Risk factors for immersion pulmonary edema: hyperoxia does not attenuate pulmonary hypertension associated with cold water-immersed prone exercise at 4.7 ATA


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Fraser JA, Peacher DF, Freiberger JJ, Natoli MJ, Schinazi EA, Beck IV, Walker JR, Doar PO, Boso AE, Walker AJ, Kernagis DN, Moon RE. Risk factors for immersion pulmonary edema: hyperoxia does not attenuate pulmonary hypertension associated with cold water-immersed prone exercise at 4.7 ATA. J Appl Physiol 110: 610–618, 2011. First published December 9, 2010; doi:10.1152/japplphysiol.01088.2010.—Hyperoxia has been shown to attenuate the increase in pulmonary artery (PA) pressure associated with immersed exercise in thermoneutral water, which could serve as a possible preventive strategy for the development of immersion pulmonary edema (IPE). We tested the hypothesis that the same is true during exercise in cold water. Six healthy volunteers instrumented with arterial and PA catheters were studied during two 16-min exercise trials during prone immersion in cold water (19.9–20.9°C) in normoxia (0.21 atmospheres absolute (ATA)) and hyperoxia (1.75 ATA) at 4.7 ATA. Heart rate (HR), Fick cardiac output (CO), mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), central venous pressure (CVP), arterial and venous blood gases, and ventilatory parameters were measured both early (E, 5–6 min) and late (L, 15–16 min) in exercise. During exercise at an average oxygen consumption rate (VO_{2}) of 2.38 ml·kg⁻¹·min⁻¹, CO, CVP, and pulmonary vascular resistance were not affected by inspired PO_{2} or exercise duration. Minute ventilation (V_{E}), alveolar ventilation (V_{A}), and ventilation frequency (f) were significantly lower in hyperoxia compared with normoxia (mean ± SD: V_{E} 58.8 ± 8.0 vs. 65.1 ± 9.2, P = 0.003; V_{A} 40.2 ± 5.4 vs. 44.2 ± 9.0, P = 0.01; f 25.4 ± 5.4 vs. 27.2 ± 4.2, P = 0.04). Mixed venous pH was lower in hyperoxia compared with normoxia (7.17 ± 0.07 vs. 7.20 ± 0.07), and this result was significant early in exercise (P = 0.002). There was no difference in mean PAP (MPAP: 28.28 ± 8.1 and 29.09 ± 14.3 mmHg) or PAWP (18.0 ± 7.6 and 18.7 ± 8.7 mmHg) between normoxia and hyperoxia, respectively. PAWP decreased from early to late exercise in hyperoxia (P = 0.002). These results suggest that the increase in pulmonary vascular pressures associated with cold water immersion is not attenuated with hyperoxia.

diving; cold; immersion; pulmonary edema

IMMERSION PULMONARY EDEMA (IPE, often referred to as swimming-induced pulmonary edema, SIPE) is a condition occurring in otherwise healthy individuals during surface swimming or diving that is characterized by cough, dyspnea, hemoptysis, and hypoxemia. The syndrome was first described by Wilmshurst in 1981 in three individuals who developed pulmonary edema while scuba diving in cold water (43) and later in 11 individuals, 7 of whom went on to develop hypertension (44). Many cases have been reported since that time (1, 4, 9, 14, 16, 17, 23, 24, 35, 39), but the incidence of IPE is difficult to assess as many cases go unreported or misdiagnosed. Most people fully recover with observation, normobaric oxygen, or β₂-agonist therapy, but fatalities have been reported (9).

The exact pathophysiology of IPE is unknown, but several lines of evidence suggest that it has a hemodynamic cause (17, 20, 24, 44). Risk factors for the development of IPE include immersion, heavy exertion, cold temperature, negative transrespiratory pressure (37), and oral fluid loading before diving (40). The condition is likely a result of increased pulmonary vascular pressure leading to stress failure, pulmonary capillary leak, and transudative edema (17, 20, 41).

The increase in pulmonary vascular pressure during swimming and diving is due to several factors. Pulmonary vascular pressure is increased during exercise (41, 42) due to an increase in cardiac output. Immersion in water causes passive redistribution of venous blood from the extremities to the heart and pulmonary vessels, which increases both systemic and pulmonary arterial pressure (13, 42). The immersion-induced increase in intrathoracic blood volume can be measured as a decrease in vital capacity (VC) that is augmented at lower water temperature. In cold water VC is reduced to 91% of baseline (18). Cold water presumably accentuates the immersion-induced increase in central blood volume and preload through peripheral vasoconstriction, a heat-conserving mechanism (45). The cold water effect is regulated primarily by exposure of the torso and extremities rather than the head or face (42).

