Chicago, Ill.), in which expired gas passes through a turbine flow meter (0–20 $L{\cdot}s^{-1}$ ± 1%, resolution 4 mL) that measures $\dot{V}_E$, respiratory frequency (f_R) and tidal volume (V_T) breath by breath. Unlike laminar flow element pneumotachographs, turbine-flow meters are insensitive to gas viscosity. Oxygen and carbon dioxide partial pressures were sampled immediately downstream of the turbine, through a length of Nafion tubing to extract water vapor. Values were used

to determine $\dot{V}O_2$ in air and $P_{ET}CO_2$. The non-dispersive infrared (NDIR) CO_2 analyzer (response time <120 milliseconds (ms) for 90% full scale) has a reported range of 0-8% but agreed with a mass spectrometer (MGA 1100, Marquette Electronics, Milwaukee, Wis.) to just above 10%.

Although $P_{ET}CO_2$ overestimates arterial CO_2 partial pressure (P_aCO_2), the two values are correlated at exercise in subjects younger than 40 years old [4, 20], with a reported difference of about 5 Torr at heavy exercise [4]. In this study $P_{ET}CO_2$ was used as a surrogate for P_aCO_2, with values expressed on a dry gas basis.

Variables were measured breath by breath, but averages over 1.5 to 2 minutes were used. Data were graphed as functions of time and inspected for steady state conditions before the duration of the averages was chosen. Most values reported are for periods ending 30 seconds before termination of the endurance exercise. However, average $P_{ET}CO_2$ is also reported for the 1.5- to 2-minute period when it was highest, usually early in the endurance exercise.

We measured ventilatory sensitivity to CO_2 at rest using the rebreathing method described by Read and Leigh [21]. Subjects inhaled 7% CO_2 in O_2 from residual volume and rebreathed for no more than six minutes or until $P_{ET}CO_2$ reached 70 Torr (9.3 kPa). Ventilatory sensitivity to CO_2 was measured as the slope of the line relating $\dot{V}_E$ to $P_{ET}CO_2$.

Statistics

Comparisons of $\dot{V}_E$ and $P_{ET}CO_2$ within each phase were made using repeated measures analysis of variance (ANOVA) with contrasts. Phase 1 contrasts compared 0% CO_2 to 2% inhaled CO_2 and 2% to 3% inhaled CO_2. Phase 2 contrasts compared baseline (no resistance or inhaled CO_2) to the averages of moderate and high resistance and of 2% inhaled CO_2 with and without resistance. Phase 3 contrasts compared O_2 with no resistance or inspired CO_2 (baseline O_2) to each of O_2 with moderate resistance, O_2 with 2% inspired CO_2, and O_2 with resistance and inspired CO_2. Within Phase 3 effects of background gas alone (air only *vs.* O_2 only) were assessed using paired T-tests. Differences were considered significant if $p<0.05$. Exercise endurance times and changes in endurance times were not normally distributed. Changes in endurance time were assessed using the Wilcoxon Rank Sum test. Fisher's Exact test was used to examine correlations between reports of symptoms that might relate to hypercapnia and $P_{ET}CO_2$.

TABLE 3 – *Unencumbered sustained $\dot{V}_E$ [L·min^{-1}] during heavy exercise*

		mean	SD	median	max.	min.
air	Phase 1	84	20	88	116	48
	Phase 2	101	23	96	154	72
	Phase 3	96	19	96	143	72
O_2	Phase 3	81	11	81	100	62

RESULTS

In Phase 1, $\dot{V}_E$ and $P_{ET}CO_2$ are reported for only 10 of the 12 subjects. For one subject, a female non-diver participating in both Phases 1 and 2, the mask seal could not be maintained; and for one subject, a male diver, the workload was incorrect for one of the conditions. Endurance data are reported for only nine subjects because we stopped one male diver after 60 minutes of exercise under each condition.

Some Phase 2 subjects were excluded from analysis also. Only nine of the 12 subjects were in included in statistical analysis of $\dot{V}_E$ and $P_{ET}CO_2$: data were not used from the subject excluded in Phase 1 because her mask did not seal, or from two other subjects who had evidence of occasional mask leaks during sessions with high resistance or inspired CO_2 and moderate resistance. The endurance data were used for the subjects with transient leaks, but data from one male non-diver were excluded because he failed to follow restrictions on heavy exercise before experiments. Data in Phase 3 are reported for 12 subjects, except that endurance data are reported for only 11. Again, we stopped one diver after 60 minutes of exercise under some conditions.

