EFFECTS OF CARBON DIOXIDE AND UBA-LIKE BREATHING RESISTANCE ON EXERCISE ENDURANCE

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19. ABSTRACT: Effects of inspired CO_2 and of resistance on exercise endurance were tested dry at sea level. Resistance R was designed to mimic that of the MK 16 underwater breathing apparatus (UBA) at 50 feet of seawater. The MK 16 UBA has turbulent inspiratory and laminar expiratory pressure drops. At the design flow, expiratory pressure was twice inspiratory pressure. Endurance was assessed as duration of exercise on a bicycle ergometer at 85% peak oxygen consumption. Ventilatory parameters and end tidal CO_2 also were measured. Three groups of twelve subjects participated: one breathing air with 0%, 2%, or 3% CO_2 without R; one breathing air against moderate, high, or no R without CO_2 and against moderate R with 1% or 2% CO_2; and one breathing O_2 with or without 2% CO_2, once with moderate and once with no R. Endurance in air was reduced by 20% or more relative to that with neither R nor CO_2 in: 2 of 10 subjects breathing against moderate R, 3 of 10 subjects breathing against high R, 4 of 9 subjects with 2% CO_2, 6 of 9 subjects with 3% CO_2, 3 of 10 subjects breathing against moderate R with 1% CO_2, and 5 of 10 subjects breathing against moderate R with 2% CO_2. Among 10 subjects breathing O_2, endurance was reduced similarly in 2 subjects breathing against moderate R, 3 with 2% CO_2, and 2 breathing against moderate R with 2% CO_2. When CO_2 was added without R, minute ventilation increased relative to that with air alone without R, but when R was present, minute ventilation decreased with or without inspired CO_2. Average end tidal CO_2 remained normal during air breathing without CO_2 but increased in all other cases. A few subjects reached alarmingly high end tidal CO_2 with combinations of R and CO_2 or with 3% CO_2 in air. We conclude that to allow inspired CO_2 in the MK 16 or other UBAs with similar pressure-flow characteristics would be hazardous.

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INTRODUCTION

Each model of rebreather underwater breathing apparatus (UBA) has its own pressure-flow (resistance) characteristics that depend on laminar and turbulent pressure drops within the apparatus. These characteristics determine the work of breathing (WOB) for the UBA. Testing for acceptable WOB assumes normal ventilatory requirements based on a diver's external workload. However, if the CO_2 in the inspiratory gas is allowed to climb to 2% rather than 0.5% surface equivalent value (SEV) before the scrubber is considered to be expended,[1] divers may need to increase respiratory minute ventilation (V_E). Conversely, the UBA's resistance characteristics may reduce ventilatory sensitivity to CO_2 and thus increase CO_2 retention. The effects of inhaling CO_2 while breathing against typical rebreather UBA resistance must be known before any consideration is given to relaxing the criteria for scrubber lifetime.

Subjects who inhale gas containing CO_2 when the resistance of their breathing circuit is minimal increase V_E both at rest and during mild to moderate (below ventilatory threshold) exercise.[2–8] However, when CO_2 is inhaled during heavy or maximal exercise, V_E does not increase over that without CO_2,[2,3,6,8] and, aerobic capacity decreases[2,3] — probably because the metabolic acidosis of heavy exercise cannot be cleared.[4,6]

During mild exercise the increases in V_E with exercise and from CO_2 inhalation are more than additive.[2,3,7] Absent any impediment to breathing, inspired CO_2 causes subjects to increase V_E by the factor $P_aCO_2/(P_aCO_2 - P_{in}CO_2)$, where P_aCO_2 is arterial and $P_{in}CO_2$ is inspired CO_2 partial pressure.[9,10] For example, for a subject to maintain P_aCO_2 at 45 mm Hg (6% SEV) when inhaling with 2% instead of 0% CO_2, the subject will increase V_E by 50%.

Breathing resistance in the absence of inhaled CO_2 can reduce exercise endurance[11–14] and maximum oxygen uptake, because V_E is reduced relative to that without breathing resistance, although not so much that WOB remains constant.[15] The reduced V_E leads to CO_2 retention; during exercise with a resistive breathing circuit, P_aCO_2 as indicated by end tidal P_{CO_2} ($P_{ET}CO_2$) increases.[14]

Subjects who inhale gas containing CO_2 when the resistance of their breathing circuits is more than minimal show a much smaller increase in V_E with inhaled CO_2 than without it both at rest and during exercise.[16,17] Inspiratory WOB in subjects at rest with elevated inspired CO_2 has been reported to remain constant for a given $P_{ET}CO_2$ across a range of resistances.[16] During exercise with elevated inspired CO_2, V_E is lower when an inspiratory resistance is present than when it is not, a result suggesting a trade-off between increased effort and increased CO_2.[17]

Rebreather UBAs have both inspiratory and expiratory resistance to breathing. If the inspiratory resistance is partially turbulent, pressure for flow increases as the square of the flow, and inspiratory WOB increases precipitously for high flows. However, the strategy of increasing inspiratory time to decrease flow may be limited by the need to overcome expiratory resistance. Although 2% SEV CO_2 may not be problematic for a short period of light to moderate exercise against minimal breathing resistance,[1] a UBA's resistance is not minimal. Naval Sea Systems Command (NAVSEA) Task 08-06 initiated an exploration of the effects of CO_2 and UBA breathing resistance, first with background air and then with background O_2, with PO_2 of approximately 1 atmosphere (atm).[18] Navy Experimental Diving Unit (NEDU) measured ventilatory and metabolic values and exercise endurance for subjects who exercised on a cycle ergometer in a dry environment at atmospheric pressure, where work is safer, faster, and less expensive than that in water at depth.

METHODS

GENERAL

The Institutional Review Board at NEDU approved the protocol. Military subjects from NEDU, its neighboring commands, and NEDU Reserve Unit Great Lakes gave written informed consent. Only those whose risk of a cardiovascular event in the next 10 years was less than 5% as estimated from parameters of the Framingham study,[10] participated in this study. Twelve subjects completed each phase.

Exercise was imposed with a bicycle ergometer. Heart rate, V_E, and end tidal CO_2 fraction ($F_{ET}CO_2$) were recorded on a breath-by-breath basis. Compressed breathing gas was regulated to low pressure and fed into a reservoir, a 120 L spirometer, at atmospheric pressure. The subject breathed from that reservoir through wide-bore tubing and a system of one-way valves attached to an oronasal mask (Hans Rudolph; Kansas City, MO). Expired gas passed through a turbine flow meter, past a gas sampling port (Cosmed USA; Chicago, IL) , and then through a wide-bore expiratory hose. For CO_2 in air, CO_2 was added with a system designed for this experiment (Fig. 1) and described below (**EQUIPMENT AND INSTRUMENTATION**, Gas Mixing System). For CO_2 in O_2, premixed gas was used.

Graded incremental exercise to peak exercise capacity was used to determine the exercise level for later tests in each phase. During remaining testing, the ergometer was set to 80–85% of that at termination. Each subject then performed constant-load exercise to termination — that is, an endurance test under each different testing condition. Endurance test conditions were imposed in pseudorandom order.

Resting ventilatory sensitivity to CO_2 was measured separately, as described in **PROCEDURES**, Ventilatory Sensitivity to CO_2.

EXPERIMENTAL DESIGN AND ANALYSIS

Variables recorded continuously as functions of time included, in Phases 1 and 2, partial pressures of oxygen and carbon dioxide in the mask, tidal volume, respiratory frequency, V_E, and heart rate; in Phase 3, mask pressure, but not partial pressure of oxygen, which was exceeded the range of the analyzer. Exercise endurance time also was recorded for all phases. Within each phase of the study, conditions were presented to different subjects in different orders, and the subject was not told which gas or resistance was used.

To study effects of the experimental conditions on endurance and respiratory variables, NEDU compared subjects to themselves in repeated measures designs for each phase of the protocol. Because not all subjects participated in all phases, group responses were compared across phases.

Phase 1 (CO_2 only): Endurance was measured with
air only,
air plus 2% CO_2, and
air plus 3% CO_2.

Resistance elements for Phases 2 and 3 were constructed to mimic the pressure-flow characteristics of the MK 16 UBA at 50 feet of seawater (fsw), as is described below (**EQUIPMENT AND INSTRUMENTATION**, Choice of Resistance Elements). High resistance was then defined as an element that would produce the maximum acceptable WOB per tidal volume (WOB/V_T) at the median exercise V_E with air alone, and moderate resistance as one that would produce that WOB/V_T at the median V_E for 2% CO_2 in air.

Phase 2 (Resistance and CO_2): Endurance was measured with
air only;
air and just the resistance of the valve and tube assembly;
air and moderate inspiratory resistance and the expiratory resistance;
air and high inspiratory resistance and the expiratory resistance;
1% CO_2 in air, with moderate inspiratory resistance and the expiratory resistance; and
2% CO_2 in air, with moderate inspiratory resistance and the expiratory resistance.

Phase 3 (Resistance and CO_2 in O_2): Endurance was measured with
air and just the resistance of the valve and tube assembly;
O_2 and just the resistance of the valve and tube assembly;
O_2 with moderate inspiratory and expiratory resistance;
2% CO_2 in O_2, with just the resistance of the valve and tube assembly; and
2% CO_2 in O_2, with moderate inspiratory and expiratory resistance.

EQUIPMENT AND INSTRUMENTATION

We measured breath-by-breath gas concentration and flow during exercise with the COSMED k2b4 (Cosmed USA; Chicago, IL). Flow was measured with a turbine flow meter (range 0–20 L/s, resolution 4 mL, and accuracy ±1%) and gases with fast response (<120 ms for 90% full scale) analyzers. The nondispersive infrared sensor CO_2 has a reported range of 0–8% but agreed with a mass spectrometer to just above 10%. The galvanic fuel cell to measure O_2 has a range of 7–24%. To measure mask pressure in Phase 3 we used a solid-state differential pressure transducer (Honeywell, DC020NDR5; Freeport, IL; range, ±20 inches of water).