The combined effect of immersion, cold temperature, and exertion augments both preload and afterload, leading to an increased volume of blood in the central veins, heart, and pulmonary circulation. During exercise, pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP) are increased in immersion and to an even greater extent in cold water (42). This may explain why most cases of IPE occur in cold water (10, 17, 40); however, cases of IPE have been reported in thermoneutral water without exertion (15, 17). Thus additional mechanisms may also exist, such as impaired left ventricular function (3, 9), high blood volume, or high venous tone. A neurogenic variant of pulmonary edema has been described, with elevated catecholamine levels causing peripheral vasoconstriction, increased pulmonary artery and wedge pressures, and subsequent stress failure and leak of pulmonary capillaries, leading to a high-permeability pulmonary edema (7, 32, 41).

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There is evidence that some individuals are more likely to develop IPE than others. It tends to recur (14), and individuals who have recovered from IPE demonstrate an exaggerated vasoconstrictive response to cold (44). Postevent evaluation of individuals with IPE typically reveals normal PAP and PAWP pressure (14, 21), echocardiogram (31), lung volumes, spirometry, and diffusing capacity of the lung for carbon monoxide (DLCO) (21). A study comparing four individuals with a history of IPE to healthy controls revealed no differences in forearm vascular resistance, left ventricular systolic and diastolic function, and plasma levels of vasoreactive hormones (epinephrine, norepinephrine, cortisol) (31). However, a study in which volunteers were monitored during immersed exercise demonstrated individual variability in hemodynamic response, with a wide range in mean PAP and PAWP and some PAP values exceeding 40 mmHg (29, 42). This is consistent with different individual susceptibility in that people with higher pulmonary vascular pressures may represent those who are more likely to develop IPE.

In a recent report, pulmonary and systemic hemodynamics and gas exchange were studied in healthy volunteers during sustained immersed exercise in thermoneutral water while breathing normoxic and hyperoxic gases [0.2, 1.75 atmospheres absolute (ATA), respectively]. Pulmonary vascular pressures were highly variable, and in some individuals PAWP exceeded the pressure at which pulmonary capillary leak is believed to occur (17–20 mmHg). In that study, the rise in PA pressure associated with immersed exercise at depth was attenuated while breathing hyperoxic gas. However, diving operations often occur in cold water. Thus, in the present study, we tested the hypothesis that hyperoxia attenuates the rise in pulmonary vascular pressures during sustained immersed exercise in cold water. This study has implications for the use of hyperoxia as a potential strategy for the reduction in risk of developing immersion pulmonary edema in military divers, who can use breathing gas mixtures with P02 as high as 1.75 ATA.

MATERIALS AND METHODS

Subject selection. After institutional approval and informed consent, six volunteer subjects were studied. Screening before the experimental day included a medical history, physical exam, 12-lead electrocardiogram, posterior-anterior and lateral chest radiograph, measurement of vital capacity, forced expiratory volume in 1 s (FEV1), maximal midexpiratory flow (FEV25–75), body composition by caliper skinfold measurement, aerobic capacity [maximal oxygen uptake (VO2max)], and hypercapnic ventilatory response (HCVR) (8). VO2max testing was completed on a cycle ergometer using a graded exercise protocol described previously (8). Grounds for exclusion from the study included VO2max < 30 ml kg⁻¹ min⁻¹, ratio of FEV1 to forced vital capacity < 0.75, or estimated body fat more than three percent higher than the age- and sex-based upper limits (male: < 35 yr = 25%; ≥ 35 yr = 28%; female: < 35 yr = 38%; ≥ 35 yr = 41%), contraindications to diving (ear or sinus infection and inability to autoinflate the middle ear), and pregnancy. The aerobic fitness minimum threshold was established in order that the subjects might reasonably model US Navy divers.