Minute ventilation

Heavy endurance exercise was accompanied by the anticipated high $\dot{V}_E$ (Table 3, *above*), mean 92 SD 19) L·min^{-1} if averaged over all the air-only measurements, and 81 (SD 11) L·min^{-1} when measured in O_2. The addition of CO_2 in the absence of added resistance increased $\dot{V}_E$ in air (*Figure 1a*) and in O_2 (*Figure 1b*; both $p<0.01$ – *both on facing page*) with no difference between 2% and 3% inspired CO_2 in air *(Figure 1a)*. The increased $\dot{V}_E$ in air resulted from an increased f_R, while that in O_2 was generated by

FIGURE 1a – *Percentage change from air alone*

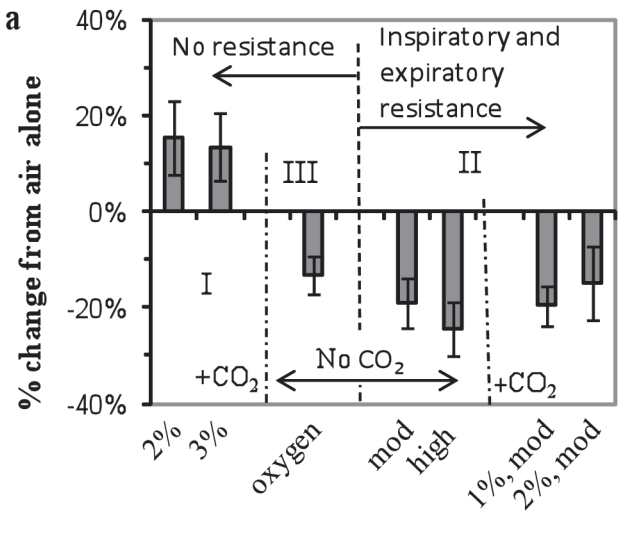


FIGURE 1b – *Percentage change from O_2 alone*

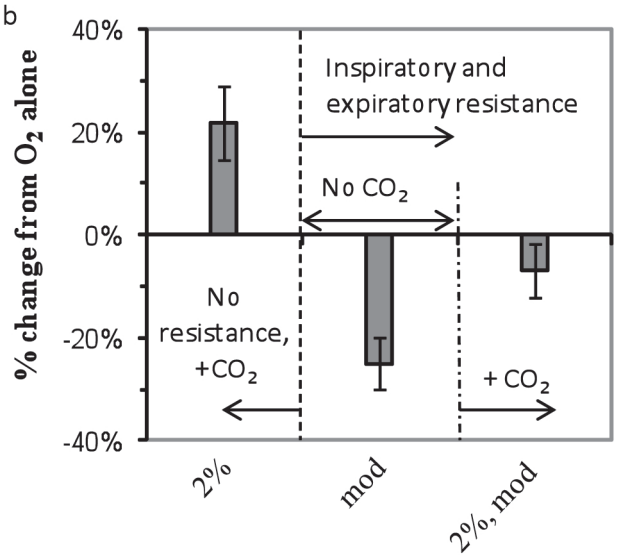


Figure 1. Minute ventilation at end exercise, fractional changes from baseline, mean and standard error.
a) Changes in $\dot{V}_E$ relative to unencumbered air breathing. Roman numerals I – III indicate experimental phase.
b) Phase 3, background O_2. Percentages are inspired CO_2, and mod (moderate) and high refer to combined inspiratory and expiratory resistance.

increasing V_T. Resistive elements in the circuit decreased $\dot{V}_E$ in air and O_2 when no CO_2 was added (*Figures 1a, b*; both $p<0.01$), by decreasing f_R in both gases, and by also decreasing V_T when O_2 was breathed. $\dot{V}_E$ was lower with high resistance in air than with moderate resistance in air ($p<0.02$) *(Figure 1a)*. Surprisingly, when the circuit contained moderate resistance, the addition of 1% or 2% CO_2 to air did not change $\dot{V}_E$ from that with moderate resistance alone (*Figure 1a*; $p>0.9$), while the addition of 2% inspired CO_2 to O_2 restored $\dot{V}_E$ with moderate resistance to a value not different from that in O_2 without resistance (Figure 1b). With breathing resistance and 2% inspired CO_2 in O_2, f_R did not differ from that without CO_2, but V_T matched that at O_2 baseline.

Without added resistance or inspired CO_2, $\dot{V}_E$ during O_2 breathing was 13% lower than that during air breathing in Phase 3 ($p<0.01$), with a marginal difference in f_R between them (Air: 44 [SD 9] breaths·min^{-1}; O_2: 39 [SD 9] breaths·min^{-1}; $p<0.051$). Inspiration of 2% CO_2 in O_2 restored $\dot{V}_E$ to the value in air (Phase 3 air: 95.8 [SD 19] L·min^{-1}; 2% CO_2 in O_2: 98.1 [SD 17] L·min^{-1}, $p>0.4$).

End tidal CO_2 partial pressure

With air without added resistance or inspired CO_2, mean end-exercise $P_{ET}CO_2$ was 38.2 (SD 4.8) Torr, averaged across all three phases. When CO_2 was inhaled without added resistance, mean $P_{ET}CO_2$ at the end of exercise was elevated above baseline (*Figures 2a, 2c – Page 820*; inspired 2% CO_2: 45.5 [SD 4.8] Torr; inspired 3% CO_2: 51.0 [SD 4.7] Torr; $p<0.01$). With either moderate or high resistance without added CO_2 during air breathing, mean $P_{ET}CO_2$ at end exercise did not increase significantly from the no-resistance condition (*Figure 2b*; moderate: 38.6 [SD 3.9] Torr; high: 38.3 [SD 7.2] Torr). However, with moderate resistance without added CO_2 in O_2, mean $P_{ET}CO_2$ with O_2 increased (O_2 only: 38.8 [SD 5.3] Torr; moderate R in O_2: 44.5 [SD 4.8] Torr; $p<0.01$). With moderate resistance added to the breathing circuit with inhaled CO_2 in air or O_2, mean end-exercise $P_{ET}CO_2$ was elevated above baseline (*Figures 2b, 2c – Page 820*; air and 1% CO_2: 42.4 [SD 6.8] Torr; air and 2% CO_2: 49.0 [SD 5.9] Torr; O_2 and 2% CO_2: 51.1 [SD 4.5] Torr; all $p<0.01$).