For all of Phases 1 and 2 and for some subjects in Phase 3, we used a cycle ergometer built at NEDU — a successor to the Collins Pedal Mate ergometer, a device no longer available. A pedal shaft drives the shaft of a hysteresis brake (Magtrol, HB210; Buffalo, NY) through a gear train with an overall gear ratio of 1:19.2. The torque necessary to turn the brake is regulated by the electric current supplied to the brake. Because of hysteresis in the brake rotor (in addition to that which causes braking), torque at a given setting is higher if the current is decreased to the value than if it is increased. A constant (regulated) current power supply was used to provide a stable load. Subjects, who watched their pedal cadence on an analog meter connected to an electronic pickup, pedaled at 60 revolutions per minute (rpm) to maintain a constant power output.

For some subjects in Phase 3, we used a Monarch (Vansbro, Sweden) Ergomedic 839E cycle ergometer. This mechanically-braked ergometer adjusts torque for changes in cadence to maintain a constant power output. The Monarch ergometer is more comfortable to ride than the ergometer built at NEDU because both seat and handlebars adjust. It is also much quieter. We would have used it for all of Phase 3 , but its arrival was delayed. Results from the Monarch and the calibrated, hysteresis brake ergometer 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.

Subjects wore a silicone rubber oronasal nonrebreathing face mask with a T-shaped valve (Hans Rudolph 8920 [large], 8930 [medium], or 8940 [small]; Kansas City, MO). The mask was held to the head by a mesh headpiece and Velcro straps. The T-piece that contains the one-way valves has dimensions of 28.6 mm i.d. and 35 mm o.d., over which we slid large-bore respiratory tubing. The tubing on the inspiratory side connected to the spirometer, and that on the expiratory side held the turbine flow meter and the expiratory resistance element when resistance was added. The inspiratory resistance element, when used, was inserted inside the end of the T-piece. To keep the T-piece dry, expiratory resistance was kept as far as possible from exhaled moisture.
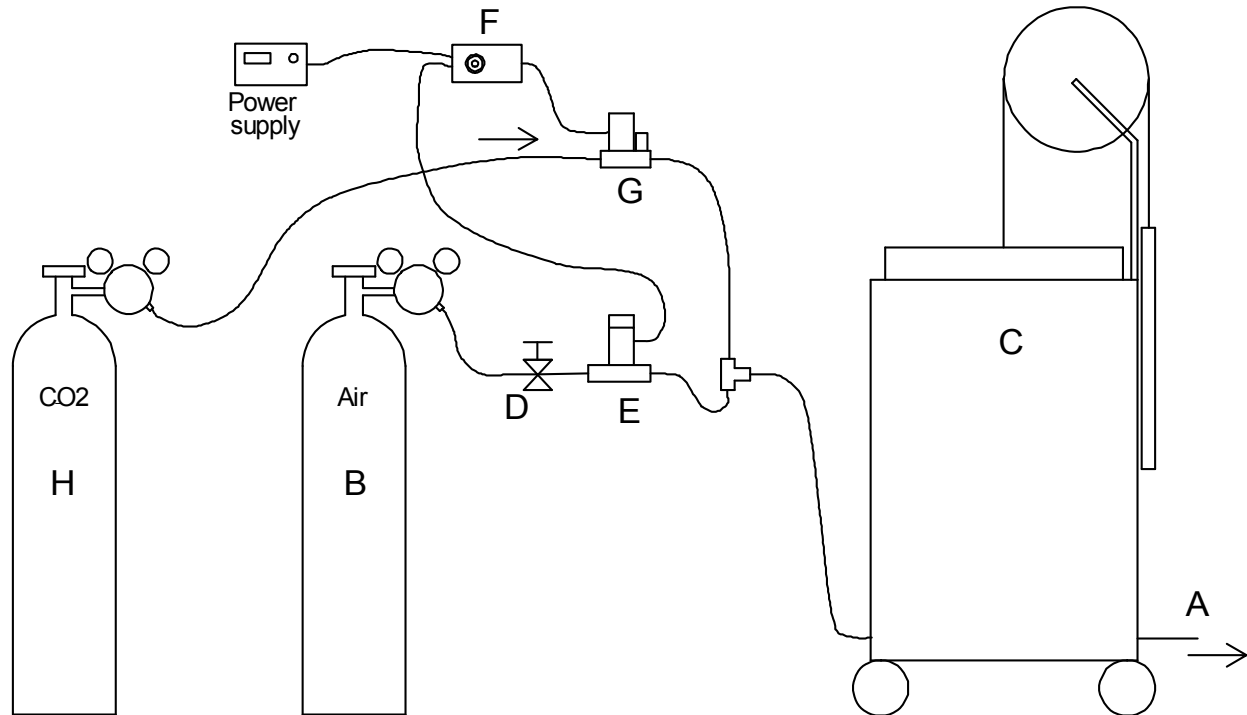
Figure 1. Apparatus to provide air with adjustable CO_2 concentration. The subject breathed from the system at point (A). Compressed air from a storage tank (B) was delivered at whatever flow was required to maintain a suitable volume in the 120 L spirometer (C), and that flow was controlled manually with a needle valve (D). The flow was measured with a mass flow meter (E), which provided an input to the control box (F), where the desired CO_2 concentration, was set manually. The control box (F) caused the CO_2 mass flow regulator (G) to deliver CO_2 from a tank (H). A two-channel CO_2 analyzer (not shown) monitored the gas compositions entering the spirometer and being delivered (A) to the subject (not pictured).

Air and CO_2 were mixed using a system designed and built for this experiment and detailed in Figure 1. Breathing gas, either air or air mixed with CO_2, was available for the subjects to breathe at ambient pressure from a volume tank, a 120 L spirometer (Collins; Braintree, MA). We set the flow manually (Valve D, Fig. 1,) to accommodate V_E, and a mass flow meter (E in Fig. 1; Omega Engineering, model FMA1843, serial number 205587-1; range, 0–200 L/min standard temperature pressure, dry [STPD]) provided the measured value to a control box (F, Fig. 1) that had been built in-house for

this experiment. On that control box, we set the desired CO_2 concentration. The box provided the resultant output from the two inputs, namely measured V_E and selected CO_2 concentration, to a mass flow controller for CO_2 (G, Fig.1; Matheson Gas Products, model 8272-0414, serial number A735124327; range, 0–10 L/min STPD), which allowed an appropriate flow of CO_2 into the inlet line to the spirometer. Gas could continue to mix inside the spirometer tank (C, Fig. 1). We used a two-channel CO_2 analyzer (Rosemont MLT, Rosemount Analytical Inc.; Solon, OH), to monitored the composition of the gas entering the spirometer and of that leaving the spirometer to the subject (at A, Fig. 1).

Choice of Resistance Elements

We wanted to match the pressure-volume characteristics of the MK 16 and its ratio of inspiratory to expiratory WOB/V_T. The target was to provide the maximum tolerable WOB/V_T if subjects maintained V_E as measured without resistance. Maximum tolerable WOB/V_T varies with water depth, but at the surface it is 2.99 J/L.[19]

When Phase 1 subjects breathed room air, their median exercise V_E measured 80 L/min, and that with 2% CO_2 was 100 L/min. Those rates were used as the design V_E levels for high and moderate resistance, respectively. In other words, the high resistance caused WOB/V_T = 3 J/L at 80 L/min, and moderate resistance caused WOB/V_T = 3 J/L at 100 L/min.

Pressure-volume loops from unmanned testing of the MK 16 were analyzed for inspiratory and expiratory WOB, and the ratios were calculated for data from three depths (0, 50, and 100 fsw) and four V_E (22.5–90 L/min) per depth. At 100 fsw the WOB was too high when flow was 90 L/min, but the average ratio of expiratory to inspiratory WOB/V_T was 1.9 across the other tests (SD = 0.29, n = 11). This became our target ratio. In other words, we chose to partition the WOB/V_T into approximately 1 J/L on inspiration and 2 J/L on expiration at the target V_E of 80 L/min for high resistance and 100 J/L for moderate resistance.

We selected the pressure-volume and pressure-flow data from the MK 16 at 50 fsw as our pattern. From these data we found resistive pressure drops by subtracting the static and elastic components of pressure — that is, the line connecting end inspiration and end expiration, including offset. The remaining resistive pressure-flow data were then split into inspiratory and expiratory components, and polynomials were fitted to each segment. Expiratory pressure was nearly linear with flow (laminar) and inspiratory resistance was quadratic with flow (turbulent); the fitted equations were

$$\Delta P_{res,\,insp} = C_{x2} \cdot Q^2, \quad C_{x2} = 0.0618, \quad r^2 = 0.69, \text{ linear term insignificant,}$$

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and

$$\Delta P_{res,\ exp} = C_x \cdot Q, \quad C_x = 0.413, \quad r^2 = 0.82, \text{ quadratic term insignificant,}$$

where Q is volumetric flow in L/s and C_x and C_{x2} are the fitted coefficients of linear and quadratic terms, respectively.

With numerically simulated sinusoidal flow, these values gave WOB/V_T = 2.8 and WOB/V_T = 1.7 J/L at 100 L/min and 80 L/min, respectively. However, a 5% increase in the coefficients increased WOB/V_T to 2.97 J/L at 100 L/min, and an 8% increase brought WOB/V_T to 2.98 J/L at 80 L/min.

Turbulent pressure drops can be generated by flow through orifices. Flow through a straight-holed orifice relates to its cross-sectional area and ΔP as

$$Q = 0.62 \cdot A \cdot (2 \cdot \Delta P/\rho)^{0.5},$$

where ρ is density of the fluid.