Chamber and conditions. The experiment was conducted in a small water-filled pool (volume 4.42 m³) inside a hyperbaric chamber that was pressurized to 4.7 ATA (equivalent to a depth of 122 ft or 37 m of sea water). Subjects exercised in the prone position using an electronically braked ergometer as previously described (8). Inspired and expired gas was conducted to and from the subject via tubing connected to an adjacent chamber that was maintained at a slightly higher pressure to compensate for water depth and maintain transrespiratory pressure (Pt) at ±3–4 cmH2O. All trials were conducted in cold water (19.9–20.9°C). The average bottom time (time from leaving the surface to the start of decompression) for each experiment ranged from 64 to 85 min (mean 70.7 min). The subjects did not wear thermal protective suits. Decompression tables were designed for the study using 100% O2 breathing with intermittent breaks during which the subjects breathed air.

Equipment. A mixing box made in-house was used to ensure homogeneous mixing of expired gas samples. The details of the apparatus were previously described (8).

Instrumentation. At the start of each experiment, a radial artery (20 gauge, Arrow International, Reading, PA) and pulmonary artery (model 131HF7 standard 4-lumen monitoring catheter with antimi
crobial heparin coating, Edwards Lifesciences, Irvine, CA) catheter were inserted. The PA catheter was inserted via an antecubital vein. Radiographic imaging was used to confirm that the tip was in a pulmonary artery (8).

Procedure. The hyperbaric chamber was pressurized to 4.7 ATA. Each subject was submerged in water to ~50-cm depth measured at the midcheste in the prone position and studied during two 16-min exercise trials separated by 5 min of rest. Each subject breathed O2-N2 gas mixture with either 0.21 ATA P02 (4.3% O2) or 1.75 ATA P02 (37% O2) during exercise. The gas mixture was switched between trials and the order of gas exposure (normoxia or hyperoxia first) was determined randomly. Exercise levels were set at either 100 or 125 W externally measured power (set according to each subject’s exercise capacity as measured by VO2max and ability to tolerate underwater exercise, each assessed on a day before the study) for underwater exercise, and subjects pedaled at a rate of 60 rpm. Earlier studies had estimated the power required to move the legs through the water at ~50 W; thus the total power was either 150 or 175 W. Hemodynamic parameters were measured during the 5th and 15th minute of exercise. Blood samples and expired gas were collected during the 6th and 16th minutes of each exercise period and used for gas exchange and cardiac output measurement. Arterial and mixed venous blood samples were collected anaerobically in heparinized glass syringes over a 15- to 20-s period during the 6th and 16th minutes.

Measurements. Monitoring and data collection were as previously described (8). ECG, arterial pressure, pulmonary arterial pressure, and central venous pressure were continuously recorded, with intermittent PAP and PAWP measurement. Mean arterial pressure (MAP), mean PAP (MPAP), and mean central venous pressure (CVP) were obtained using digital averaging over an even number of breath cycles, typically 10 s. Pressure transducers (Hospira, Lake Forest, IL) were positioned at the water surface level. The pressure of the chamber containing the breathing gases was maintained equal to the hydrostatic pressure at the subject’s midchest level as previously described (8, 29). Core body temperature was monitored by the pulmonary artery catheter and recorded during the experiment. At the end of each experiment the digital output from the PA catheter was calibrated in water against an analytic thermometer. Samples of arterial and mixed venous blood (3–4 ml) were drawn anaerobically and kept on ice until analysis (~30 min) (8). Each blood sample obtained at depth was maintained in ice within a PVC (polyvinyl chloride) pressurized container, removed via air lock, and analyzed by blood gas analyzer (Synthesis 15, Instrumentation Laboratory, Lexington, MA) in a separate chamber pressurized to 18.2 m of seawater (2.82 ATA) as previously described (8). For each blood sample total CO2 (TCO2) was calculated according to a previously described method (5). Hb was measured at 1 ATA using a CO-oximeter (model 682, Instrumentation Laboratory). To avoid a potential error induced by a second exposure of blood samples to ambient air during the time the syringe was open during aspiration of blood into the analyzer, hemoglobin-oxygen saturation was assessed using the value calculated by the...
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>$\dot{V}O_2_{\text{max}}$</th>
<th>V̇ O2max</th>
<th>Work Rate, W</th>
<th>Estimated Body Fat, %</th>
<th>HCVR</th>
<th>FVC, l</th>
<th>PWC100</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>35</td>
<td>170</td>
<td>88.1</td>
<td>32.5</td>
<td>125</td>
<td>7.7</td>
<td>2.71</td>
<td>4.87</td>
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</tr>
<tr>
<td>2</td>
<td>M</td>
<td>35</td>
<td>183</td>
<td>72.6</td>
<td>48.6</td>
<td>125</td>
<td>12.4</td>
<td>0.93</td>
<td>6.08</td>
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<tr>
<td>3</td>
<td>M</td>
<td>28</td>
<td>185</td>
<td>79.5</td>
<td>35.8</td>
<td>100</td>
<td>12.9</td>
<td>0.80</td>
<td>5.26</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>M</td>
<td>23</td>
<td>198</td>
<td>106.8</td>
<td>41.7</td>
<td>125</td>
<td>13.9</td>
<td>1.38</td>
<td>6.72</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>M</td>
<td>23</td>
<td>175</td>
<td>72.7</td>
<td>37.5</td>
<td>100</td>
<td>7.3</td>
<td>3.01</td>
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<tr>
<td>6</td>
<td>M</td>
<td>25</td>
<td>170</td>
<td>71.7</td>
<td>60.8</td>
<td>125</td>
<td>6.8</td>
<td>2.19</td>
<td>6.47</td>
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$\dot{V}O_2_{\text{max}}$, maximal $O_2$ uptake; HCVR, hypercapnic ventilatory response; FVC, forced vital capacity; M, male.