FIGURE 2a – *CO_2 inspired in air*

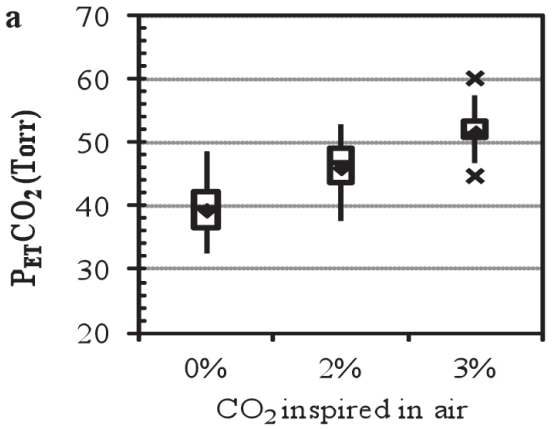


FIGURE 2b – *Resistance, CO_2 inspired in air*

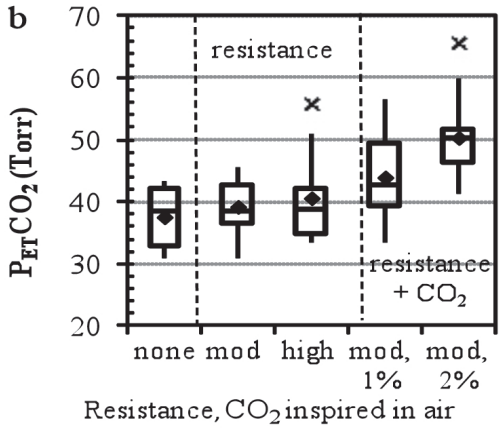
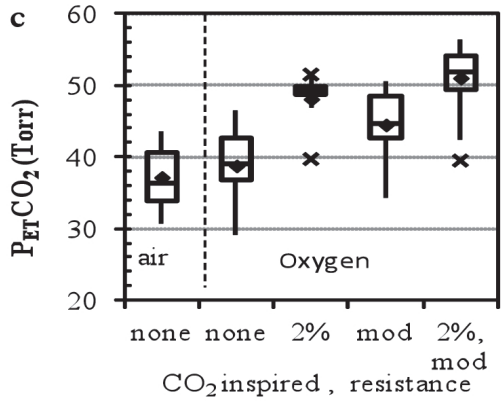


Figure 2. $P_{ET}CO_2$ at end exercise, box and whisker plots, a) Phase 1; b) Phase 2; c) Phase 3.

Rectangles mark the first to third quartiles of the distribution, with the dividing line at the median. The whiskers indicate the lesser difference from the median of maximum and minimum or 1.5 times the interquartile difference (IQD).

♦ indicates the mean; **x** indicates a value more than 1.5 • IQD from the median, that is, an outlier; mod means moderate resistance.

FIGURE 2c – *CO_2 inspired, resistance*



The two outliers in Figure 2c represent the same individual. Although those $P_{ET}CO_2$ values were near normal for someone at rest, they were higher than normal for someone exercising at 80-85% of peak $\dot{V}O_2$. For this subject, those values were elevated 36% and 37% over that for oxygen-breathing without resistance or added CO_2, when his $P_{ET}CO_2$ = 29.2 Torr.

When O_2 was the general background gas without added resistance or inhaled CO_2, $P_{ET}CO_2$ was only marginally different (p<0.1 by paired t-test) between air (37.2 [sd 4.0] Torr) and O_2 breathing (38.8 [sd 5.3] Torr) *(Figure 2c)*.

Some individual $P_{ET}CO_2$ values deviated from the group *(Figure 2)*. Additionally, some subjects showed high $P_{ET}CO_2$ early in the exercise period but decreased it by end exercise. Table 4 *(facing page)* indicates the number of subjects with $P_{ET}CO_2$ elevated to values of concern.

Endurance times

Endurance times and changes in endurance times were not normally distributed. Table 5 *(facing page)* describes the durations of cycle exercise for air without CO_2 or resistance in Phases 1 and 2 and for O_2 without CO_2 or resistance in Phase 3.

The median decrease in endurance times was significant (p<0.05 by Wilcoxon Rank Sum test for 2% inspired CO_2 with moderate resistance in air (median decrease 3.0 minutes, median fractional decrease 22%) and for 3% CO_2 in air (median decrease 4.1 minutes, median fractional decrease 28%). None of the other conditions consistently changed endurance time *(Table 6, facing page)*, although individual subjects were affected, as can be seen from the large interquartile range. Further, although in the absence of resistance or inspired CO_2 no subjects reported stopping exercise because of difficulty breathing, a number did when either was present *(Table 7, Page 823)*.