But

$$\Delta P = C_{x2} \cdot Q^2, \text{ or}$$

$$A = [\rho \cdot (2 \cdot 0.62^2 \cdot C_{x2})^{-1}]^{\ 0.5},$$

from which the orifice diameter can be calculated. Design orifice diameters were 14.1 mm (0.56 in) and 12.3 mm (0.48 in) for moderate and high resistance, respectively. The machine shop provided us with a series of plugs with holes of 11.2, 12.2, 13.2, 14.2, and 15.2 mm (0.44, 0.48, 0.52, 0.56, and 0.60 inches). For laminar elements we used jersey knit cloth stretched over the end of the expiratory hose. We measured the pressure drop across the cloth for a number of flows.

To confirm our calculations, we measured WOB/V_T with our resistive elements on a breathing simulator. A mask with a T-piece like the one used with the subjects was attached to the breathing simulator head, and the simulator was run with all the plugs, one at a time, on the inspiratory side. Resistance elements (two, four, six, or eight layers of cloth) were attached to the expiratory side. Inspiratory and expiratory loads were tested in combination and separately, and WOB/V_T was determined by the standard software in NEDU's Testing and Evaluation Department. The measurements confirmed that even though the inspiratory elements were long plugs rather than orifice disks, the hole diameters of 0.56 and 0.48 inches gave the desired inspiratory WOB/V_T. Corresponding expiratory resistances required four and seven layers of cloth, respectively. However, early during exercise testing we found the expiratory resistance to be unworkably high, and we used three layers of cloth for all resistive runs.

PROCEDURES

Testing was conducted at ambient room temperature. A large fan provided extra cooling for the subjects when they wanted it. Subjects who used the hysteresis brake were required to maintain a cadence of 60 rpm, at which the ergometer had been calibrated, while those riding the Monarch ergometer were free to alter cadence during the test. Once the graded test was complete, experimental conditions were presented in varying order for each subject. No individual performed more than one test on any day.

Graded testing began at 25 W, and loading continued in increments of 50 W — or 25 W, when we deemed that a subject was nearing peak power capacity — to voluntary termination or termination necessitated by the apparatus: the hysteresis brake we used began to overheat at settings >250 W, but the Monarch ergometer was not so limited. Each load lasted for three minutes.

Endurance testing began with a two-minute warm-up at 50 W and was followed by a steady load of 80–85% of the peak load achieved. In general, 85% was chosen if the subject completed most of a three-minute increment, and 80% if the duration at the peak lead was short, with the same load used for all endurance tests. Testing continued until the subject stopped cycling or could not maintain cadence. To prevent subjects from setting specific time goals for themselves, they were told neither how long they had cycled nor which condition had been presented in any test until the series ended, and they were not permitted to wear watches or to have a clock visible. They were permitted to listen to music.

Ventilatory Sensitivity to CO_2

Each subject sat in a chair and held an oronasal mask to his or her face. The COSMED unit was connected to the mask and, through the adaptor used for this study, to the wide-bore respiratory tubing and to the spirometer. The spirometer contained 8 to 10 L of 7% CO_2 in O_2.[20] Subjects were instructed to exhale to residual volume and then signal, after which the valve to the spirometer was opened and the subjects rebreathed the CO_2-rich gas. Inspired and end tidal CO_2 and respiratory variables were recorded, while the computer screen displayed V_E as a function of end tidal CO_2 in real time. Rebreathing continued for no more than six minutes and until end tidal P_{CO_2} reached 70 Torr — or until a clear relationship could be seen between ventilation and end tidal CO_2. Although no subject felt a need to end the test early, early termination could have been accomplished simply by removing the mask. Ventilatory sensitivity to CO_2 was measured as the slope of the line relating V_E to end tidal CO_2 and, when there was an offset, as the end tidal CO_2 at which ventilation first began to increase.

RESULTS

Twelve subjects completed each phase. Seven subjects completed both Phases 1 and 2; three, both Phases 1 and 3; and two, both Phases 2 and 3. (The two subjects who completed Phases 2 and 3 in fact completed all three phases). Several subjects began phases of testing but were unable to complete them, and their data are not included.

Data from Phase 1 generally are reported for ten subjects, but endurance values are reported only for nine. We excluded all data except end tidal CO_2 from one subject (for whom we had set the workload inconsistently) and all data from one for whom we had had great difficulty maintaining a face seal. We include all but endurance data for a third subject who cycled under each condition without evidence of fatigue for one hour, after which we stopped him.

Data for Phase 2 also are reported for only ten of the twelve subjects. We disregarded all but end tidal CO_2 data from one subject because he frequently reported to the laboratory a short time after performing exhaustive leg exercise although the protocol proscribed it. We also excluded all data from the subject for whom a good face seal was difficult.

Endurance data from Phase 3 are reported for only ten subjects, because we stopped two subjects while they could have continued. One was stopped after 60 min with each of two test conditions (100% O_2 without resistance and 2% CO_2 in O_2 with moderate resistance), and then at 30 min on each of his subsequent tests. We stopped the other when we exhausted the gas supply after 35 min of 2% CO_2 in O_2 with moderate resistance. However, all other data from those two subjects have been considered.

We measured variables breath-by-breath, but values averaged over the last 1.5 to 2 minutes of endurance cycling were considered to represent each subject. Cross-subject means of those average values are reported.

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

	Phase 1	Phase 2	Phase 3
	10 men, 2 women	10 men, 2 women	12 men, 0 women
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 2. Average baseline values, by phase.

	n	Mean	SD	Median	Max	Min
Phase 1: CO$_2$ in air, no Resistance						
Endurance time [min]	9	17.0	8.6	14.7	33.5	6.8
V_E [L/min]	10	86	20	88	116	48
V_T [L]	10	2.3	0.6	2.5	2.8	1.2
f [breaths/min]	10	37	5	37	45	30
T_I [s]	10	0.63	0.10	0.63	0.78	0.43
T_E [s]	10	0.96	0.11	1.00	1.09	0.81
T_I/T_{tot}	10	0.40	0.05	0.40	0.49	0.33
$F_{ET}CO_2$ [%]	10	5.5	0.7	5.6	6.8	4.6
Phase 2: Resistance with or without CO$_2$ in air						
Endurance time [min]	10	17.5	12	13.5	49.8	9.1
V_E [L/min]	10	93	27	91	153	49
V_T [L]	10	2.3	0.6	2.5	3.0	1.2
f [breaths/min]	10	42.4	8.9	42.0	56.3	27.2
T_I [s]	10	0.63	0.11	0.62	0.78	0.43
T_E [s]	10	0.80	0.13	0.81	0.99	0.64
T_I/T_{tot}	10	0.46	0.04	0.47	0.52	0.38
$F_{ET}CO_2$ [%]	10	4.9	0.9	4.6	7.3	4.2
Phase 3: Resistance with or without CO$_2$ in O$_2$						
Endurance time [min]	10	19.2	9.2	18.1	38.0	8.2
V_E [L/min]	12	81	11	81	100	62
V_T [L]	12	2.2	0.5	2.3	1.1	0.8
f [breaths/min]	12	39	9	35	27	58
T_I [s]	12	0.63	0.17	0.64	0.92	0.38
T_E[s]	12	0.97	0.19	0.97	1.31	0.65
T_I/T_{tot}	12	0.39	0.03	0.38	0.43	0.34
$F_{ET}CO_2$ [%]	12	5.4	0.7	5.5	4.1	6.5

Mean endurance time was not affected by resistance alone or with 1% or 2% CO_2, or by 2% CO_2 alone. Endurance time was reduced ($p<0.03$) by 3% CO_2 (Fig. 2a). None of the other conditions was different from baseline by repeated measures ANOVA and testing of difference contrasts.
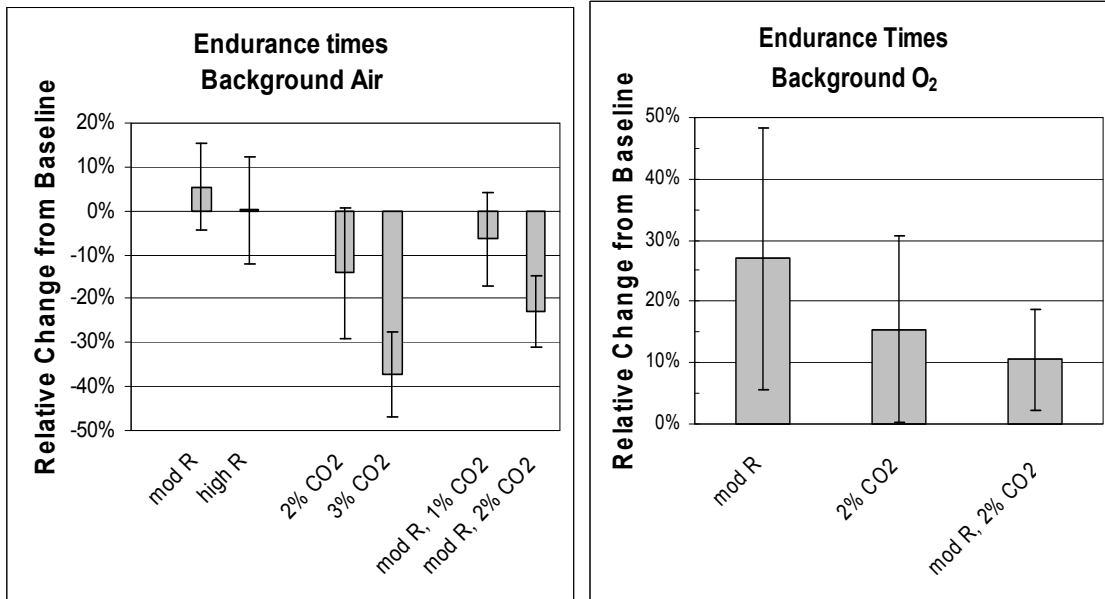

Figure 2. Endurance time, change from baseline, mean and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. Only mean endurance with 3% CO_2 in air is different from baseline.