Table 2. Systemic hemodynamics during immersed exercise

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th></th>
<th>Hyperoxia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>133.7 ± 16.1</td>
<td>138.8 ± 11.7</td>
<td>120.6 ± 19.5</td>
<td>125.9 ± 15.2</td>
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<tr>
<td>MAP, mmHg</td>
<td>124.6 ± 14.2</td>
<td>123.5 ± 10.5</td>
<td>128.6 ± 14.0</td>
<td>124.9 ± 14.5</td>
<td></td>
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<tr>
<td>CVP, mmHg</td>
<td>12.1 ± 4.5</td>
<td>11.6 ± 5.9</td>
<td>16.1 ± 3.6</td>
<td>10.9 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>SVR, dyn·s⁻¹·cm⁻⁵</td>
<td>556 ± 74.6</td>
<td>484 ± 83.5</td>
<td>531 ± 166.3</td>
<td>498 ± 61.1</td>
<td></td>
</tr>
<tr>
<td>SV, ml</td>
<td>121.0 ± 26.7</td>
<td>126.9 ± 20.2</td>
<td>135.9 ± 34.8</td>
<td>141.8 ± 30.0</td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2$, l/min (STPD)</td>
<td>2.23 ± 0.20</td>
<td>2.42 ± 0.16</td>
<td>2.40 ± 0.23</td>
<td>2.46 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>$\dot{V}CO_2$, l/min (STPD)</td>
<td>2.34 ± 0.31</td>
<td>2.35 ± 0.35</td>
<td>2.22 ± 0.26</td>
<td>2.29 ± 0.17</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Early: exercise values, 5–6 min; Late: exercise values, 15–16 min; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; SV, stroke volume; SVR, systemic vascular resistance; $\dot{V}O_2$, $O_2$ consumption rate; $\dot{V}CO_2$, $CO_2$ elimination rate. Significant difference ($P < 0.05$): *from early to late exercise; †hyperoxia compared with normoxia.

RESULTS

Subjects. Subject characteristics are found in Table 1. None of the subjects were smokers. Of the six subjects, five completed all exercise trials. One subject (subject 3) stopped during exercise at 0.21 ATA PO2 after the 6-min measurement due to fatigue, which resolved shortly after cessation of exercise. After 5 min of rest, exercise was resumed using 1.75 ATA PO2.

Effect of hyperoxia on systemic hemodynamics. Systemic hemodynamic results appear in Table 2. HR was significantly lower in hyperoxia compared with normoxia ($P < 0.0001$). By pairwise comparison, HR was significantly lower in hyperoxia during both early ($P = 0.005$) and late ($P = 0.006$) exercise. In normoxia, HR increased by 3.78% from early to late exercise ($P = 0.009$) but did not change during hyperoxia ($P = 0.14$). Stroke volume was significantly higher in hyperoxia compared with normoxia ($P = 0.045$). Mean arterial pressure was 3.2%
higher in hyperoxia \((P = 0.047)\) and decreased by 3.6% from early to late exercise in both conditions \((P = 0.025)\). CO, CVP, and SVR were not affected by inspired oxygen concentration or exercise duration.

