Effect of acute increases in pulmonary vascular pressures on exercise pulmonary gas exchange


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Over the past several decades, pulmonary gas exchange in humans has been well characterized and shown to be impaired with incremental exercise. Wagner et al. (30) demonstrated a strong correlation between mean pulmonary artery pressure (PAP) and ventilation/perfusion mismatch as measured by the multiple inert gas elimination technique and theorized that interstitial pulmonary edema develops secondary to the increased PAP. West (32–35) has described how edema and pulmonary damage or hemorrhage can develop with incremental exercise secondary to high pulmonary vascular pressures. This has lead to speculation that the increased alveolar-to-arterial PO2 difference (A-aD02) typically observed in healthy subjects during exercise is the result of pulmonary edema. Although evidence suggests that pulmonary edema or vascular damage may develop with exercise (4, 10, 12, 15, 26, 38), the effect of manipulating pulmonary vascular pressure on A-aD02 during incremental normoxic exercise has not been reported.

Therefore, the primary purpose of this investigation was to increase pulmonary vascular pressures with lower-body positive pressure (LBPP) during exercise to determine the relationship between pulmonary hemodynamics and A-aD02. Recently, anatomical intrapulmonary (IP) shunts were shown to develop during exercise in healthy humans (7, 27, 36), and we (27) have shown that the recruitment of these shunts is related to the widened A-aD02. In this present study, we expanded on our previous study and report the effects of increasing pulmonary pressures on anatomical IP shunt recruitment. Because shunt vessels may act as “pop-off valves” in response to increased pulmonary vascular pressure (2), we expected shunts to be recruited at a lower exercise intensity with LBPP. A secondary purpose of this study was to examine the effects of increased pulmonary vascular pressures on ventilation, since stimulation of vascular pressure-sensitive C-fiber afferents may cause increases in breathing frequency and minute ventilation during exercise (17, 18). Based on previous research, we hypothesized that increasing pulmonary vascular pressures with LBPP during exercise would increase A-aD02, IP shunt recruitment, and ventilation.

METHODS

Research Design

This paper reports a predefined study completed in conjunction with a study reported previously (27). Institutional ethics review board approval was obtained, and all subjects provided written, informed consent to participate. Three experimental sessions were completed during a 3-wk period in the following order: a graded exercise test to determine ventilatory threshold (Tvent) and maximum oxygen consumption (VO2max), a noninvasive practice session to familiarize the subject with the exercise protocol, and the experimental day.

Subjects

The data from eight healthy male subjects [mean age: 30 yr (SD 9.0); VO2max: 4.28 l/min (SD 0.6); 54.7 ml·kg⁻¹·min⁻¹ (SD 9.0)] are reported. All participants were screened for exercise-induced bron-
chospasm (i.e., no decrease in forced expiratory volume in 1 s > 10% postexercise) and hematological abnormalities (complete blood count), and all had a normal exercise ECG. Based on previous water-immersion and LBPP investigations (1, 6, 8), we estimated a mean increase of 6 ± 1.5 mmHg in PAP with LBPP, and therefore eight subjects provided sufficient power to detect hemodynamic differences between control and LBPP conditions.

Experimental Trial

Subject preparation. A radial artery catheter (20-gauge Angiocath, Becton-Dickson, Sandy, UT) was inserted into the left radial artery using sterile technique and local anesthetic (1% lidocaine HCl, Astra, Mississauga, ON, Canada). A Swan-Ganz catheter (Edwards Life-sciences, Irvine, CA) was inserted through a standard Cordis sheath via an antecubital vein and advanced under fluoroscopy into a pulmonary artery. Patency of the catheters was maintained with a pressurized flush system of normal saline. Following instrumentation, each subject rested quietly for 10 min before baseline data were obtained.

