Effects of elevated oxygen and carbon dioxide partial pressures on respiratory function and cognitive performance

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1Divers Alert Network, Durham, North Carolina; 2Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; 3U.S. Naval Submarine Medical Research Laboratory, Groton, Connecticut; 4Center for Hyperbaric Medicine and Environmental Physiology, Duke University Medical Center, Durham, North Carolina; and 5Center for Aging, Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina

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Gill M, Natoli MJ, Vacchiano C, MacLeod DB, Ikeda K, Qin M, Pollock NW, Moon RE, Pieper C, Vann RD. Effects of elevated oxygen and carbon dioxide partial pressures on respiratory function and cognitive performance. J Appl Physiol 117: 406–412, 2014. First published June 19, 2014; doi:10.1152/japplphysiol.00995.2013.—Hy- peroxia during diving has been suggested to exacerbate hypercapnic narcosis and promote unconsciousness. We tested this hypothesis in male volunteers (12 at rest, 10 at 75 W cycle ergometer exercise) breathing each of four gases in a hyperbaric chamber. Inspired Po2 (Po2) was 0.21 and 1.3 atmospheres (atm) without or with an individual subject’s maximum tolerable inspired CO2 (PCO2 = 0.055–0.085 atm). Measurements included end-tidal CO2 partial pressure (PETCO2), rating of perceived discomfort (RPD), expired minute ventilation (Ve), and cognitive function assessed by auditory n-back test. The most prominent finding was, irrespective of PETCO2, that minute ventilation was 8–9 l/min greater for rest or exercise with a PIO2 of 1.3 atm compared with 0.21 atm (P < 0.0001). For hyperoxic gases, PETCO2 was consistently less than for normoxic gases (P < 0.01). For hyperoxic hypercapnic gases, n-back scores were higher than for normoxic gases (P < 0.01), and RPD was lower for exercise but not rest (P < 0.02). Subjects completed 66 hyperoxic hypercapnic trials without incident, but five stopped prematurely because of serious symptoms (tunnel vision, vision loss, dizziness, panic, exhaustion, or near syncope) during 69 normoxic hypercapnic trials (P = 0.0582). Serious symptoms during hypercapnic trials occurred only during normoxia. We conclude serious symptoms with hyperoxic hypercapnia were absent because of decreased PETCO2, consequent to increased ventilation.

oxygen toxicity; carbon dioxide poisoning; respiratory function; cognitive performance; oxygen diving

JOHN SCOTT HALDANE reported the narcotic effect of carbon dioxide was a limiting factor for divers when helmet ventilation was inadequate, resulting in CO2 accumulation with exercise intolerance and unconsciousness (“deep water blackout”) (4, 20, 25). Normal function was possible when breathing an inspired CO2 partial pressure (PiCO2) of 0.03 atm, but PiCO2 in excess of 0.04 atm limited work capacity, and unconsciousness was almost certain above a PiCO2 of 0.1 atm.

During the Second World War, British Navy combat divers using oxygen rebreathers would occasionally lose consciousness in less than 6 m of sea water (msw, 1.6 atm), which appeared too shallow for oxygen toxicity according to experimental trials (4, 10, 11). This phenomenon was described as “shallow water blackout”,1 which was hypothesized to result from the narcotic properties of CO2 that were exacerbated by high inspired oxygen partial pressures (PiO2). To investigate this hypothesis, Donald (10, 11) had volunteers exercise at sea level while rebreathing oxygen with or without CO2 absorption. The exposures were terminated by vertigo, tremors, loss of balance, dissociation, unconsciousness, weakness, cyanosis, or inability to stand. Respiratory distress was minimal or absent despite high ventilation rates and mean inspired CO2 partial pressures of 0.068–0.128 atm corresponding to mean CO2 partial pressures in the counterlung of 0.051–0.081 atm. For operational purposes, it was concluded, “that the chief factor in shallow water blackout is carbon dioxide intoxication” (4), but the influence of PiO2 could not be known as Donald had conducted no normoxic controls (10, 11). Our objective was to repeat this work with a full set of controls to investigate the secondary role of PiO2 on CO2 intoxication.