Median relative endurance times, the lowest relative time seen in each group, and the number of subjects with endurance less than 80% of baseline are shown in Table 3.

Table 3. Endurance times relative to baseline.

Phase (gas)	Condition	Median	n	# subjects with endurance time reductions of ≥10%	≥20%	≥30%
2 (air)	Mod R, 0% CO_2	0.94	10	4	2	0
2 (air)	High R, 0% CO_2	0.89	10	6	3	2
1 (air)	No R, 2% CO_2	0.90	9	4	4	2
1 (air)	No R, 3% CO_2	0.72	9	7	6	4
2 (air)	Mod R, 1% CO_2	0.96	10	4	3	3
2 (air)	Mod R, 2% CO_2	0.78	10	6	5	4
3 (O_2)	Mod R, no CO_2	1.06	10	3	2	1
3 (O_2)	No R, 2% CO_2	1.07	10	3	3	2
3 (O_2)	Mod R, 2% CO_2	1.12	10	3	2	0

<u>Subjective reports — Reasons for stopping exercise</u>

Subjects stopped exercise sometimes because of generalized fatigue, leg fatigue, or achy knees. Sometimes they stopped because breathing was too difficult, sometimes for other reasons, and sometimes for a combination of reasons. Some subjects stopped because of symptoms likely resulting from elevated $F_{ET}CO_2$. In Table 4 the "breathing" heading includes complaints of air hunger and inability to exhale fast enough. Not included in Table 4 is the report from one Phase 2 subject that he was nauseated initially but felt better as he continued to exercise; he maintained $F_{ET}CO_2$ of approximately 7% throughout.

In Phases 1 and 2 all but one of the reports of nausea, headache, or tunnel vision (Table 4) corresponded to $F_{ET}CO_2$ >7%, but not all occasions of elevated $F_{ET}CO_2$ were accompanied by symptoms. With 3% inhaled CO_2 in Phase 1, subjects reported no symptoms connected with seven incidences of $F_{ET}CO_2$ >7%, but they reported symptoms connected to three others. In Phase 2 the association of symptoms and an elevated $F_{ET}CO_2$ was no different from that expected if symptoms were independent of $F_{ET}CO_2$. In Phase 3 two reports (Table 4) of headache occurred with a normal $F_{ET}CO_2$, and irritability was reported once with a $F_{ET}CO_2$ of 6.8%. The other reports of headache, irritability, and feeling "zoney" corresponded to a $F_{ET}CO_2$ >7%. Additionally, four of the exercise terminations in Phase 3 because of general fatigue (Table 4) corresponded to a $F_{ET}CO_2$ >7%.

Table 4. Reasons for stopping exercise. Some subjects reported multiple reasons, and some of the listings under "Other" were symptom reports given following exercise but not stated as reasons that the subject had stopped.

| Phase 1 — Air	Legs, fatigue	Breathing	Other
No CO_2	10	0	1 headache 1 stopped at 1 hr
2% CO_2	9	2	2 headaches 1 vertigo 1 stopped at 1 hr
3% CO_2	5	5	1 headache 1 headache, red tunnel vision 1 nausea
Phase 2 — Air			
No R, 0% CO_2	12	0	0
Mod R, 0% CO_2	6	5	1 not recorded
High R, 0% CO_2	7	5	1 not recorded
Mod R, 1% CO_2	5	5	2 not recorded 1 nausea
Mod R, 2% CO_2	3	9	1 nausea 1 headache 1 headache and tunnel vision
Phase 3 — O_2			
No R, 0% CO_2	7	0	4 not recorded 1 stopped
Mod R, 0% CO_2	7	1	4 not recorded 1 stopped
No R, 2% CO_2	6	1	1 "stich in the side" 3 not recorded 1 stopped 1 headache 1 felt irritable but continued
Mod R, 2% CO_2	6	1	2 stopped 1 felt "zoney" 3 headaches 1 felt irritable but continued
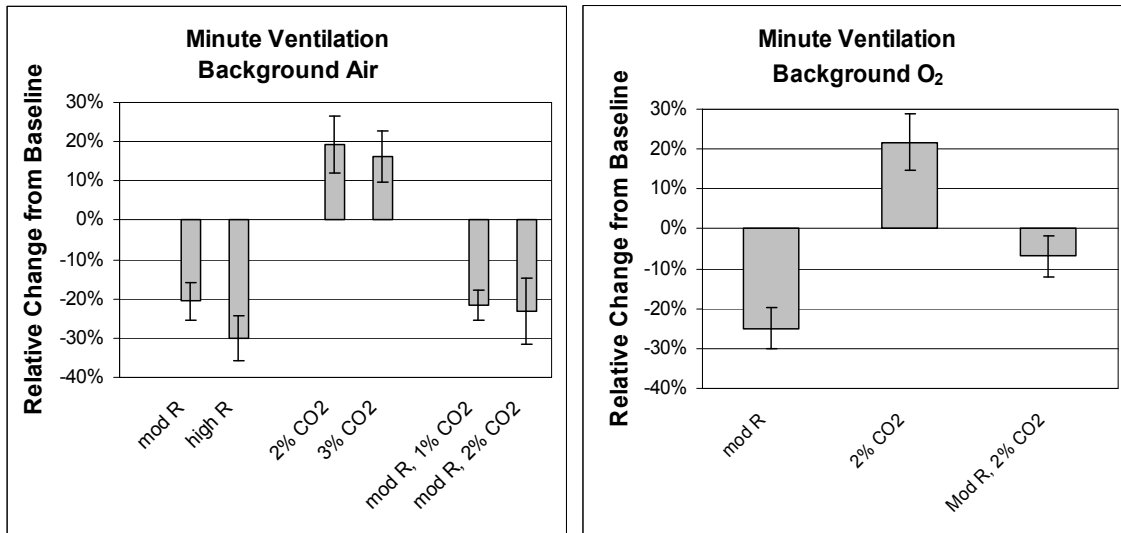
Figure 3. , V_E change from baseline, means and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance, "mod" is moderate.

V_E changed under most conditions (Fig. 3). The addition of CO_2 without resistance increased V_E ($p<0.01$ in air or O_2) without dose response. When resistive elements were present, V_E decreased ($p<0.01$ in air and O_2), with no difference when CO_2 was added to inspired air. When 2% CO_2 was added to O_2, V_E remained no different from baseline. V_E was lower ($p<0.02$) with high resistance than with moderate resistance.
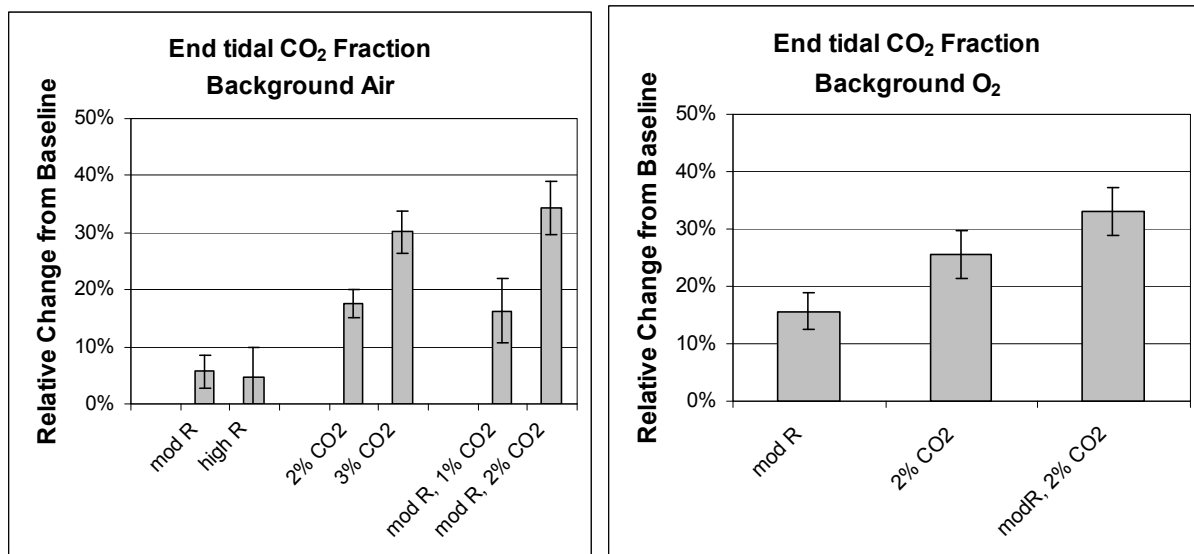
Figure 4. $F_{ET}CO_2$, percentage change from baseline, means and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. Elevation above baseline with moderate and high resistance in air is not significant, but all other changes are. Each of the conditions with background O_2 is different from all the others.

Despite reduced V_E, mean $F_{ET}CO_2$ was unchanged with moderate resistance and no added CO_2 in air (Fig. 4), but it increased with moderate resistance (p<0.01) during O_2 breathing. With inspired CO_2, mean $F_{ET}CO_2$ was elevated above baseline (p<0.01) to 6.4% with 2% inspired CO_2 in air, to 6.8% with 2% inspired CO_2 in O_2 (in different subjects), and to 7.2% with 3% inspired CO_2 in air (Fig. 4). Note that 1% inspired CO_2 in air with moderate resistance is similar to 2% inspired CO_2 in air without resistance, and 2% inspired CO_2 in air with moderate resistance is similar to 3% inspired CO_2 in air without resistance.