TABLE 4 – ***Number of subjects with elevated $P_{ET}CO_2$ [P, Torr] in each range***

		END EXERCISE		EARLY EXERCISE ONLY	
		a	**b**	**a**	**b**
	Condition	$51 \leq P < 60$	$P \geq 60$	$5 \leq P < 60$	$P \geq 60$
no *R*	Air, 2% CO_2	2	0	0	0
	Air, 3% CO_2	6	1	0	1
	O_2, 2% CO_2	7	0	1	0
R	M, Air, 0% CO_2	0	0	0	0
	H, Air, 0% CO_2	0	0	1	0
	M, O_2, 0% CO_2	0	0	0	0
	M, Air, 1% CO_2	2	0	2	1
	M, Air, 2% CO_2	2	2	0	0
	M, O_2, 2% CO_2	7	0	7	0

a: $P_{ET}CO_2$ at which cognitive effects have been reported [16];
b: If one person reaches or exceeds this $P_{ET}CO_2$ during the testing of dive gear, the gear is unacceptable [15].

TABLE 5 – ***Baseline cycle endurance times at 85% $\dot{V}O_2$ max***

Times (min)	**minimum**	**First quartile**	**Median**	**Third quartile**	**Maximum**
Phase 1 air	6.8	12.3	14.7	20.5	33.5
Phase 2 air	6.8	11.6	13.4	15.1	40.3
Phase 3 O_2	8.2	13.9	19.1	25.8	44.2

TABLE 6 – ***Endurance times normalized to baseline conditions***

		Median	**1st to 3rd inter-quartile range**
Phase 1	2% CO_2 only, in air	0.90	0.18
	3% CO_2 only, in air	0.72*	0.27
Phase 2	Moderate *R* only, in air	0.94	0.50
	Moderate *R*, 1% CO_2, in air	0.96	0.44
	Moderate *R*, 2% CO_2, in air	0.78*	0.42
	High *R* only in air	0.89	0.36
Phase 3	Moderate *R* only, in O_2	1.09	0.50
	2% CO_2 only, in O_2	1.00	0.41
	Moderate *R*, 2% CO_2, in O_2	1.12	0.56

* Median decrease different from zero ($p<0.05$) by Wilcoxon Rank Sum test

Association of symptoms and elevated $P_{ET}CO_2$

The most severe symptoms (Tables 7) were often associated with high $P_{ET}CO_2$:

1. Tunnel vision and headache were reported in Phase 1 with $P_{ET}CO_2$ = 60 Torr, and in Phase 2 with $P_{ET}CO_2$ = 66 Torr.
2. Nausea and panicky sensation were described as having occurred early in Phase 1, when $P_{ET}CO_2$ = 61 Torr. The subject did not feel the need to stop exercise, and symptoms abated as $P_{ET}CO_2$ decreased to 54 Torr at end exercise.
3. An altered mental state (feeling zoned-out) was reported in Phase 3 with $P_{ET}CO_2$ = 56 Torr. Two other reports of nausea were associated with $P_{ET}CO_2$ of 51 Torr and 52 Torr.

Not all severe symptoms were associated with high $P_{ET}CO_2$, and not all elevated $P_{ET}CO_2$ produced symptoms: One subject reporting vertigo and headache in Phase 2 had $P_{ET}CO_2$ = 41 Torr, while two subjects with $P_{ET}CO_2$ = 60 Torr (Phases 1 and 2) reported no symptoms other than leg fatigue. Overall, no association was found between $P_{ET}CO_2$ and symptoms.

Ventilatory sensitivity to CO_2

Ventilatory sensitivity to CO_2 at rest was measured in all but four subjects: three who became unavailable for testing, and one who declined to be tested because CO_2 exposure during exercise testing had triggered migraine headaches post testing. Results from another three subjects could not be interpreted.

For the 19 subjects with available data, the median ventilatory sensitivity to CO_2 was 2.5 $L{\cdot}min^{-1}{\cdot}Torr^{-1}$, and the minimum and maximum values measured were 1.2 and 7.6 $L{\cdot}min^{-1}{\cdot}Torr^{-1}$. Four subjects, all male, three of whom were divers, had sensitivities greater than 4.0 $L{\cdot}min^{-1}{\cdot}Torr^{-1}$. Normal subjects show a range of response between 0.57 and 8.16 $L{\cdot}\ min^{-1}\ {\cdot}\ Torr^{-1}$, and the response for 80% of the population falls between 1.00 and 3.99 $L{\cdot}\ min^{-1}{\cdot}Torr^{-1}$. The distribution of ventilatory sensitivities to CO_2 is known to be non-normal and skewed to the right [22]. Ventilatory sensitivity to CO_2 measured at rest did not correlate with end tidal CO_2 during exercise.

Ergometers

Results from the Monarch and the hysteresis brake ergometers are entirely comparable. One subject performed Phase 1 exercise with the hysteresis brake and Phase 3 exercise with the Monarch, and the relation between oxygen consumption and ergometer workload were superimposable.