\(\dot{V}O_2\) and \(\dot{V}CO_2\). Results for \(\dot{V}O_2\) and \(\dot{V}CO_2\) appear in Table 2. There was no difference in the rates of \(\dot{V}O_2\) between normoxia and hyperoxia at either the 6- or 15-min time points. There was a trend toward a decrease in \(\dot{V}CO_2\) in hyperoxia compared with normoxia that was not statistically significant (4% reduction, \(P = 0.078\)).

Pulmonary hemodynamics. Pulmonary hemodynamic results are shown in Fig. 1. Mean pulmonary artery pressures were high during cold water-immersed exercise (15-min average: 28.28 mmHg \(\pm\) 8.1 and 29.09 mmHg \(\pm\) 14.3 in normoxia and hyperoxia). Significant individual variability is illustrated in Fig. 2, which shows MPAP and PAWP values by subject. Mean pulmonary artery pressure and pulmonary vascular resistance were not affected by inspired PO2 or exercise duration. There was no effect of PO2 on mean pulmonary artery wedge pressure. Mixed model analysis revealed a significant effect of exercise duration on PAWP \((P = 0.0002)\). By pairwise comparison, PAWP decreased by 21.4% from early to late exercise in hyperoxia only \((P = 0.002)\). Core body temperature, measured using the PA catheter, remained constant from the start of the first exercise trial (mean 36.6°C \(\pm\) 0.5) to the end of the second trial (mean 36.6°C \(\pm\) 0.6).

Baseline maximal oxygen consumption and pulmonary hemodynamics. The correlation between mean pulmonary artery pressure in normoxia and hyperoxia and baseline maximal oxygen consumption \((\dot{V}O_{2\text{max}})\) is shown in Fig. 3. For both oxygen conditions, there was no correlation between baseline \(\dot{V}O_{2\text{max}}\) and MPAP.

Respiratory parameters. Respiratory parameter results are found in Fig. 4. Minute ventilation was significantly lower in hyperoxia compared with normoxia both early (15.2%, \(P = 0.02\)) and late (3.7%, \(P = 0.03\)) in exercise (mixed model \(P = 0.003\)). There was no effect of exercise duration on minute ventilation in either normoxia or hyperoxia. Tidal volume did not change from early to late exercise and was not affected by PO2. Ventilatory frequency was significantly lower during hyperoxia \((P = 0.04)\). \(V_A\) was significantly lower in hyperoxia compared with normoxia \((P = 0.01)\). There was no effect of exercise duration on \(V_A\). Respiratory exchange ratio (RER) during exercise was significantly lower with hyperoxia (0.91) compared with normoxia (1.02, \(P = 0.043\)).

Hypercapnic ventilatory response (HCVR) as a function of arterial PCO2 (PaCO2) for both normoxia and hyperoxia is shown in Fig. 5. There was no correlation between HCVR and PaCO2 for either breathing gas.
Blood gas parameters. Arterial \( \text{PO}_2 \), \( \text{PCO}_2 \), pH, bicarbonate, BE, and \( \text{TCO}_2 \) during exercise trials are shown in Table 3. \( \text{PaO}_2 \) was significantly increased in hyperoxia compared with normoxia \( (P < 0.0001) \) and decreased by 9.3% from early to late exercise in normoxia \( (P = 0.05) \). \( \text{PaCO}_2 \) did not change from early to late exercise in either \( \text{PO}_2 \) condition; however, \( \text{PaCO}_2 \) was significantly higher early in exercise in hyperoxia compared with normoxia \( [49.3 \text{ mmHg} \pm 3.8 \text{ and } 46.0 \text{ mmHg} \pm 2.7, \text{ respectively} (P = 0.035)] \). There was no difference in \( \text{PaCO}_2 \) between normoxia and hyperoxia late in exercise. Arterial pH, bicarbonate, BE, and \( \text{TCO}_2 \) did not differ from early to late exercise or with \( \text{PO}_2 \) condition.