The adverse effect of hypercapnia on cognitive or psychomotor performance has been demonstrated in various studies (13, 23, 24, 42), but only one investigated a possible interaction between O2 and CO2, and there were no performance decrements in postural sway, tremor, hand steadiness, simple reaction time, or choice reaction time with either normoxia or hyperoxia for gases containing a PiCO2 of 0.06 atm (22).

The effect of hyperoxic hypercapnia on consciousness in divers remains relevant because of CO2 retention during underwater exercise (8, 15, 38), especially with closed-circuit rebreathers where CO2 can be present in the inspired gas. Symptoms suggestive of oxygen toxicity were reported in Israeli Navy combat swimmers using rebreathers at 3–6 msw (1), although the low PiO2 at these shallow depths (1.1–1.2 atm) (21) indicated hypercapnia as the causative agent. Hypercapnia alone impairs cognition in divers (48), occasionally with fatal results (34). Here we describe the results of an investigation of the effects of hyperoxia on respiratory function and cognitive performance in volunteers who breathed hypercapnic gas to test the hypothesis that hyperoxia potentiates CO2 intoxication.

METHODS

Subjects. The Institutional Review Board of Duke University Medical Center approved the study, subjects provided informed consent, and a medical history review with a baseline physical examination by

1 In current usage, the term “shallow water blackout” more commonly refers to unconsciousness from hypoxia during breath-hold diving (8a). The original usage referred to diving with oxygen rebreathers (1).
a hyperbaric physician ensured they were healthy. Sixteen male volunteers were recruited from among local certified scuba divers or people who had previous hypobaric/hyperbaric chamber experience at the laboratory. Women were not included because of variations in hypercapnic ventilatory response (HCVR) during the menstrual cycle (35, 43). Body fat composition of <20% was required as estimated by seven-site skinfold measures (33).

### Assessment of cognitive function
Cognitive function was assessed with an auditory n-back test (27), which has consistently been found to activate frontal and parietal cortical regions in a meta-analysis of 24 studies and is a standard for evaluating working memory (37). The test presented subjects with a train of long (200 ms) and short (100 ms) tones of random frequency separated by 1-s intervals. Subjects were required to identify the length of the most recent tone as equal to or different from the previous tone. For subjects who consistently exceeded 90%, a higher level of difficulty was introduced by asking for comparison of the most recent tone with a tone 2–3 stimuli earlier (the “n” in n-back). Subjects trained until they could achieve 80–90% correct responses.

**Determination of the highest tolerable inspired CO2 limit.** There was wide variability of CO2 tolerance among subjects. The highest tolerable limit was determined for each subject from among gases containing 0.065, 0.075, and 0.085 atm PICO2. (These gases were blended from pure N2, O2, and CO2.) Each gas of progressively increasing CO2 concentration was inspired for 6 min separated by a 6-min interval breathing CO2-free gas to allow recovery (Table 1). Tolerance limits were determined separately with subjects seated at rest or seated on a bicycle ergometer and exercising at 75 W. Previous work had shown that ventilation approaches steady state in 4 min (18).

### Order of gas administration, from lowest to highest CO2 concentration. Each CO2 exposure was preceded by a 6-min, normoxic, normocapnic control gas. Time indicates start time for each gas breathing period.

<table>
<thead>
<tr>
<th>Time, min</th>
<th>PO2, atm</th>
<th>PICO2, atm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.21</td>
<td>0.065</td>
</tr>
<tr>
<td>12</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>18</td>
<td>0.21</td>
<td>0.075</td>
</tr>
<tr>
<td>24</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>30</td>
<td>0.21</td>
<td>0.085</td>
</tr>
<tr>
<td>36</td>
<td>0.21</td>
<td>End test</td>
</tr>
</tbody>
</table>

The pressure transducer, pneumotachometer, and mass spectrometer were calibrated at pressure from +50 to −50 cmH2O using an electronic manometer (Sper Scientific, Scottsdale, AZ), a 3-liter syringe and gasometer (model DTM 325–4, American Meter, Nebraska City, NE), and three premixed gas samples of known O2 and CO2 concentration. After instrument calibration, the subject breathed ambient chamber air through the mouthpiece while performing a practice n-back test battery. This was followed by the test gases in Table 1 until the maximum tolerable PICO2, or 0.085 atm, was achieved. Separate tolerance tests were conducted at rest and with 75 W exercise. At the end of each breathing period, the subject was asked to report a rating of perceived discomfort (RPD) on a 0–10 visual analog scale with zero being no discomfort and 10 being the maximum tolerable discomfort. At the end of each breathing period the subject reported any symptoms that had occurred.