DISCUSSION

In these subjects, endurance exercise at 80-85% $\dot{V}O_{2\,max}$ without exposure to inspired CO_2 or breathing resistance (baseline) was accompanied by high $\dot{V}_E$ as expected. Subjects could and did increase $\dot{V}_E$ when presented with CO_2 in inspired gas during heavy exercise, but the increase was not sufficient to maintain $P_{ET}CO_2$ at baseline levels. V_E increased as much with 2% as with 3% inspired CO_2. Relative to baseline, exercise $\dot{V}_E$ decreased in the presence of combined inspiratory and expiratory resistance like that of a rebreather UBA with high WOB/V_T, but without inspired CO_2 a corresponding increase in $P_{ET}CO_2$ was measured overall only when the background gas was O_2. However, in the presence of resistance, $P_{ET}CO_2$ increased above baseline when CO_2 was added to inspired gas. Under the conditions with resistance and inspired CO_2, $\dot{V}_E$ during air breathing did not increase and $\dot{V}_E$ during O_2 breathing increased only slightly. Surprisingly, though, exercise endurance time decreased consistently only with the challenge of 3% CO_2 in inspired air or 2% inspired CO_2 in air in the presence of moderate resistance. For those two conditions, $P_{ET}CO_2$ at end exercise exceeded acceptable limits established for tests of breathing gear [15] – 60 Torr in any individual test subject *(Table 4)*. With resistance and 1% inspired CO_2 in air, $P_{ET}CO_2$ exceeded 60 Torr for one subject early in the heavy exercise period *(Table 4)*, but that individual was able to increase ventilation enough to lower $P_{ET}CO_2$ slightly as he continued to exercise.

Subjects sometimes, but not always, experienced symptoms commensurate with their $P_{ET}CO_2$ levels, a finding consistent with other reports; awareness of CO_2 intoxication is known to be poor [23]. Although people can be trained to improve their recognition of hypercapnia symptoms [23], the lack of association of symptoms and elevated $P_{ET}CO_2$ makes it all the more important to reduce the chance that a diver will retain CO_2.

Our results strongly favor the concept of dual chemical and mechanical control of ventilation presented by Clark, Sinclair and Lenox [6] and more fully developed by Poon [24]. Ventilation is controlled not only to maintain arterial carbon dioxide partial pressure (P_aCO_2) but also to limit the work done by the respiratory muscles. Poon described the resulting $\dot{V}_E$ as the optimization of a function of those two opposing factors: Mass balance gives P_aCO_2 as a function of $\dot{V}_E$ and CO_2 production:

TABLE 7 – *Reasons for stopping exercise*

PHASE 1 – Air *n*=11	**Legs, fatigue**	**Breathing**	**Other**
No CO_2	10	0	headache
2% CO_2	9	2	headache in two subjects vertigo
3% CO_2	5	5	headache headache, red tunnel vision nausea (nausea and panic, but continued)
PHASE 2 – Air *n*=12	**Legs, fatigue**	**Breathing**	**Other**
No *R*, 0% CO_2	12	0	
Mod *R*, 0% CO_2	6	5	
High *R*, 0% CO_2	7	5	
Mod *R*, 1% CO_2	5	5	nausea
Mod *R*, 2% CO_2	3	9	nausea headache headache and tunnel vision
PHASE 3 – O_2 *n*=11	**Legs, fatigue**	**Breathing**	**Other**
No *R*, 0% CO_2	7	0	
Mod *R*, 0% CO_2	7	1	
No *R*, 2% CO_2	6	1	stitch in the side headache felt irritable but continued
Mod *R*, 2% CO_2	6	1	altered mental state headache in 3 subjects (felt irritable but continued)

Each entry under other is a different subject.

Table 7. *Reasons for stopping exercise.* Some subjects reported multiple reasons, and some none. Listings under Other were symptom reports given following exercise but not necessarily stated as reasons that the subject had stopped. Symptoms in parentheses resolved when the subjects continued to exercise. Only the subjects who were told to stop have been excluded.

$$P_aCO_2 = P_ICO_2 + k \cdot \dot{V}CO_2 \cdot [\dot{V}_E \cdot (1-V_D/V_T)]^{-1} \quad [1]$$

where P_ICO_2 is inspired CO_2 partial pressure; k is a correction factor for units, temperature and humidity; $\dot{V}CO_2$ is the rate of metabolic carbon dioxide production; and V_D is physiologic dead space. According to Poon's optimization model, the chemical component of ventilatory drive, if acting alone, would produce ventilation $\dot{V}_{E\,chem}$:

$$\dot{V}_{E\,chem} = k_2 \cdot (P_aCO_2-\beta) \cdot \dot{V}CO_2 \cdot (1-V_D/V_T)^{-1} \quad [2]$$

where $(P_aCO_2-\beta)$ is the error signal, that is, the difference in P_aCO_2 from its set point β, and the other terms give the effective gain. Parameter k_2 relates to CO_2 chemoreceptor sensitivity and includes correction for units. (Another term would be required to account for $\dot{V}_E$ above the ventilatory threshold.) However, to limit energy expenditure by the respiratory muscles, respiratory controller output is lower than $\dot{V}_{E\,chem}$. Under the simplifying assumption that V_D/V_T does not change with increasing $\dot{V}_E$, the model predicts that $\dot{V}_E$ called for by the respiratory controller will be:

$$\dot{V}_E = \dot{V}_{E\,chem} \cdot [1 + \dot{V}_{E\,chem}/\dot{V}_{E\,max}]^{-1} \quad [3]$$

where $\dot{V}_{E\,max}$ is the maximum ventilation that the respiratory controller will demand. $\dot{V}_{E\,max}$ may be the

predicted maximum ventilation that the respiratory muscles can sustain indefinitely based on feedback from the respiratory system. Because P_aCO_2 increases when $\dot{V}_E$ differs from $\dot{V}_{E\,chem}$, $\dot{V}_{E\,chem}$ thus increases. If P_aCO2 continues to rise, $\dot{V}_{E\,chem}$ approaches infinity, and $\dot{V}_E$ approaches $\dot{V}_{Emax}$.