Mixed venous pH, \( \text{PO}_2 \), \( \text{PCO}_2 \), and \( \text{TCO}_2 \) are also shown in Table 3. There was no difference in pH from early to late exercise. Mixed venous pH was significantly lower in hyperoxia early in exercise \( (7.20 \pm 0.07 \text{ and } 7.17 \pm 0.07 \text{ in normoxia and hyperoxia, respectively}; P = 0.002) \). Mixed venous \( \text{PCO}_2 \) increased significantly from early to late exercise in normoxia only \( (P = 0.04) \). Mixed venous \( \text{PCO}_2 \) was increased in hyperoxia compared with normoxia early in exercise \( (P = 0.03) \) and nonsignificantly late in exercise \( (P = 0.06) \). Mixed venous \( \text{PO}_2 \) was not affected by exercise duration but was elevated significantly in hyperoxia both early \( (P = 0.001) \) and late \( (P = 0.002) \) in exercise. \( \text{TCO}_2 \) was not affected by exercise duration or \( \text{PO}_2 \).

\( \text{P}_{\text{AO2}}-\text{P}_{\text{PO2}} \) difference during exercise trials is shown in Fig. 6. \( \text{P}_{\text{AO2}}-\text{P}_{\text{PO2}} \) difference did not change significantly from early to late exercise in either normoxia \( (P = 0.27) \) or hyperoxia \( (P = 0.33) \).
PULMONARY HEMODYNAMICS DURING IMMERSED EXERCISE IN COLD WATER

DISCUSSION

In this investigation, we exposed healthy volunteers to sustained immersed exercise in cold water that simulates conditions seen by recreational, commercial, and Navy divers and measured ventilation and pulmonary hemodynamics in response to both normoxic and hyperoxic gas mixtures.

Systemic hemodynamics. There was a significantly lower HR associated with exercise in hyperoxia compared with normoxia both early and late in the exercise trials. This is consistent with previous observations of decreased HR during hyperoxia due to increased parasympathetic tone (22). There was no difference in cardiac output as a result of either exercise duration or inspired PO2 in normoxia (29). In hyperoxia, cardiac output was maintained in the setting of a decreased HR by an increase in stroke volume.

Previous study of systemic and pulmonary hemodynamics during immersed exercise in thermoneutral water demonstrated a decrease in MAP and CVP with hyperoxia compared with normoxia (29) that was not observed during this study in cold water. In the present study, there was no effect of inspired PO2 or exercise duration on CVP or MAP. These values were higher compared with those in Peacher et al. (29). The higher MAP in cold water compared with thermoneutral water during hyperoxia was statistically significant both early (P = 0.02) and late (P = 0.05) in exercise. CVP values in this study were 4–5 mmHg higher than previously reported in thermoneutral water. In hyperoxia, cardiac output was maintained in the setting of a decreased HR by an increase in stroke volume.

Effect of hyperoxia on SVR, and the values seen in the present study were similar to those seen in thermoneutral water despite higher MAP. The higher afterload and trend toward higher preload in this study in cold water may explain the ineffectiveness of high PO2 in reducing pulmonary artery pressure during exercise.

Pulmonary hemodynamics. This study demonstrated that immersed exercise in cold water is associated with high mean pulmonary artery pressure and pulmonary vascular resistance. MPAP averaged 28.28 ± 8.1 and 29.09 ± 14.3 mmHg over the duration of exercise in normoxia and hyperoxia, respectively, and demonstrated wide individual variability (12.2–54.2 mmHg) consistent with previous observations (29). Several subjects exhibited MPAP values that approached the threshold for pathologic pulmonary artery pressures (MPAP > 30 mmHg in exercise), indicating that these conditions could favor the development of pulmonary edema. Similarly, for both groups, several subjects exhibited PAWP values that approached the value at pulmonary capillary leak is believed to occur (17–20 mmHg). These values appear to be about 3–5 mmHg higher than those seen during exercise in thermoneutral water (29), although the effect was not statistically significant.

While hyperoxia was previously shown to attenuate the rise in pulmonary vascular pressures associated with immersed exercise in thermoneutral water, this study did not demonstrate a decrease in MPAP or PVR associated with hyperoxia during immersed exercise in cold water. At rest, hyperbaric oxygen has been shown to dilate pulmonary vasculature (25). In this study the PO2 effect at 1.75 ATA was insufficient to offset the effect of hyperoxia on SVR, and the values seen in the present study were similar to those seen in thermoneutral water despite higher MAP. The higher afterload and trend toward higher preload in this study in cold water may explain the ineffectiveness of high PO2 in reducing pulmonary artery pressure during exercise.