$F_{ET}CO_2$ in the final 90 to 120 s of each exercise condition is shown for each subject in Figure 5.
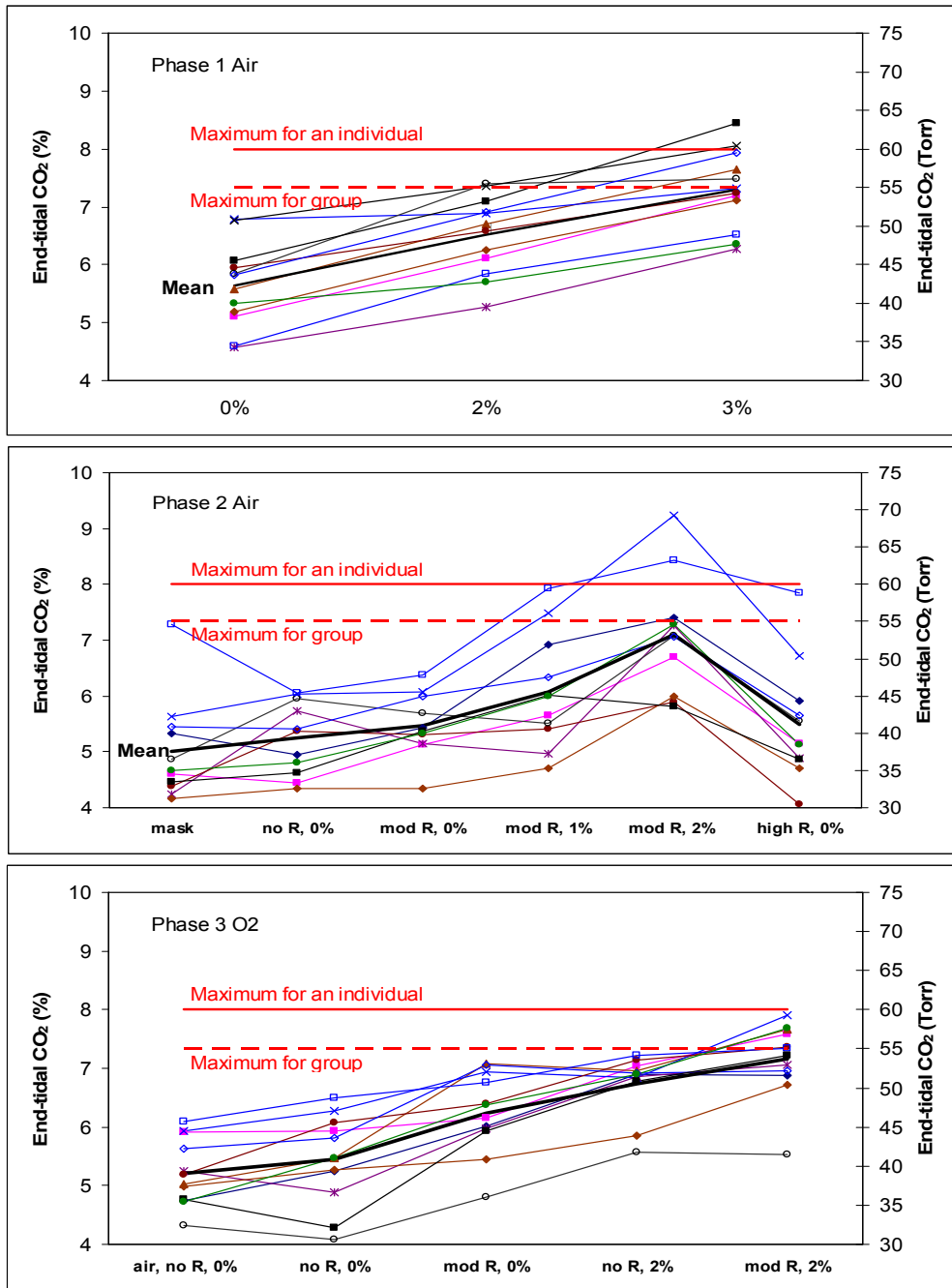
Figure 5. $F_{ET}CO_2$ for all subjects and all conditions. Lines join values for the same individual, but the same symbol on two panels does not indicate the same subject in both cases. "R" indicates resistance, "mod" means moderate, and percentages are those of inhaled CO_2. Maximum limits refer to those for manned acceptance testing of diving gear.[20]

Figure 6 shows part of the time course of $F_{ET}CO_2$ for one subject, the one with the highest recorded end tidal CO_2 in this study. Note that the peak $F_{ET}CO_2$ for each recording was reached at about five minutes, about three minutes after the end of the warm-up period. At about 10 minutes, $F_{ET}CO_2$ was somewhat decreased again.

This subject reached dangerously high $F_{ET}CO_2$ with the combination of 2% inhaled CO_2 and moderate resistance in air, but when breathing air without resistance, he exercised with normal end tidal values.
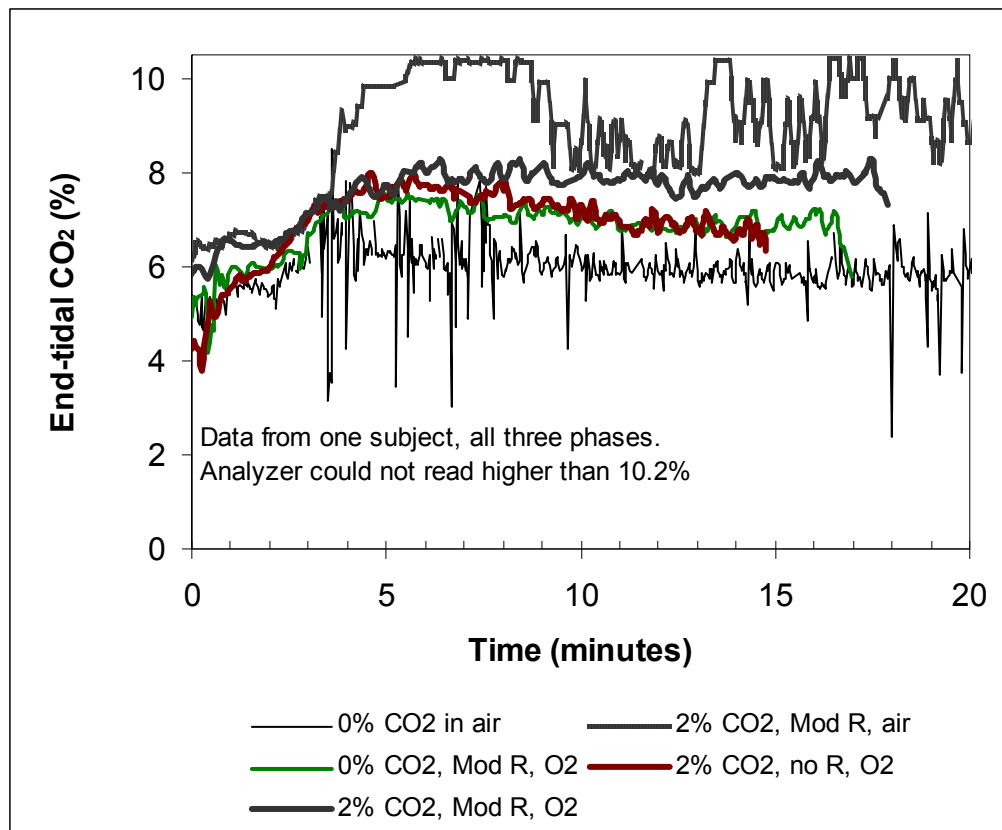

Figure 6. $F_{ET}CO_2$ for the subject with the highest values recorded in this study. Five experimental conditions are given. Several of the endurance measurements continued longer than the 20 minutes shown.
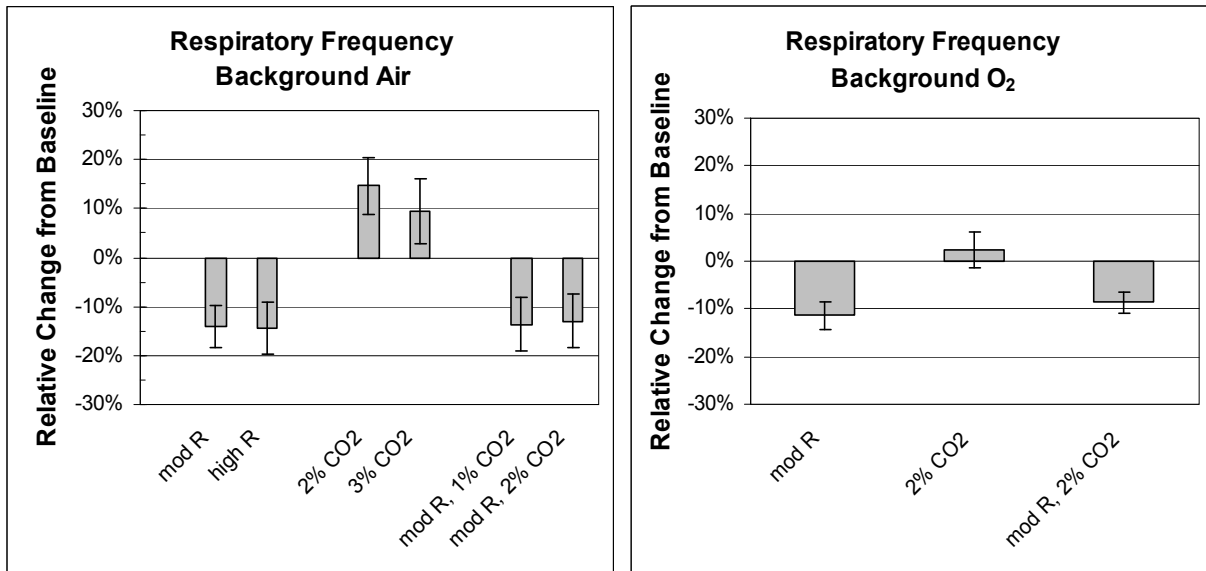
Figure 7. Breathing frequency f, percentage change from baseline, means and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. The f was lower than baseline with R ($p<0.01$) but not different from baseline with different R, breathing gas, or CO_2 fraction. It was higher than baseline ($p<0.03$) only with 2% CO_2 in air.
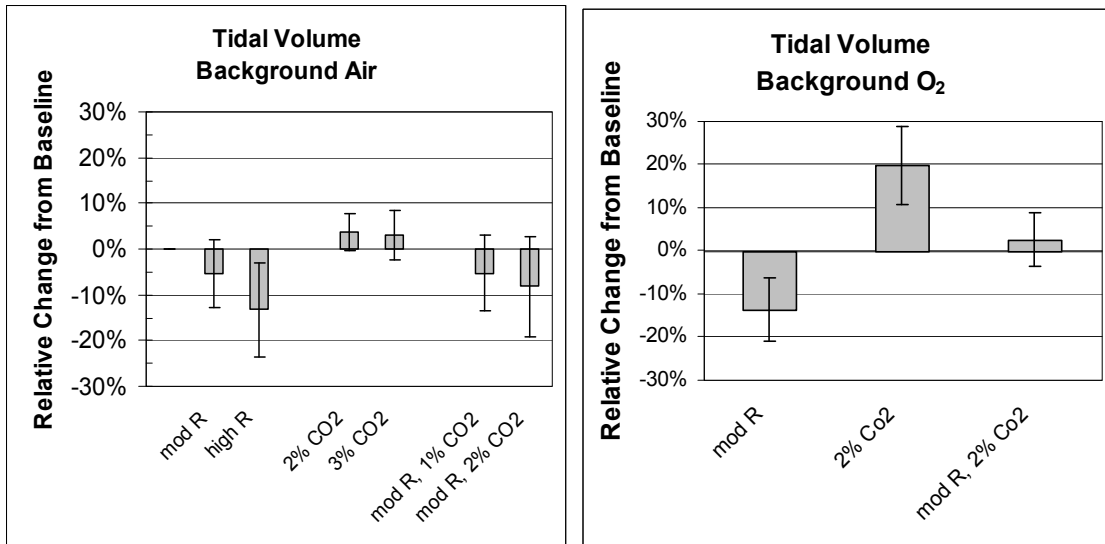
Figure 8. V_T, percentage change from baseline, means and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. V_T differed from baseline ($p < 0.03$) only for 2% CO_2 in O_2.