**Determination of hyperoxic and hypercapnic effects.** These procedures were similar to those described above except for the pattern of breathing gases. Four gases were presented to the subject (Table 2): gas A, a normoxic control with no CO2; gas B, an experimental gas with an oxygen partial pressure of 1.3 atm and no CO2; gas C, a normoxic experimental gas containing the tolerable CO2 limit for that subject; and gas D, a hyperoxic, hypercapnic experimental gas with a PO2 of 1.3 atm and the tolerable CO2 limit. A PO2 of 1.3 atm was selected because this approaches the highest value believed to have a very low probability of causing central nervous system oxygen toxicity (45) and is the value used in the US Navy Mk 16 closed-circuit mixed gas breathing apparatus (44a).

Subjects were tested on three different days. On each day the subject was presented with three pairs of gases, for example, AB, AC, and AD, in which each experimental gas was preceded by a control gas to return the subject to steady state before breathing the next experimental gas. The 6-min washout period with control gas A before

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**Table 1. Determination of the highest tolerable PICO2**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>PO2, atm</th>
<th>PICO2, atm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.21</td>
<td>0.065</td>
</tr>
<tr>
<td>12</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>18</td>
<td>0.21</td>
<td>0.075</td>
</tr>
<tr>
<td>24</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>30</td>
<td>0.21</td>
<td>0.085</td>
</tr>
<tr>
<td>36</td>
<td>0.21</td>
<td>End test</td>
</tr>
</tbody>
</table>

**Table 2. Respired gas mixtures for determination of hyperoxic and hypercapnic effects**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Gas</th>
<th>PO2, atm</th>
<th>PICO2, atm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Control</td>
<td>0.21</td>
<td>0.0</td>
</tr>
<tr>
<td>B</td>
<td>Experimental</td>
<td>1.30</td>
<td>0.0</td>
</tr>
<tr>
<td>C</td>
<td>Experimental</td>
<td>0.21</td>
<td>0.065–0.085</td>
</tr>
<tr>
<td>D</td>
<td>Experimental</td>
<td>1.30</td>
<td>0.055–0.085</td>
</tr>
</tbody>
</table>
each experimental gas reduced the carryover effects from the previous experimental gas. To eliminate an effect of experimental gas order, the presentation of gas pairs was randomized in a Latin square design on the three separate days as illustrated in Table 3 (12).

The seated subject was fitted with mouthpiece and headphones (Fig. 1) and completed a practice n-back test battery while breathing chamber air during instrument calibration. The subject, attendant, and investigators were blinded to the gas breathed and the order of the gas pairs (Table 3). Each gas was breathed for 6 min. The first 2 min allowed the previous gas to be washed out of the circuit and PetCO2 to reach steady state before a 4-min n-back test period. Respiratory parameters for each gas were reported as the means of those recorded during the last 30 s of the 6-min period. Subjects were exposed at the same time of day to control for diurnal variation in HCVR. Recorded data included symptoms, symptom severity score (RPD), inspiratory and expiratory mouthpiece pressure, PetCO2, PetO2, pulmonary ventilation (Ve), and heart rate.

Experiments were repeated on a separate day with subjects pedaling on a cycle ergometer at a work rate of 75 W. Exercising subjects were allowed an extra 2 min of rest after each exercise bout, but there were no other differences between resting and exercising trials.