Table 3. Blood gas results during immersed exercise

<table>
<thead>
<tr>
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<th>Normoxia</th>
<th>Hyperoxia</th>
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<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Arterial Blood Gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, mmHg</td>
<td>108.4 ± 13.6</td>
<td>98.0 ± 8.4</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>46.0 ± 2.7</td>
<td>48.9 ± 4.0</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 ± 0.06</td>
<td>7.29 ± 0.01</td>
</tr>
<tr>
<td>Bicarbonate, mmol/l</td>
<td>22.8 ± 3.5</td>
<td>24.0 ± 2.4</td>
</tr>
<tr>
<td>Base excess, mmol/l</td>
<td>−3.5 ± 3.9</td>
<td>−2.5 ± 2.1</td>
</tr>
<tr>
<td>Total CO2, mmol/l</td>
<td>24.2 ± 3.9</td>
<td>25.5 ± 2.1</td>
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<tr>
<td>Mixed venous blood gases</td>
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<tr>
<td>pH</td>
<td>7.20 ± 0.07</td>
<td>7.22 ± 0.02</td>
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<tr>
<td>PVO2, mmHg</td>
<td>26.8 ± 3.4</td>
<td>27.0 ± 3.6</td>
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<tr>
<td>PVO2, mmHg</td>
<td>70.8 ± 5.2</td>
<td>72.5 ± 3.8*</td>
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<td>Total CO2, mmol/l</td>
<td>29.3 ± 5.1</td>
<td>31.9 ± 1.7</td>
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Values are mean ± SD. Normoxia, inspired PO2 (PO2) = 0.21 atmospheres absolute (ATA); Hyperoxia, 1.75 ATA PO2; Early: exercise values, 6 min; Late: exercise values 15 min; PaO2, arterial PO2; PaCO2, arterial PCO2; PVO2, mixed venous PO2; PVO2, mixed venous PCO2. Significant difference (P < 0.05): †from early to late exercise; ‡ hyperoxia compared with normoxia.
peripheral vasoconstriction induced by cold immersion. Acidemia associated with heavy exertion induces pulmonary vasoconstriction, but this effect appeared to be equally present in both normoxia and hyperoxia as arterial pH was unchanged between the two conditions. Mixed venous pH, however, was lower in hyperoxia, and this difference was statistically significant early in exercise. Mixed venous PCO2 was also increased in hyperoxia consistent with the Haldane effect. During exercise in thermoneutral water, mixed venous pH was constant at 7.23 in both normoxia and hyperoxia (29). Thus the presence of acidemia in mixed venous blood could offset the tendency for hyperoxia to dilate pulmonary vasculature and be responsible for the lack of reduction in MPAP and PVR with hyperoxia in cold water. Conceivably, the mixed venous acidemia could be the result of an interaction between cold and hyperbaric hyperoxia on peripheral flow distribution during exercise resulting in regional hypoperfusion.

It has been shown that fitness level can modulate an individual’s hemodynamic response to exercise, with fitter individuals demonstrating better left ventricular diastolic function and compliance and a trend toward lower mean pulmonary artery pressure during maximal exercise (36). To determine whether baseline physical fitness influenced pulmonary vascular pressures in this study, we plotted MPAP during exercise in normoxia and hyperoxia against baseline VO2max (measured during prestudy procedures). As seen in Fig. 3, with both breathing gases there was no relationship between MPAP and baseline VO2max.

Ventilation. Minute ventilation was significantly lower in hyperoxia compared with normoxia, which is consistent with previous observations (29). Depression of VE and VA by hyperoxia could conceivably be due to direct inhibition of respiratory drive or to an attenuation in metabolic acidosis due to a reduction of hypoxic tissue acidosis from exercise. In this study, blood gas analysis did not reveal any change in arterial pH with hyperoxia, but PCO2 was higher in hyperoxia than normoxia during the early portion of exercise, suggesting a slight decrease in metabolic acidosis associated with hyperoxia. The decrease in minute ventilation in hyperoxia was due to a decrease in ventilatory frequency in the setting of a constant tidal volume, consistent with previous findings that hyperoxia diminishes the ventilatory response to elevated PaCO2 by attenuating the responsiveness of the carotid body to hypercarbia (11, 12, 26, 30). Unlike previous observations (29), there was no hyperoxic increase in VT/VT to suggest impaired ventilation-perfusion (V/Q) matching in this study.