Protocol. Data were collected during 14 separate conditions, 7 each under control and LBPP conditions. At rest, supine control data were first collected and then 52-mmHg LBPP (1 psi). The subject then sat on the cycle ergometer, and resting data were collected (control, then 52-mmHg LBPP). In six subjects, 104-Torr (2 psi) LBPP was also applied at rest, although this did not further increase pulmonary vascular pressures. The exercise protocol was conducted at each of the following intensities: 1) 75 W, 2) 150 W, 3) power output at TVent, 4) 25 W above TVent, 5) 90% of previously determined VO2max. At lower intensity exercise, absolute power output was used so that comparisons could be made between subjects at the same absolute cardiac output (Q) and metabolic rate. At higher intensities, workload was based on TVent since arterial pH may affect PAP, whereas 90% of VO2max represented the highest intensity that could be maintained for sufficient time to complete data collection. With the exception of peak exercise, at each exercise workload, the order of condition (control vs. 52-mmHg LBPP) was randomized. For the peak exercise intensity, control always preceded LBPP condition. Five-minute recovery periods were given between each condition to rest and allow for redistribution of blood volume.

LBPP. LBPP was applied via a Canadian Sting II antigravity suit, which has an inflatable air bladder to increase pressure around the calves, thighs, and abdomen (9). This device is similar to military anti-shock trousers that have been used previously during exercise (8). Antigravity suits have been shown to increase both cardiac preload and afterload, with little effect on Q (16). Before the experimental session, each subject was fitted with the suit such that, under the control condition, no pressure was exerted on the legs or abdomen; however, on inflation, the pressure was distributed around the entire lower body. Pants were inflated quickly (<15 s) to 52 mmHg, which was the highest pressure comfortably tolerated by all subjects during exercise.

Cardiorespiratory measures. Respiratory gas-exchange data were collected by using a nonbreathing valve (Hans-Rudolph, 2700, Kansas City, MO) and a metabolic measurement system (ParvoMedics, Truemax, Salt Lake City, UT). Arterial blood samples (2-3 ml) were drawn from the radial artery catheter, whereas mixed venous samples (2-3 ml) were drawn from the pulmonary artery through the distal port of the Swan-Ganz catheter. Blood gases were corrected for pulmonary arterial temperature as measured by the Swan-Ganz catheter, with arterial and venous oxygen saturation corrected for both temperature and pH. Alveolar PO2 was calculated using the alveolar gas equation with water vapor pressure corrected for temperature. Alveolar ventilation (VA) was calculated from expired CO2 (VCO2) and arterial PCO2, and deadspace ventilation was determined from the difference between minute ventilation (Ve) and VA. In the upright resting position and at workload 3, an additional 5 ml of arterial blood was obtained for later analysis of plasma epinephrine and norepinephrine with high-performance liquid chromatography.

Mean right atrial (RAP), PAP, and pulmonary artery wedge pressure (PAWP) were obtained from the Swan-Ganz catheter, whereas systemic arterial blood pressure was measured from the radial arterial catheter. The pressure transducers were set at the level of the right atrium with the positioning monitored continuously. Q was calculated from the Fick equation, and heart rate was obtained from the ECG.

Contrast echocardiography. Echocardiograms were performed by one experienced sonographer using cardiac ultrasound (Sonos 5500, Hewlett Packard, Andover, MA). Standard procedures were employed for injection of the agitated saline solution as detailed previously (27). We (27) and others (7) have proposed this method to be valid for detection of anatomical pulmonary arteriovenous shunting during exercise (see Ref. 27 for further discussion). Four of the 110 saline contrast echocardiographic injections conducted in the study, all from the same subject, were nondiagnostic and occurred under both the control and LBPP conditions at workloads 1 and 4. At each workload, two-dimensional short-axis fractional area change was also obtained in each subject (results not reported).

Statistical Analysis

Group data for each variable are expressed as means ± SE. Because we were interested in the effect of condition (control vs. LBPP) at each exercise intensity, planned comparisons using t-tests for repeated measures were used. All subjects completed workload 5 in the control condition, but two of the eight subjects were unable to maintain workload 5 during LBPP for sufficient time to gather complete data. Workload 5 is thus reported for all subjects in the control condition (n = 8) and six subjects in the LBPP condition. At rest and through workload 4, all eight subjects were used for analysis, whereas, due to missing data, data from only six participants were used for analysis at workload 5. For all inferential analyses, the probability of type I error was set at 0.05.