**Statistical analysis.** The crossover, randomized Latin square design allowed each subject to serve as his own statistical control while permitting designed manipulation of potentially confounding factors and their interactions (sequence order, CO2 tolerance level, and individual n-back difficulty). Effects on outcomes were modeled by repeated-measures multiple linear regression (SAS Version 9.1, Cary, NC). Outcome variables of interest were Ve, PetCO2, RPD, and n-back.

Analysis was conducted with two objectives: 1) to investigate how outcomes varied with PetCO2 as a continuous and homogeneous predictor and with PrO2 as a binary predictor and 2) to investigate how hyperoxia independently affected outcomes for normocapnic gases (A and B) and for hypercapnic gases (C and D). The second analysis was conducted in the event that the heterogeneity of subject CO2 tolerance distorted the relationships of PetCO2 to outcomes in the first analysis.

Differences in the incidence of serious symptoms for gases C and D were evaluated by a two-tailed Fisher’s exact test. Significance was accepted at $P < 0.05$.

**RESULTS**

**Subjects.** Four of the 16 volunteers declined to finish the lengthy n-back training and withdrew. The remaining 12 completed the resting phase of the study, and 10 of these completed the exercise phase. The physical characteristics of those who completed the trials are shown in Table 4.

The n-back and CO2 tolerance limits for each subject are listed in Table 5. The mean maximum PrO2 tolerated by the 12 resting subjects was 0.081 ± 0.007 atm (61.6 mmHg) and 0.074 ± 0.12 atm (56.2 mmHg) for the 10 exercising subjects. CO2 tolerance decreased with age ($P < 0.0001$). During exposure to gas C (normoxic hypercapnia), Subject 1 developed serious symptoms (Table 6) at a PrO2 of 0.075 atm (57.0 mmHg), and his subsequent resting trials were conducted with PrO2 of 0.065 atm (49.4 mmHg). This was also true for Subject 3, and his PrO2 was reduced from 0.085 to 0.075 atm for rest and from 0.065 to 0.055 atm during exercise.

**Correlation of Ve, RPD, and n-back with PetCO2.** Figure 2, A–C, illustrates raw data for n-back, RPD, and Ve as functions of PetCO2 independent of PrO2 for resting subjects. Linear regression lines were fit to the raw data as visual aids but do not reflect the repeated-measures analysis.

n-Back score was negatively, but modestly, correlated with PetCO2 ($P < 0.0001$), with n-back decreasing (reduced performance) at 0.51 (rest) and 0.58 (exercise) %/mmHg (Fig. 2A). With PetCO2, as the predictor variable, n-back was unaffected by PrO2 but was negatively correlated with age at 0.27%/yr for rest (data not shown). There was no age effect with exercise (data not shown).

RPD was positively correlated with PetCO2 for rest and exercise. There was an interaction between PrO2 and PetCO2, but PrO2 was not significant for exercise. The increase in RPD was greatest at low values of PetCO2 where dyspnea was minimal. RPD was also associated with age for both rest and exercise ($P = 0.0001$). RPD increased by 0.06 units per year of age (rest) and 0.08 (exercise). Peak-to-peak mouthpiece pressures did not exceed 7 mbar, well within the European Standard for Personal Protection Equipment (EN14143:2003).

Ve was strongly associated with both PrO2 and PetCO2 ($P < 0.0001$), with Ve increasing at 1.77 (rest) and 1.39 (exercise) %/H11021

<table>
<thead>
<tr>
<th>Day</th>
<th>Gas Pair 1</th>
<th>Gas Pair 2</th>
<th>Gas Pair 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AB</td>
<td>AC</td>
<td>AD</td>
</tr>
<tr>
<td>2</td>
<td>AC</td>
<td>AD</td>
<td>AB</td>
</tr>
<tr>
<td>3</td>
<td>AD</td>
<td>AB</td>
<td>AC</td>
</tr>
</tbody>
</table>

Table 3. Gas pair sequences based on a Latin square design

Table 4. Physical characteristics of subjects who completed the study

Table 5. n-Back level and CO2 tolerance of all subjects

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Arrows indicate subjects who changed from a higher to lower CO2 tolerance gas after they developed serious manifestations. *Did not complete exercise phase.
Table 6. Outcome variables and gases for rest and 75 W exercise