Changes in V_E were caused only by changes in *f* during air breathing and in *f* or V_T during O_2 breathing (Figs. 7 and 8).
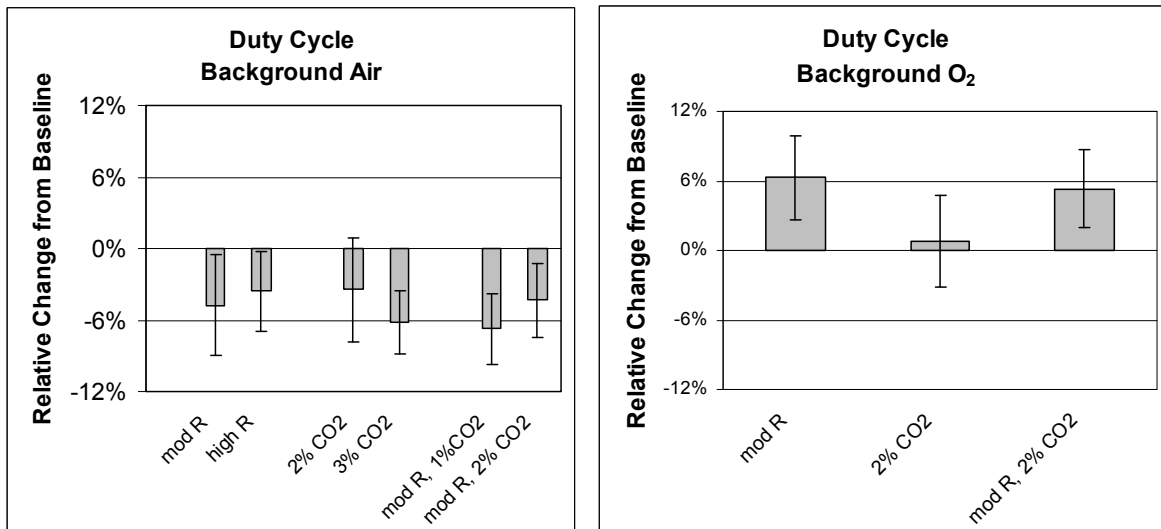

Figure 9. Respiratory duty cycle, percentage change from baseline, means and standard errors. Baseline (valve system without resistance of CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. None of the differences from baseline was significant.

Respiratory duty cycle (T_i/T_{tot}) was not changed by any of the conditions of this experiment (Fig. 9). However, duty cycle is difficult to interpret when, as in these measurements, *f* varies so much across measurements.
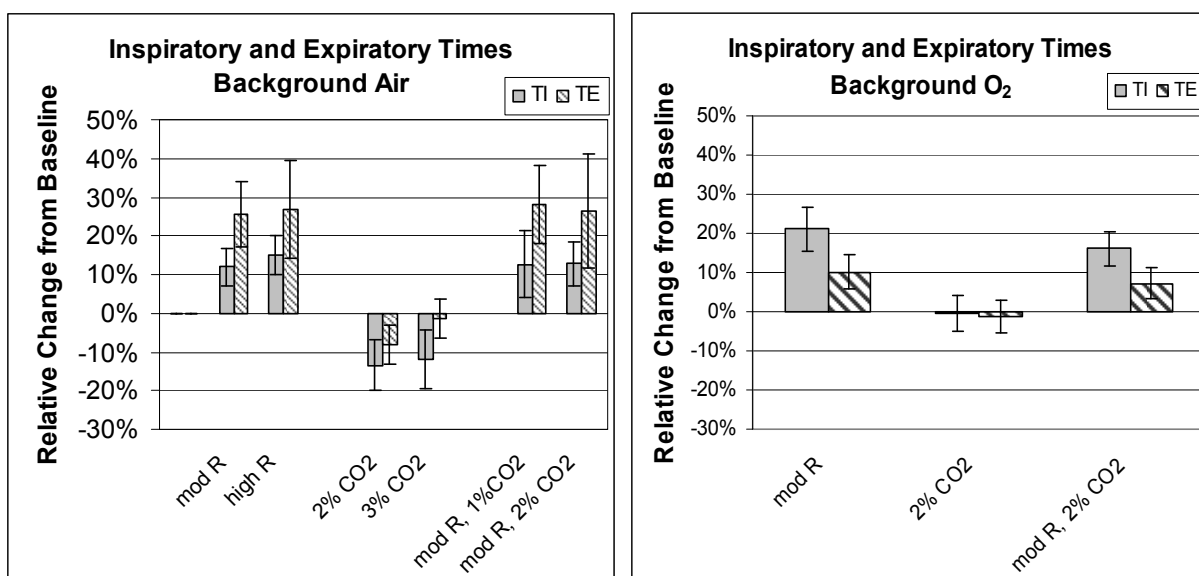

Figure 10. Inspiratory and expiratory times, percentage change from baseline, means and standard errors. Baseline (valve system without resistance or CO_2) values are listed in Table 2. "R" means resistance; "mod" is moderate. With background air, T_E increased ($p<0.02$) when resistance was present, and T_I decreased with 2% CO_2. With background O_2, T_I increased when resistance was present. No other difference from baseline was significant.

In the presence of resistance with or without CO_2, T_E increased ($p<0.02$) with air as the background gas, and T_I increased with O_2 as background gas ($p<0.01$; Fig. 10). With 2% inspired CO_2 in air but no added resistance, T_I decreased ($p<0.03$). None of the other changes was significant (Fig. 10).

We did not measure mask pressure or instantaneous flow in Phases 1 and 2. In Phase 3, water at the pressure tap sometimes compromised the measurement of mask pressure, and only expiratory flow profiles were available. However, we measured expiratory pressures ranging from 5.0 to 13.8 cm H_2O.

The valve system alone had no significant effect; in Phase 2 we conducted a second control measurement, valve and tubing system versus oronasal mask only, and measured no difference in any parameter considered. The pressure drop of the one-way valves is nominally 1.1 cm H_2O for inspiration and 1.0 cm H_2O for expiration at 100

L/min, and 3.0 cm H_2O for inspiration and 2.8 cm H_2O for expiration at 300 L/min.[22] In Phase 3 we measured sample expiratory pressures of 2.7 cm H_2O at 194 L/min and 4.3 cm H_2O at 356 L/min.

Our target peak expiratory pressure was twice the peak inspiratory pressure, and we achieved that ratio. From seven Phase 3 measurements with moderate resistance where we have flow and pressure drops for all conditions, the mean ratio of expiratory to inspiratory pressures was 1.75, with a range from 1.4 to 2.3. Overall results are summarized in Table 5.

Table 5. Summary of changes on the average.

Background Air:

	Endurance	V_E	f	V_T	T_I	T_E	$P_{ET}CO_2$
CO_2	↓	↑	↑	↔	↓	↔	↑
Resistance	↔	↓	↓	↔	↔	↑	↔
Both	↔	↓	↓	↔	↔	↑	↑

Background O_2:

	Endurance	V_E	f	V_T	T_I	T_E	$P_{ET}CO_2$
CO_2	↔	↑	↔	↑	↔	↔	↑
Resistance	↔	↓	↓	↔	↑	↔	↑
Both	↔	↔	↓	↔	↑	↔	↑

Key: ↓ = decrease, ↔ = no change, ↑ = increase.

Phase 3: O_2 breathing versus air breathing

We measured Phase 3 subjects under both air- and O_2-breathing baseline conditions. On the average, V_E with O_2 was lower than that with air (mean, 13%; standard error, 4%; p<0.01 by paired t-test), and T_I increased (mean, 14%; standard error, 5%; p<0.02). None of the other differences between air- and O_2-breathing was significant. Changes in endurance times ranged from −45% to +229%; those in $F_{ET}CO_2$, from −10% to +17%; those in f, from −24% to +17%; those in V_T, from −44% to +42%; those in duty cycle, from −8% to +11%; and those in expiratory time, from −16% to +39%.