RESULTS

LBPP at Rest

In the resting supine position, there were no significant differences between control and LBPP for RAP (5.8 ± 0.7 vs. 6.2 ± 0.6 mmHg), PAP (17.0 ± 1.3 vs. 17.8 ± 1.1 mmHg), PAWP (12.2 ± 1.3 vs. 13.0 ± 0.9 mmHg), or Q (7.8 ± 0.4 vs. 7.7 ± 0.4 l/min), respectively. Supine A-aDO2 was similar in control and LBPP (3.1 ± 1.1 vs. 3.6 ± 1.6 mmHg, respectively). Two subjects had evidence for shunt in the supine control condition. During LBPP, one of these subjects continued to shunt, whereas the second no longer had evidence of shunt. A third subject developed shunt with LBPP but did not have evidence of shunting in the control condition.

During rest in the upright position, 52-mmHg LBPP increased (P < 0.05) RAP (5.5 mmHg), PAP (3.5 mmHg), PAWP (4.8 mmHg), and Q (2.5 l/min) (Fig. 1). With LBPP, one subject shunted in the upright position, and this subject had an increased A-aDO2 relative to the group (Fig. 2); however, there was no main effect of LBPP on A-aDO2. No other changes in respiratory or blood gas data were observed between control and LBPP at rest (Tables 1 and 2, Figs. 2–5).

LBPP During Exercise

LBPP consistently increased RAP, PAP, and PAWP at all points during exercise (mean increase 4.1, 3.4, and 3.9 mmHg,
respectively) (Fig. 1); however, Q and oxygen uptake (Fig. 5) were not significantly affected. The alveolar-arterial pressure difference was not increased by LBPP at any workload (Fig. 2). At workload 1 (75 W), three subjects developed shunt during control and one additional subject developed shunt with LBPP; however, LBPP did not affect shunt frequency during the subsequent higher workloads. One subject failed to develop IP shunts at any point during exercise in both control and LBPP conditions.

At workloads 1 and 3, LBPP resulted in increased V\text{E} and breathing frequency (Table 1). However, V\text{CO}_2 (Fig. 5) was elevated in both workloads with LBPP, whereas blood lactate (Table 1) and epinephrine (Table 2) were increased at workload 3 with LBPP. Arterial PCO\text{2} (Fig. 3) and V\text{A} (Fig. 4) were not significantly different between conditions at any workload. No other differences in respiratory or blood gas data were observed between control and LBPP conditions.

**Shunt Onset**

Figure 6 reports the pulmonary hemodynamics before and after IP shunt recruitment both in control and LBPP condition. Considerable variability in pulmonary hemodynamics at the onset of shunting was observed between subjects. In six of the seven subjects who developed shunt, an increase in Q was associated with shunt recruitment, whereas higher PAP was associated with shunt in three subjects. Grouped data indicate that shunting onset is associated with increases in both Q (~8 l/min) and PAP (~5 mmHg).

**DISCUSSION**

This investigation demonstrated that 1) 4- to 5-mmHg increases in pulmonary vascular pressures via LBPP do not impair exercise pulmonary gas exchange; 2) elevated pulmonary pressures increased shunt frequency slightly at rest and during low-intensity exercise, but LBPP did not affect IP shunt recruitment during moderate to very heavy exercise; and 3) ventilation was not affected by acute increases in pulmonary vascular pressures.

**Exercise Pulmonary Gas Exchange**

Wagner et al. (30) previously reported a correlation between V\text{A}/Q mismatch and mean PAP during exercise at sea level and acute hypoxia, and reasoned that V\text{A}/Q mismatch was due to the development of hydrostatic edema secondary to high pulmonary vascular pressures. Examination of the published data revealed that gas-exchange impairment (A-aDO\text{2}) was related to PAP (r = 0.94), whereas an equally strong relationship was observed between A-aDO\text{2} and Q (r = 0.94). It is therefore difficult to determine whether PAP, Q, or the progressive decline in mixed venous Po\text{2} with exercise was the dominant factor explaining the widened A-aDO\text{2}. In the present investigation, pulmonary vascular pressures were increased with LBPP, whereas Q and mixed venous Po\text{2} remained similar to control values, enabling separation of absolute pressure from flow. Using our present data, pulmonary capillary wall stress can be estimated based on assumptions by West and Mathieu-Costello (35). If we assume capillary pressure is midway between PAP and PAWP and fixed values for both blood-gas barrier thickness (0.34 \mu m) and capillary radius (3.6 \mu m), then LBPP increased capillary wall stress from 1.97 \times 10^5 to 2.38 \times 10^5 N/m^2 and 2.36 \times 10^5 to 2.78 \times 10^5 N/m^2 at workloads 4 and 5, respectively. Surprisingly, despite an estimated increase in capillary wall stress of over 20% with LBPP, A-aDO\text{2} was not affected.