<table>
<thead>
<tr>
<th>Gas</th>
<th>A (n = 108)</th>
<th>B (n = 36)</th>
<th>P</th>
<th>C (n = 36)</th>
<th>D (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_{O_2}, ata</td>
<td>0.21</td>
<td>1.3</td>
<td>A→B</td>
<td>0.21</td>
<td>1.3</td>
<td>C→D</td>
</tr>
<tr>
<td>P_{CO_2}, ata</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td>0.065–0.085</td>
<td>0.065–0.085</td>
<td></td>
</tr>
<tr>
<td>PET_{CO_2}, mmHg</td>
<td>36.3 (±3.1)</td>
<td>31.8 (±3.3)</td>
<td>&lt;0.0001</td>
<td>60.7 (±3.9)</td>
<td>57.4 (±4.9) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ve, l/min BTPS</td>
<td>11.9 (±2.7)</td>
<td>14.3 (±3.2)</td>
<td>0.0013</td>
<td>60.3 (±15.5)</td>
<td>59.5 (±16.5) ns</td>
<td></td>
</tr>
<tr>
<td>RPD (0–10)</td>
<td>7.5–17.8</td>
<td>8.8–20.1</td>
<td></td>
<td>28.5–75.4</td>
<td>28.1–75.9</td>
<td></td>
</tr>
<tr>
<td>n-back, %correct</td>
<td>84.6 (±6.0)</td>
<td>84.4 (±5.8)</td>
<td>ns</td>
<td>70.2 (±9.1)</td>
<td>73.5 (±9.1) 0.003</td>
<td></td>
</tr>
<tr>
<td>Gas</td>
<td>A (n = 90)</td>
<td>B (n = 30)</td>
<td>P</td>
<td>C (n = 30)</td>
<td>D (n = 30)</td>
<td>P</td>
</tr>
<tr>
<td>Exercise at 75 w (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P_{O_2}, ata</td>
<td>0.21</td>
<td>1.3</td>
<td>A→B</td>
<td>0.21</td>
<td>1.3</td>
<td>C→D</td>
</tr>
<tr>
<td>P_{CO_2}, ata</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td>0.055–0.085</td>
<td>0.055–0.085</td>
<td></td>
</tr>
<tr>
<td>PET_{CO_2}, mmHg</td>
<td>37.8 (±3.0)</td>
<td>34.8 (±3.2)</td>
<td>0.0003</td>
<td>64.9 (±6.9)</td>
<td>61.6 (±6.7) 0.0081</td>
<td></td>
</tr>
<tr>
<td>Ve, l/min BTPS</td>
<td>33.6–42.0</td>
<td>31.1–40.3</td>
<td>0.018</td>
<td>82.3 (±11.9)</td>
<td>86.6 (±11.0) 0.0149</td>
<td></td>
</tr>
<tr>
<td>RPD (0–10)</td>
<td>34.1–46.8</td>
<td>37.6–50.7</td>
<td></td>
<td>53.1–96.8</td>
<td>56.8–95.2</td>
<td></td>
</tr>
<tr>
<td>n-back, %correct</td>
<td>85.3 (±6.7)</td>
<td>86.3 (±9.6)</td>
<td>ns</td>
<td>69.0 (±8.6)</td>
<td>73.4 (±8.5) 0.0092</td>
<td></td>
</tr>
</tbody>
</table>

Means, SD, and minimum/maximum values for outcome variables and gases for rest and 75 w exercise. ns, Not significant.