The HCVR is variable between individuals and has been shown to correlate negatively with arterial PCO2 during exercise (19, 27). In this study of six subjects, we did not demonstrate a correlation between baseline HCVR and arterial PCO2 during either normoxic or hyperoxic exercise.

P<sub>AO2</sub>-P<sub>AO2</sub> gradient. It has been well documented that alveolar-arterial oxygen pressure difference increases during exercise under dry conditions at sea level (38). In Peacher et al. (29), an increase in P<sub>AO2</sub>-P<sub>AO2</sub> gradient associated with immersed exercise in thermoneutral water during normoxia was attributed to a possible increase in lung water during exercise. In the present study, alveolar-arterial O2 difference did not increase significantly from early to late exercise in either oxygen condition and remained within normal limits in normoxia (this value cannot be interpreted reliably in hyperoxia). If there were an effect it would probably have been obscured by the single-session crossover design.

Implications for IPE. Our results suggest that hyperoxia does not protect against the increase in PA pressures associated with immersed exercise in cold that could be a precipitating factor for the development of IPE. The ameliorative effect of oxygen was present during immersed exercise in thermoneutral water (29), indicating that a benefit from hyperoxic gas breathing may be achieved using adequate thermal protection. It has been suggested by other authors that hyperoxia may actually be a risk factor for the development of IPE. Coulange and colleagues (10) observed that hyperoxia was a common feature in dives that resulted in the development of IPE, with an average inspired PO2 of 0.99 bar in a series of 22 divers. In a series of 2,527 closed-circuit oxygen dives (average PO2 of 119 kPa), there was a 1.4% incidence of “bloody sputum,” suggesting pulmonary edema during or immediately following a dive (2). This proportion is very similar to the incidence reported by Adir et al. (1) in surface swimmers. Unlike these observations, our data demonstrate at least a neutral effect of hyperoxia on pulmonary vascular pressures, suggesting that hyperoxia should not affect the risk of IPE in cold water. If indeed IPE has a hemodynamic cause, then the results of a previous study (29) and the present experiment are not consistent with hyperoxia as a risk factor for IPE.

Limitations. The relatively small sample size precluded detection of small effects due to lack of statistical power. However, given the similarity of PAP and PAWP between the two conditions, it is unlikely that a larger data set would have revealed a statistically significant effect of PO2 on the primary outcome variables of this study, PAP and PAWP, as previously reported for thermoneutral water (29). In that study exercise trials in normoxia and hyperoxia were performed on two occasions separated by several days. In the present study, the two exercise trials were separated by a 5-min break in which subjects remained immersed in water. The intertrial interval may not have been sufficient for systemic and pulmonary pressures and blood gases to return to baseline pretrial levels. While it is conceivable that the difference in results obtained in this study compared with the thermoneutral study could have been due to the temporal...
proximity of the two exercise trials, we do not believe that this is the case for the following reasons. First, trial order was randomized with half of the subjects breathing normoxic gas first and half breathing hyperoxic gas first such that any effect of gas order would be minimized. Second, while there were no differences in PA pressure between normoxia and hyperoxia, other parameters including HR, stroke volume, \( \dot{V}_E \), \( \dot{V}_A \), and ventilatory frequency (\( f \)) all changed as expected in response to hyperoxia. These same changes were seen in the thermoneutral study in which trials were separated by several days. Also, the changes in the above parameters were immediately evident in response to a change in inspired \( P_{O_2} \). Dive times (and hence immersion times) were only slightly longer in the present study (mean 70 min vs. 50 min in Peacher’s study), and there was no drop in core temperature.

**Summary.** We found that breathing an enriched oxygen mixture during exercise in cold water is associated with a decreased HR, ventilation and mixed venous \( \text{pH} \) and an increase in arterial \( P_{O_2} \), confirming previous observations of high pulmonary pressures during exercise in cold water (42) and wide individual variability of PA pressures in response to immersed exercise (29). High pulmonary vascular pressures were not attenuated by breathing a hyperoxic gas during exercise in cold water as previously seen in thermoneutral water. The results of this experiment are consistent with enhanced peripheral vasoconstriction and its effects on cardiac afterload and preload and possibly an additional effect of mixed venous acidemia as an explanation for the lack of an effect of hyperoxia on pulmonary artery pressure.

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**REFERENCES**