Ventilatory Sensitivity to CO_2

Ventilatory sensitivity to CO_2 was not measured in three subjects: two who became unavailable for testing, and one who declined to be tested because the CO_2 exposure during testing had triggered debilitating headaches. Results from another three subjects could not be interpreted, perhaps because of technical flaws. The distribution of values for all other subjects from all three experimental phases is summarized in Figure 11.

Generally, $P_{ET}CO_2$ increased without change in ventilation when the subject first began to breathe from the reservoir of 7% CO_2, 93% O_2; then ventilation began to increase steeply. When the increase of V_E with $P_{ET}CO_2$ seemed to have two components, the second, longer-lasting linear segment was used, and its slope was considered to be the ventilatory sensitivity to CO_2.
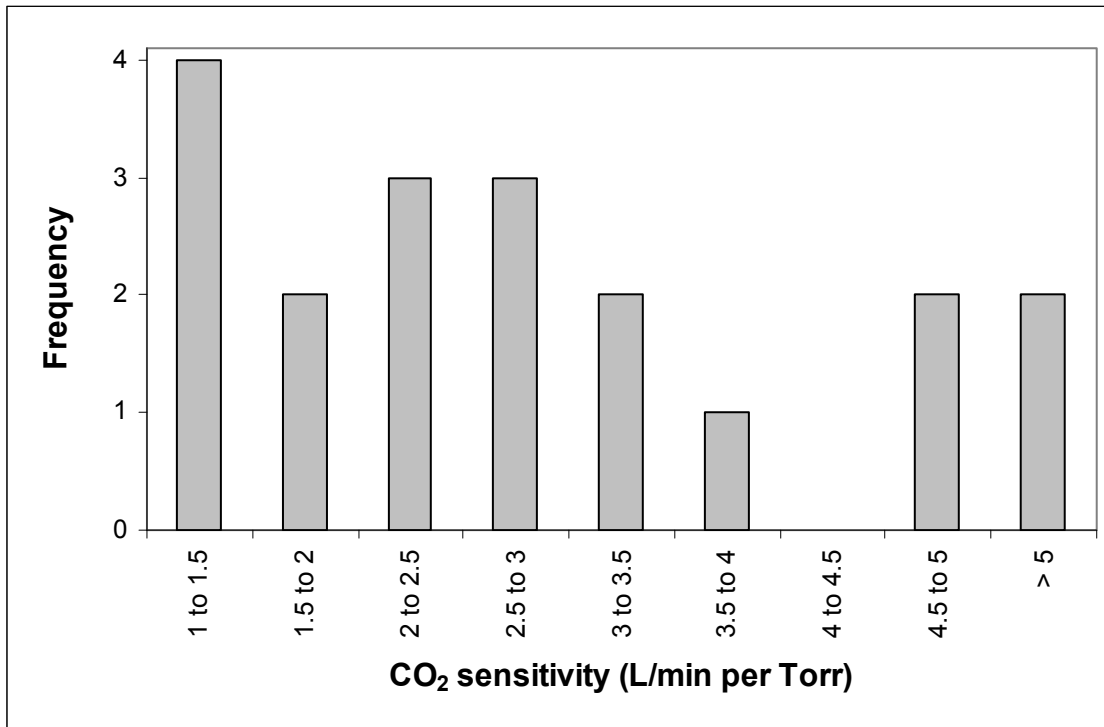

Figure 11. Histogram of ventilatory sensitivity to CO_2 at rest, rebreathing method, 19 subjects from all three phases. Note that four subjects were insensitive to CO_2, and four were hypersensitive.

Ventilatory sensitivity to CO_2 measured at rest did not correlate with end tidal CO_2 during exercise.

DISCUSSION

The average values presented in Figure 2 suggest that subjects breathing air or O_2 and exercising at 80 to 85% of peak aerobic capacity were able to compensate for 2% inspired CO_2 and for inspiratory and expiratory resistance patterned on that of the MK

16 at 50 fsw. Of the conditions tested, only 3% CO_2 in air decreased mean endurance time relative to that for subjects breathing unimpeded.

Individual results suggest a very different conclusion: neither can a dive be planned nor can equipment be designed for the population average. Rather, the individual who is most impaired is the one who must be accommodated. The effects on group endurance are thus better portrayed in Table 3 than in Figure 2. With background air, moderate resistance patterned after the MK 16 at 50 fsw reduced endurance time by 10% or more in four of ten subjects. That resistance, accompanied by 2% CO_2, reduced endurance time by at least 30% in four of ten subjects. With oxygen as background gas, the reduction in endurance affected fewer subjects, but even then the combination of CO_2 and UBA-like resistance impaired performance for some. Further, some subjects continued to exercise when they probably should have stopped because of CO_2 accumulation (Figs. 5 and 6, and Table 4).

The risk of elevated, inhaled CO_2 is real: exercising, air-breathing subjects have been seen to become confused and irrational with $F_{ET}CO_2$ of 8.5% and higher[23] — a CO_2 level matched or exceeded by the two of our subjects who reported tunnel vision, and almost matched by one who reported a sense of altered mental status (feeling "zoney"). These subjects did not have to cope with increases in internal WOB like those that result from submersion. Further, elevated arterial CO_2 increases the risk of central nervous system (CNS) oxygen toxicity even at oxygen partial pressures that are otherwise considered to be safe, either in rats in dry studies[24] or in human divers using rebreather UBAs at P_{O_2} as low as 1.2 atm.[25] In divers, CNS toxicity at shallow depths has included loss of consciousness. In four cases where divers lost consciousness and the UBAs were tested, inspired CO_2 measured from the rig after the accident was between 2.5% and 8%.[14]

According criteria used for acceptance of dive gear,[21] two air-breathing subjects showed that a diving rig with the resistance we called moderate and 2% inspired CO_2 is unsafe: they exceeded the limit of end tidal CO_2 allowed for outliers from the group. Using the same criteria, the mean of O_2-breathing subjects at the end of exercise came close to the group limit that would declare that combination to be unsafe. Early in exercise, the group mean may have crossed that threshold; Figure 6 indicates the usual pattern of a $F_{ET}CO_2$ increase that occurs early in exercise and is moderated after about 10 minutes.

Subjects who inhaled CO_2 in air without added resistance generally increased V_E enough to moderate but not to prevent CO_2 buildup, while those breathing CO_2 in O_2 allowed more CO_2 accumulation (Figs. 3, 4). Subjects who breathed air without added CO_2 against resistance decreased V_E without significant increase in CO_2. However, those breathing O_2 without added CO_2 against resistance decreased V_E enough to accumulate CO_2 (Figs. 3, 4). These results are consistent with others that show that the body will accept some accumulation of CO_2 to moderate the increase in WOB and some increase in WOB to moderate the accumulation of CO_2.[17] However, subjects who

breathed air against moderate resistance failed to respond to inspired CO_2 (Fig. 3), and $F_{ET}CO_2$ became considerably higher than baseline (Fig. 4). Some subjects reached very high $F_{ET}CO_2$ (Fig. 5). Subjects who breathed O_2 against moderate resistance had higher V_E with inspired CO_2 than they had without it. But V_E did not approach that level for the same inspired CO_2 without resistance (Fig. 3), and $F_{ET}CO_2$ was elevated above baseline (Fig. 4). Because these different levels of V_E seen across conditions were supporting similar external work and thus similar metabolic CO_2 production, they represent different ventilatory responses to exercise and V_E/V_{CO_2} for different breathing conditions.

For Phase 2, in the absence of pressure measurements we used the measured pressure-flow characteristics of the resistance elements to estimate mask pressures. Although we recognize this to be a first approximation only, we modeled flow as a sinusoid with the measured tidal volume and frequency. Mean estimated pressures were similar with or without inhaled CO_2, because mean V_E and f were similar across all conditions with resistance present (Figs. 3 and 7). The mean of estimated peak inspiratory pressures for moderate resistance was 11 (SD, 3) cm H_2O, and that for high resistance was 22 (SD, 10) cm H_2O. If we accept the sinusoidal approximation for inspiration, the estimated inspiratory WOB/V_T in Phase 2 was 1.1 (SD, 0.4) J/L for moderate resistance on inspiration and 2.1 (SD, 0.8) J/L with high resistance, independent of inspired CO_2. The ratio of pressure drops measured in Phase 3 indicates expiratory work of about 2 J/L.

In addition to reducing f, subjects faced with inspiratory resistance often increase duty cycle to prolong inspiratory time and thus to reduce peak inspiratory pressure and flow. However, unlike many devices that introduce an impediment to breathing, the MK 16 and other rebreather UBAs have higher expiratory than inspiratory resistance, because the diver must force gas through the scrubber. Duty cycle did not change significantly in these measurements (Fig. 9), and, for air breathing, expiratory time increased more than inspiratory time when f slowed (Fig. 10).

Because the expiratory resistance was laminar, expiratory pressure was directly proportional to flow, or for the same V_T, it was almost inversely proportional to expiratory time. That is, any change in pressure resulted in a proportional change in flow, independent of flow magnitude. However, because the inspiratory resistance was turbulent, the inspiratory pressure drop changed rapidly as flow changed. The change in inspiratory pressure was proportional to the change in the square of flow: a small decrease in a previously high inspiratory flow rewarded the subject with a large decrease in inspiratory pressure. Subjects unconsciously had to balance the inspiratory and expiratory pressure demands, as well as the penalty of CO_2 accumulation if the minute ventilation became too low. The balance intriguingly appears to be subtly different when the background gas is O_2 rather than air.

Baseline exercise V_E was lower during O_2 breathing than during air breathing in the same subjects and at the same ergometer settings, but with unchanged $F_{ET}CO_2$. We

speculate that this unchanged $F_{ET}CO_2$ with lower V_E may be a result of hyperoxic pulmonary vasodilation: CO_2 elimination in the lungs is perfusion limited.