Individual tolerance for P_{CO_2} varied widely (0.055–0.085 atm) among our subjects, suggesting that CO_2 exposure safety cannot be characterized by a single value. We might have chosen the lowest maximum P_{CO_2} all subjects could tolerate, and this would have simplified interpretation and analysis, but the most CO_2-resistant individuals would have contributed no information to the study. Instead, we chose the maximum P_{CO_2} tolerated by each individual as a measure of population heterogeneity because this provided the most information. Henning et al. (22) and Sheehy et al. (44) found no performance effects with hypoxia, perhaps because they used lower values of P_{O_2} and P_{CO_2} than did we or because the n-back test was more sensitive.
values as though they pertained to the same subject. Lacking such detailed information, we used binary tests that evaluated the effect of hyperoxia on pairs of gases with and without hypercapnia. The results of this analysis appeared to be relatively unambiguous (Table 6): when $P_{O_2}$ was raised from 0.21 to 1.3 atm, $V\dot{E}$ increased in hypercapnia (except for resting hypercapnia), whereas $P_{ETCO_2}$ decreased under all conditions. RPD improved for hypercapnia with exercise (although not for rest), whereas $n$-back scores improved for both rest and exercise with hypercapnia. These observations were consistent with a straightforward interpretation: hyperoxia increased ventilation; increased ventilation eliminated more CO₂, thereby reducing $P_{ETCO_2}$; and there was less discomfort and improved performance with reduced $P_{ETCO_2}$. It should be noted, however, as Hesser et al. (24) and Sayers et al. (42) have suggested, performance (e.g., $n$-back scores) may be affected by the increased discomfort (e.g., higher RPD) that accompanies rising $P_{ETCO_2}$. (Fig. 2, A and B). Indeed, a study by Bloch-Salisbury suggests that EEG may be more sensitive to inspired CO₂ than cognitive performance (7).

Figure 2C illustrates a robust, positive correlation of $V\dot{E}$ with $P_{ETCO_2}$ for resting subjects even when $P_{ETCO_2}$ was treated as pertaining to a single subject. A smaller but significant increase of 8–9 l/min in $V\dot{E}$ was noted when $P_{O_2}$ was raised from 0.21 to 1.3 atm. (Observations were similar for exercise.) Increased ventilation and decreased $P_{ETCO_2}$ has been a common finding under both isocapnic and poikilocapnic conditions (5, 6, 18, 26), but hyperoxia has also been observed to attenuate ventilation associated with hypercapnia and ventilation during exercise in a hyperbaric environment (15, 18, 38) consistent with finding that both arterial and mixed venous CO₂ values were higher in hyperoxia (15, 38). Our $P_{ETCO_2}$ values, on the other hand, were consistently lower in hyperoxia (Table 6). Both these results are consistent with the direction of the change in ventilation.

There are several possible explanations for the higher ventilation and lower $P_{ETCO_2}$ in our study as opposed to the lower ventilation and higher arterial and mixed venous CO₂ in the Fraser et al. and Peacher et al. studies (15, 38). Our $P_{O_2}$ was only 1.3 atm, whereas Fraser and Peacher and colleagues used 1.75 atm. Perhaps the effect of hyperoxia is dose dependent such that the responsiveness of the carotid body to hypercapnia is attenuated at 1.75 atm but not at 1.3 atm (38). However, Gelfand and Lambertsen (18) found a decrease in ventilation and increase in alveolar $P_{CO_2}$ with an alveolar $P_{O_2}$ of only 0.88 atm (18). Moreover, Cherry et al. (8) did not observe any significant decrease in $P_{ACO_2}$ at $P_{O_2}$ = 1.3 atm (8).

It has been proposed that hyperoxia can cause an increase in ventilation because of the Haldane effect (5, 6). The explanation is that hyperoxia raises venous $P_{O_2}$ and hence reduces the solubility of CO₂ in blood. Under constant metabolic conditions, this in turn would cause $P_{CO_2}$ in the venous blood (and hence tissue) to rise, therefore stimulating ventilation via the central chemoreceptors. Indeed, under hypoxic conditions a small rise in $P_{O_2}$ can induce a significant increase in venous $P_{CO_2}$ due to the Haldane effect. However, during hyperoxia this effect is quite small (12). Moreover, numerous studies of hyperoxic gas breathing in which arterial $P_{CO_2}$ has been directly measured have failed to show a significant effect (14, 16, 28–32, 36, 39–41, 47, 49).
Thus it is likely that the apparent hyperventilation when using $\text{PETCO}_2$ as a surrogate for $\text{PaCO}_2$ is a reflection of an alteration in the relationship between $\text{PaCO}_2$ and $\text{PETCO}_2$. The most likely explanation for the higher ventilation as a function of $\text{PETCO}_2$ (Fig. 2C) when breathing 1.3 atm $\text{PO}_2$ is therefore a change in $\text{Ve}$ matching induced by hyperoxia. Wagner and colleagues (47) demonstrated that breathing 100% oxygen results in an effective increase in dead space. The result of this would be an increase in the arterial to end-tidal $\text{PCO}_2$ difference ($\text{PaCO}_2 - \text{PETCO}_2$). During hyperoxia, $\text{PETCO}_2$ therefore underestimates $\text{PaCO}_2$, thus leading to an apparent increase in ventilation when plotted vs. $\text{PETCO}_2$. A test of this hypothesis must wait for a study that measures both $\text{PETCO}_2$ and $\text{PaCO}_2$.