The current data may be interpreted according to that model as follows: Non-zero P_ICO_2 initially increases P_aCO_2 (Equation 1), stimulating an increase in $\dot{V}_{E\,chem}$ (Equation 2). However, because CO_2 is high at 80-85% O_2, the gain term in Equation 2 is large, and $\dot{V}_{E\,chem}/\dot{V}_{E\,max}$ in Equation 3 is non-negligible. Thus, the increase in $\dot{V}_E$ that is expected from the inspired CO_2 is moderated to prevent exhaustion of the respiratory muscles. P_aCO_2 climbs in consequence and measured $P_{ET}CO_2$ increases. Added external resistance decreases $\dot{V}_{Emax}$ to a value close to $\dot{V}_E$, which prevents an increase in $\dot{V}_E$ when CO_2 is inspired.

Importantly in Poon's optimization model, $\dot{V}_{Emax}$ is predicted by the respiratory controller and used to moderate the drive to breathe. P_aCO_2 climbs not because the respiratory system fails to deliver sufficient flow, but because the drive to breathe allows it, to protect the respiratory system from failure through fatigue. The increase in P_aCO_2 is not failure of respiratory control but represents the result of the optimized model. Certainly, many subjects *(Table 6)* had no complaints about breathing and no change in exercise duration despite elevated $P_{ET}CO_2$. Dyspnea does not seem to result from a mismatch between $\dot{V}_E$ and the chemoreceptor output. Rather, it may result from a mismatch between real $\dot{V}_{Emax}$ and that predicted from respiratory system feedback.

Ventilatory responses to CO_2 and resistance

Inspired CO_2

In the absence of mechanical limits to ventilation, to prevent changes in P_aCO_2 in the face of moderate levels of inspired CO_2, minute ventilation would have to increase by the factor $[P_aCO_2/(P_aCO_2-P_ICO_2)]$ [15, 25]. Thus, when inhaling 2% CO_2, a subject who normally maintained P_aCO_2 at 40 Torr would have to increase minute ventilation 61% over that with no inspired CO_2. However, experimental evidence shows that even at rest, although inhaled CO_2 increases $\dot{V}_E$, it causes a small sustained increase in resting P_aCO_2. The increase may be within the error of the measurement for low P_ICO_2 [26], but amounts to about 10% of P_ICO_2 at rest [26]. Our data at heavy exercise showed an increase of $P_{ET}CO_2$ of closer to 50% of P_ICO_2 despite increased $\dot{V}_E$, perhaps because $\dot{V}_E$ was close to its mechanical limits. Inhalation of gas containing CO_2 during exercise increases $\dot{V}_E$ relative to that without CO_2, but $P_{ET}CO_2$ at any level of $\dot{V}O_2$ has been seen to be higher than it would be with no inspired CO_2 [6]. Our results were consistent with those findings, as is Poon's model [24].

Respiratory loading

If a resting subject breathes against a mild to moderate inspiratory load, P_aCO_2 is maintained by unchanged $\dot{V}_E$ generated by increased V_T and decreased f_R [28, 29]. Other investigators have found that $\dot{V}_E$ during exercise with inspiratory loads can be maintained at the unloaded level for small inspiratory loads and light exercise, but that with heavy exercise or large inspiratory loads, $P_{ET}CO_2$ becomes elevated and $\dot{V}_E$ decreases relative to the unloaded condition for the same exercise [30]. When our exercising subjects breathed against combined inspiratory and expiratory loads, they reduced $\dot{V}_E$ by decreasing f_R, with V_T unchanged in air and reduced in O_2. In air, $P_{ET}CO_2$ did not change from that without resistance; presumably statistically insignificant increases in tidal volume were sufficient to maintain alveolar ventilation constant at the lower f_R when dead-space ventilation decreased.

Respiratory loading and inspired CO_2

If a resting subject breathing against a load inhales gas containing CO_2, the increase in $\dot{V}_E$ caused by the CO_2 is attenuated, and P_aCO_2 increases more than it does without resistance. The amount of work done by the inspiratory muscles has been shown to be a function of $P_{ET}CO_2$, independent of the magnitude of the resistance added – as if a different maximum inspiratory power is acceptable to the body for every degree of hypercapnia [13], more evidence for control to minimize some combination of P_aCO_2 and respiratory effort. However, subjects in this study who performed heavy exercise while breathing against a load showed no increase in $\dot{V}_E$ relative to that with air alone when they inhaled CO_2 in inspired air, and a small increase when they inhaled CO_2 in O_2 instead of O_2 alone, presumably because $\dot{V}_E$ approached or attained $\dot{V}_{Emax}$ with the combination of heavy exercise and resistance [24]. $P_{ET}CO_2$ was significantly – perhaps dangerously – elevated with the combination of resistance and inspired CO_2 in both background gases.