Other investigators have shown that breathing 100% oxygen reduces the ventilatory response to exercise.[26] Because higher oxygen fractions are unlikely to improve hemoglobin saturation in healthy subjects and dissolved oxygen at atmospheric pressure contributes little to total oxygen transport, anaerobic threshold and oxygen delivery to tissues will not be affected by the change of breathing gas. More likely, the O_2 affects chemoreceptors involved in the control of breathing. Hyperoxia at rest has been shown to decrease the CO_2 sensitivity of the central chemoreceptors by 15% and to blunt that of the peripheral receptors by 70%.[27] This result may explain the greater rise of $F_{ET}CO_2$ from baseline during O_2 breathing than during air breathing, both with 2% inspired CO_2 and no resistance (Fig. 4).

We saw no correlation between the ventilatory sensitivity to CO_2 at rest and $F_{ET}CO_2$ at end exercise. This lack of correlation may imply that, for some individuals, the hierarchy of physiological importance in balancing WOB, CO_2 accumulation, maximum pressure swings, and any other factors placed CO_2 lower than other factors. It may imply that the CO_2 accumulation was unavoidable for some subjects if exercise was to continue. Certainly, others have seen a lack of correlation between an exercise ventilatory response during unencumbered breathing and ventilatory sensitivity to CO_2 measured as we did.[26]

CONCLUSIONS

Other authors have suggested that subjects may be able to compensate for 2% inspired CO_2 in a low-resistance circuit,[28] and on the average this might be true. However, no one is "the average." Even with the low resistance conditions in this study, endurance for some subjects was limited by inability to breathe enough, and two subjects complained of headache and one of vertigo after the trials. However, with resistance like that of the MK 16 UBA at 50 fsw in the circuit, the maximum V_E attained by subjects was reduced, probably by high expiratory pressures, and even the presence of inhaled CO_2 did not drive subjects to increase their breathing. When CO_2 was present, many subjects had endurance limited by difficulty in breathing, and symptoms of CO_2 retention became increasingly common. The apparent reduction in this phenomenon when O_2 was the background gas is false: although subjects felt less limited by the breathing impediment, this was likely because their breathing and other corrective responses were less sensitive to CO_2 when O_2 was the background gas than when they breathed air, and not because consequences of CO_2 retention were any less with high O_2 than with air. The mean $F_{ET}CO_2$ with moderate resistance and 2% CO_2 in O_2 reached 7.2%, 30% above control. For diver safety with the MK 16 and other rebreather UBAs with similar pressure-flow characteristics, inspired CO_2 should be maintained as close to 0% as possible.

REFERENCES

1. M. E. Knafelc, *Physiological Basis for CO$_2$ Limits within Semiclosed- and Closed-Circuit Underwater Breathing Apparatus*, NEDU TR 4-00, Navy Experimental Diving Unit, Panama City, FL, Aug 2000.

2. S. Finkelstein, J. C. Elliott, and U. C. Luft, *The Effects of Breathing Low Concentrations of CO$_2$ on Exercise Tolerance*, Part IA, Final Report: Contract NASA 9-7009, Lovelace Foundation for Medical Education and Research, Albuquerque, NM, Feb 1970.

3. J. M. Clark, R. D. Sinclair, and J. B. Lenox, "Chemical and Nonchemical Components of Ventilation during Hypercapnic Exercise in Man," *J. Appl. Physiol.* Vol. 48, No. 6 (1980), pp. 1065–1076.

4. S. Finkelstein, J. C. Elliott, and U. C. Luft, *The Effects of Breathing Low Concentrations of CO$_2$ on Respiratory Gas Exchange, Acid-Base Balance and Electrolytes During and After Exhaustive Exercise,* Part IB, Final Report: Contract NASA 9-7009, Lovelace Foundation for Medical Education and Research, Albuquerque, NM, Feb 1970.

5. C-S. Poon and J. G. Greene, "Control of Exercise Hyperpnea during Hypercapnia in Humans," *J. Appl. Physiol*, Vol. 59, No. 3 (1985), pp 792–797.

6. S. J. Menn, R. D. Sinclair, and B. E. Welch, "Effect of Inspired P$_{CO_2}$ up to 30 mm Hg on Response of Normal Man to Exercise," *J. Appl. Physiol.*, Vol. 28, No. 5 (1970), pp. 663–671.

7. H. A. Glatte Jr., G. J. Motsay, and B. E. Welch, *Carbon Dioxide Tolerance Studies*, AD664899, School of Aerospace Medicine, Brooks Air Force Base, TX, Aug 1967.

8. T. G. Babb, D. S. DeLorey, and B. L. Wyerick, "Ventilatory Response to Exercise in Aged Runners Breathing He-O$_2$ or Inspired CO$_2$," *J. Appl. Physiol.*, Vol. 94 (2003), pp. 685–693.

9. D. E. Warkander, *Comprehensive Performance Limits for Divers' Underwater Breathing Gear: Consequences of Adopting Diver-Focused Limits,* NEDU TR 07-02, Navy Experimental Diving Unit, Panama City, FL, Jan 2007.

10. D. E. Warkander, J. R. Clarke, and C. E. G. Lundgren, "Influence of Inspired CO$_2$ on Divers' Ventilatory Demands and the Impact on Unmanned Testing of Divers' Breathing Apparatus," *Undersea & Hyperbaric Medicine*, Vol. 27 (suppl, 2000), p. 47.

11. F. N. Craig, W. V. Blevins, and E. G. Cummings, "Exhausting Work Limited by External Resistance and Inhalation of Carbon Dioxide," *J. Appl. Physiol.*, Vol. 29, No. 6 (1970), pp. 847–851.

12. D. M. Caretti and J. A. Whitley, "Exercise Performance During Inspiratory Resistance Breathing Under Exhaustive Constant Load Work," *Ergonomics*, Vol. 41, No. 4 (1998), pp. 501–511.

13. A. T. Johnson, W. H. Scott, C. G. Lausted, M. B. Benjamin, K. M. Coyne, M. S. Sahota, and M. M. Johnson, "Effect of Respirator Inspiratory Resistance Level on Constant Load Treadmill Work Performance," *AIHA Journal*, Vol. 60 (July/Aug 1999), pp. 474–479.

14. N. S. Deno, E. Kanon, and D. Kiser, "Physiological Responses to Resistance Breathing during Short and Prolonged Exercise, *Am. Indust. Hyg. Assoc.*, Vol. 42 (1981), pp. 616–623.

15. P. Cerretelli, R. S. Sikand, and L. E. Farhi, "Effect of Increased Airway Resistance on Ventilation and Gas Exchange during Exercise," *J. Appl. Physiol.*, Vol. 27, No. 5 (1969), pp. 597–600.

16. J. Milic-Emili and J. M. Tyler, "Relation between Work Output of Respiratory Muscles and End-Tidal CO_2 Tension," *J. Appl. Physiol.,* Vol. 18, No. 3 (1963), pp. 663–671.

17. C-S. Poon, "Effects of Inspiratory Resistance Load on Respiratory Control in Hypercapnia and Exercise," *J. Appl. Physiol.*, Vol. 66, No. 5, (1989), pp. 2391–2399.

18. U.S. Naval Sea Systems Command, *Task Assignment 08-06: Effect of Inspired Carbon Dioxide and Breathing Resistance on Exercise Performances*, Ser 00CM/3018, 17 Jan 2008.

19. D. E. Warkander, *Technical Memorandum No. NEDU TM 08-17*, Navy Experimental Diving Unit, 03 Sept. 08.

20. D. J. Read and J. Leigh, "Blood-Brain Tissue PCO_2 Relationships and Ventilation during Rebreathing," *J. Appl. Physiol.*, Vol. 23, No. 1 (1967), pp. 53–70.

21. D. E. Warkander, W. T. Norfleet, G. K. Nagasawa, and C. E. G. Lundgren, "Physiologically and Subjectively Acceptable Breathing Resistance in Divers' Breathing Gear," *Undersea Biomed. Res.*, Vol.19, No. 6 (1992), pp. 427–445.

22. Hans Rudolph, Inc., "New Rudolph Nasal & Mouth Breathing Face Mask: Two-Way Non-Rebreathing," Data Sheet 691149-1 5/00 Rev. F, www.rudolphkc.com, Hans Rudolph, Kansas City, MO, 2000.

23. D. E. Warkander, W. T. Norfleet, G. K. Nagasawa, and C. E. G. Lundgren, "CO_2 Retention with Minimal Symptoms but Severe Dysfunction during Wet Simulated Dives to 6.8 atm abs," *Undersea Biomed. Res.*, Vol. 16, No. 6 (November 1990), pp. 515–523.

24. R. Arieli, G. Rashkovan, Y. Moskovitz, and O. Ertracht, "P_{CO_2} Threshold for CNS Oxygen Toxicity in Rats in the Low Range of Hyperbaric P_{O_2}," *J. Appl. Physiol.*, Vol 91 (2001), pp. 1582–1687.

25. R. Arieli, Y. Arieli, Y. Daskalovic, M. Eynan, and A. Abramovich, "CNS Oxygen Toxicity in Closed-Circuit Diving: Signs and Symptoms Before Loss of Consciousness," *Aviat., Space, and Environ. Med.* Vol. (77, No. 11 (2006), pp. 1153–1157.

26. S. M. Menitove, D. M. Rapoport, H. Epstein, B. Sorkin, and R. M. Goldring, "CO_2 Rebreathing and Exercise Ventilatory Responses in Humans," *J. Appl. Physiol.*, Vol. 56, No. 4 (1984), pp. 1039–1044.

27. A. Dahan, J. DeGoede, A. Berkenbosch, and I. C. W. Olievier, "Influence of Oxygen on the Ventilatory Response to Carbon Dioxide in Man," *J. Physiol.*, Vol. 428 (1990), pp. 485– 499.

28. C. J. Lambertsen, *Carbon Dioxide Tolerance and Toxicity*, IFEM 10-71, Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, PA, 1971.