Gelfand and Lambertsen (18) and Dahan et al. (9) reported that hyperoxia appears to influence peripheral and central chemoreceptor control of ventilation with different time courses and amplitudes. We were unlikely to detect these effects, however, as our outcome measures were taken at the end of our 4 min exposures whereas the transients seen by Gelfand and Dahan had reached steady-state by about 4 min.

We found serious $\text{CO}_2$ toxicity symptoms occurred exclusively with normoxic hypercapnia although short of statistical significance. These observations were consistent with the higher ventilation rates and lower $\text{PETCO}_2$ that accompanied hyperoxia (Table 6). The higher $\text{PETCO}_2$ associated with normoxia might well be expected to be associated with a higher probability of serious symptoms.

A review of two unpublished studies puts this observation in perspective. Gray et al. (19) investigated a self-rescue device for submerged helicopter crashes in which four subjects rebreathed air or 100% oxygen from a counterlung. While rebreathing air, dyspnea proceeded rapidly to voluntary termination, with subjects exhibiting cyanosis and ending with a $\text{PO}_2 = 98.8$ mmHg and a $\text{PCO}_2 = 61.5$ mmHg. During oxygen rebreathing, hypoxia was absent and dyspnea progressed more slowly with subjects reporting vertigo, marked confusion, near syncope, and mild euphoria that relieved the dyspnea with subjects ending with a $\text{PO}_2 = 495.5$ mmHg and a $\text{PCO}_2 = 86.6$ mmHg. The authors noted the subjects would have continued rebreathing had the test not been involuntarily terminated by a medical officer.

A second study found similar results in an investigation of breath-hold diving with air, 50% oxygen, or 100% oxygen for potential use in extending the dive time of special operations swimmers (46). Anxiety, disorientation, near syncope, altered consciousness, tunnel vision, and impaired hearing occurred in 0.9% of 107 trials with air (ending $\text{PaO}_2 = 61.8$ mmHg and $\text{PETCO}_2 = 62.4$ mmHg), 1.8% of 55 trials with 50% oxygen (ending $\text{PaO}_2 = 154.5$ mmHg and $\text{PETCO}_2 = 72.7$ mmHg), and 7.3% of 137 trials with 100% oxygen (ending $\text{PaO}_2 = 357.0$ mmHg and $\text{PETCO}_2 = 75.4$ mmHg).

Both studies sought to use oxygen to extend operational capabilities, but the authors concluded this was inadvisable due to safety concerns. With air breath-hold or rebreathing, hypoxia led to extreme discomfort and voluntary termination. With oxygen, hypoxia was absent, but hypercapnia was more extreme and the ability to judge when an exposure should be ended safely was compromised. In the study reported here, increased free ventilation with hyperoxia diminished hypercapnia, thereby reducing the probability of serious symptoms. The lack of free ventilation in the breath-hold and rebreathing studies made the reduction of $\text{PETCO}_2$ impossible.

Barlow and MacIntosh (4) concluded that elevated $\text{PETCO}_2$ was the main cause of shallow water blackout, and our findings support this conclusion. However, we also found evidence indicating that hyperoxia may not increase the risk of hypercapnia and serious $\text{CO}_2$ toxicity symptoms.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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