Air versus O_2 as background gas

At rest (after at most a few minutes of hyperoxia), V_E is expected to be unchanged from that during air breathing [31]. Isocapnic $\dot{V}_E$ is higher in O_2 than in air [32].

TABLE 8 – *Postulated corrections of $P_{ET}CO_2$ for miscalibration of CO_2 analyzer for O_2 background*

Mean (sd) [Torr]	Measured $P_{ET}CO_2$	Assume 6.32% underestimation	Assume 8% underestimation	$P_{ET}CO_2$ measured during air breathing, for comparison
O_2 only	38.8 (5.3)	41.3 (5.6)	41.9 (5.7)	37.2 (4.0)
Moderate *R* in O_2	44.5 (4.8)	47.3 (5.1)	48.1 (5.2)	*38.6 (3.9)*
2% CO_2 in O_2	48.1 (3.6)	51.1 (3.8)	51.9 (3.9)	*45.5 (4.8)*
R, 2% CO_2 in O_2	51.1 (4.5)	54.8 (4.8)	55.6 (4.9)	*49.0 (5.9)*

Calibration in 100% nitrogen causes an 8% underestimation [34]. A linear correction should mean a 6.32% underestimation for air calibration. *Italics* indicate different subjects in the air and O_2 groups.

However, during heavy exercise, a change from inspired air to 100% O_2 for five to six breaths has been reported by others to cause a 20% to 25% decrease in $\dot{V}_E$ [33], partly because hyperoxia depresses both central and peripheral chemoreceptor sensitivity (incorporated in k_2 in Equation 2); in resting subjects breathing 100% O_2 at ambient pressure, the response of the central chemoreceptor is depressed by 15%, and that of the peripheral receptors by 70% [31]. In the experiments reported here, $\dot{V}_E$ at heavy exercise during continuous O_2 breathing was 13% lower than that during air breathing trials. Depressed $\dot{V}_E$ leads to increased P_aCO_2 (Equation 1). The difference between acute O_2 breathing (five to six breaths) and continuous O_2 breathing may result from partial compensation for the increase in P_aCO_2 which results from the initial decrease in $\dot{V}_E$ (Equations 1 and 2), but with a lower value of chemoreceptor sensitivity when P_IO_2 is approximately 100 kPa rather than approximately 20 kPa. With P_IO_2 up to 160 kPa during diving, the chemoreceptors may be even less sensitive and the ventilatory response to CO_2 retention even more attenuated.

$\dot{V}_E$ at heavy exercise, lower during O_2 breathing than during air breathing, was further depressed by resistance. However, with breathing resistance present, V_E at heavy exercise increased when CO_2 was added to the inspirate only when the background gas was O_2. This result is consistent with the optimization model [24]; the lower chemosensitivity during O_2 breathing generates $\dot{V}_{E\,chem}$. (Equation 2) farther from $\dot{V}_{E\,max}$ and thus permits $\dot{V}_E$ to increase when CO_2 is inspired. Because $\dot{V}_E$ was lower during O_2 breathing than during air breathing, $P_{ET}CO_2$ was expected to be relatively elevated. However, mean $P_{ET}CO_2$ without resistance or CO_2 in our Phase 3 subjects during O_2 breathing was, at most, marginally different from that in the same cohort during air breathing ($p<0.1$), though mean $P_{ET}CO_2$ was numerically greater in 9 of 12 subjects *(Figure 2c)*. The real difference in $P_{ET}CO_2$, air to O_2 breathing is probably underestimated in our data, because we calibrated the CO_2 analyzer with CO_2 mixed in air even when it was used in an O_2 background. Pressure broadening of the absorption peaks would have decreased the apparent readings. As NDIR CO_2 analyzers calibrated in nitrogen have been shown to read 8% low when used in an O_2 background (34), a linear error would suggest a 6.3% underestimation in background O_2 for an instrument calibrated at 21% O_2. Table 8 *(above)* lists $P_{ET}CO_2$ corrected for different postulated error magnitudes. The corrected values suggest considerably more CO_2 retention with O_2, commensurate with a lower ventilatory sensitivity to CO_2 in background O_2 than in air and corresponding to the depressed $\dot{V}_E$.

Possible mechanical limits to ventilation

In addition to the putative constraints sensed by the respiratory controller to determine $\dot{V}_{E\,max}$, $\dot{V}_E$ can be constrained mechanically. In elite endurance athletes at very heavy exercise, expiration has been seen to be flow-limited for part of the cycle, end expiration shifts to higher lung volumes, and peak inspiratory pressure approaches peak inspiratory pressure capacity at exercise [35]. It is probable that similar mechanical constraints were introduced for some of the participants in this study, those who told us that they could not keep up with their breathing, with the combined inspiratory and expiratory resistances.

With expiratory resistance only, available strategies are to increase expiratory pressure or duration. If the expiratory pressures that are needed to exhale the tidal volume in the time available cause dynamic flow limitation, the only avoidance strategy is to breathe at higher lung volumes: that is, to increase end expiratory volume at the expense of more inspiratory muscle effort.

With inspiratory resistance only, available strategies are similarly to increase inspiratory pressure or duration. With a turbulent resistive element, if flow is high, small increases in flow require disproportionate increases in pressure. If lung volume is high, respiratory system compliance is low, the muscular effort for any added inspiratory driving pressure becomes very large, and respiratory muscles must operate at inefficient length. With both inspiratory and expiratory resistances, increases in inspiratory and expiratory times constrain each other, and an increase in either requires a decrease in frequency of breathing, f_R. To maintain $\dot{V}_E$ with decreased f_R, though, requires an increased tidal volume, one which is itself constrained by maximum lung volumes and a need to keep end expiratory volume high. It is very likely that subjects who told us that they had to stop because they could not sustain their breathing correctly interpreted their needs to stop: not respiratory muscle fatigue, just an inability to move gas quickly enough in both directions.

Study limitations

Measurements were made using an oronasal mask with one-way valves. The results can be expected to differ somewhat from those that might have been obtained with a mouthpiece and nose clips. The breathing patterns with both mask and mouthpiece differ from those of normal breathing [36], though breathing frequency is more faithfully represented with mask than mouthpiece [37]. One disadvantage of a mouthpiece is that it can be difficult to support the system of one-way valves without subject discomfort, discomfort that can lead to premature termination of exercise. Disadvantages of a mask are that it can be difficult to prevent leaks and that expired gas is necessarily mixed with mask dead space gas before it is sampled. The combined mask and valve dead space was about 150 ml, 75 ml between the one-way valves and about 75 ml between the mask and the face, with some variation depending on a subject's facial shape. Tidal volumes were approximately 2 L. We did not quantify the error in $P_{ET}CO_2$ caused by dead space admixture in the mask and valve body, but for these measurements made after approximately 16-fold flushing, we considered the values to be reliable. Any error would have caused underestimation of CO_2 retention.

Some caution must be used in applying the results of this study to diving. Even though the external work of breathing was scaled up to account for the unchanged internal work of breathing and lack of elastic or hydrostatic loading, the subjects were impeded only by external resistance and inspired CO_2. Diving effects may interact with external resistance and inspired CO_2 in non-linear ways. However, added impediments to breathing can only decrease the maximum possible $\dot{V}_E$ and thus increase CO_2 retention. Even moderate CO_2 retention can be life-threatening for divers breathing high oxygen partial pressures underwater.

CONCLUSIONS

The combination of inspiratory and expiratory resistance depresses $\dot{V}_E$ during heavy exercise and probably depresses the maximum sustainable $\dot{V}_E$. Reduced $\dot{V}_E$ of necessity leads to relative CO_2 retention. Because $\dot{V}_E$ that is near its sustainable maximum cannot increase, the presence of CO_2 in inhaled gas exacerbates CO_2 retention. What is intriguing, though, is that for many subjects, and particularly for those breathing O_2, not only $\dot{V}_E$, but also respiratory drive did not seem to increase when CO_2 was inhaled in the presence of breathing resistance; we speculate that had respiratory drive increased, subjects would have been distressed by an inability to match it. However, many subjects felt limited only by fatigue, not by breathing, and continued exercise for as long with as without the respiratory load and inspired CO_2. Some subjects, though, could not sustain their breathing. Other authors have suggested that divers may be able to compensate for 2% inspired CO_2, at least in a low-resistance circuit [38, 39]. With resistance like that of a rebreather UBA, particularly during O_2 breathing with heavy exercise, we disagree. In this study at heavy exercise, even without added resistance some air breathing subjects retained CO_2, as did many of those who breathed O_2. With 2% inspired CO_2 and resistance like that of the MK 16 UBA at 50 fsw (154 kPa), $\dot{V}_E$ was reduced and CO_2 retention was severe for some subjects. Further, subject recognition of hypercapnia was poor. For diver safety with the MK 16 and other UBAs with both inspiratory and expiratory resistance, inspired CO_2 must be maintained as close to 0% as possible. Changes in $\dot{V}_E$ with inspired CO_2 and combined inspiratory and expiratory loads accorded with a model [24] of optimized control of dual inputs, that from the chemoreceptors to control P_aCO_2, and that from unidentified mechanoreceptors to control respiratory effort. At heavy exercise in air with added inspiratory and expiratory resistance, because $\dot{V}_E$ appeared to reach $\dot{V}_{Emax}$, effective ventilatory sensitivity to inspired CO_2 was eliminated, and CO_2 was retained. At heavy exercise in O_2, reduced baseline sensitivity to CO_2 kept $\dot{V}_E$ somewhat farther from the maximum, permitting more

ventilatory response to added CO_2 but also causing greater CO_2 retention. Some subjects could have increased $\dot{V}_E$ with unsustainable levels of respiratory effort in the short term to maintain P_aCO_2 and then quit exercise with respiratory muscle fatigue. Instead, for many subjects, respiratory control mechanisms led them to maintain sustainable $\dot{V}_E$ with elevated CO_2 but without dyspnea.

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