Previous studies in both healthy and diseased humans and animals have demonstrated that a change in Q results in a parallel change in venous-to-arterial shunt (Q\text{s}/Q\text{t}) (3, 13, 20, 24, 29, 37). Conversely, Zavorsky et al. (40) and Robertson et al. (22) have shown that acute hypervolemia does not adversely affect exercise A-aDO\text{2}, whereas Calbet et al. (5) found that plasma volume expansion of lowlanders at altitude resulted in a small (<1.5 mmHg) increase in exercise A-aDO\text{2}. Importantly, volume expansion did not increase Q in these exercise studies (5, 40), although central pressures during exercise were likely increased with hypervolemia (23). If increases in absolute pulmonary vascular pressures were the dominant explanation for the widened A-aDO\text{2} during exercise, we would expect...
a large, consistent impairment in gas exchange with hypervolemia. Based on the above-mentioned research and our present data, we suggest that a putative increase in pulmonary edema, secondary to an increase in pulmonary vascular pressures, is unlikely to be the primary contributor to the widened A-aDO2 in healthy exercising humans.

**LBPP and Exercise IP Shunt**

Increases in PAP and PAWP from LBPP had little effect on the recruitment of IP shunts during exercise. This is surprising because, assuming a passive pulmonary vasculature, increases in both PAP and PAWP should cause shunt vessel recruitment regardless of size or location of these vessels. Analysis of individual pulmonary hemodynamics before and after IP shunt recruitment (Fig. 6) demonstrates that shunts typically develop with increasing Q, whereas increasing PAP is not consistently coupled with recruitment of shunts. Driving pressure increases with exercise (19), and it is likely that shunt vessels are sensitive to a very specific opening pressure that would increase with exercise intensity (and Q). We would suggest that

**Table 1. Respiratory and blood lactate responses at rest (supine and upright) and during graded exercise in control and with LBPP**

<table>
<thead>
<tr>
<th></th>
<th>SUP</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>V\textsubscript{E}, l/min</td>
<td>12±2</td>
<td>13±1</td>
<td>38±1</td>
<td>66±3</td>
<td>97±7</td>
<td>133±9</td>
<td>163±7</td>
</tr>
<tr>
<td>Breathing frequency, breaths/min</td>
<td>14.3±2.3</td>
<td>14.7±2.1</td>
<td>22.2±2.6</td>
<td>28.8±2.7</td>
<td>34.3±2.8</td>
<td>44.9±2.8</td>
<td>55.9±4.0</td>
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<tr>
<td>Tidal volume, liters</td>
<td>1.0±0.2</td>
<td>1.0±0.1</td>
<td>1.9±0.2</td>
<td>2.4±0.2</td>
<td>2.9±0.3</td>
<td>3.0±0.2</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>Mixed venous PO\textsubscript{2}, Torr</td>
<td>41.9±1.4</td>
<td>41.4±3.5</td>
<td>30.2±1.1</td>
<td>29.3±1.7</td>
<td>27.9±1.9</td>
<td>25.2±1.8</td>
<td>24.0±1.4</td>
</tr>
<tr>
<td>Blood lactate, mM</td>
<td>0.7±0.0</td>
<td>0.8±0.0</td>
<td>1.3±0.2</td>
<td>2.3±0.5</td>
<td>4.9±0.4</td>
<td>8.4±0.7</td>
<td>11±0.6</td>
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|                  |     |    |     |     |     |     |     |
| **LBPP**         |     |    |     |     |     |     |     |
| V\textsubscript{E}, l/min | 12±2 | 13±1 | 44±2* | 68±3 | 112±11* | 138±8 | 161±10 |
| Breathing frequency, breaths/min | 14.2±1.6 | 16.4±2.0 | 25.9±2.8* | 29.0±3.2 | 40.9±5.0* | 49.0±3.4 | 64.7±3.7 |
| Tidal volume, liters | 0.9±0.1 | 0.9±0.2 | 1.8±0.2 | 2.5±0.3 | 2.9±0.3 | 2.9±0.3 | 2.5±0.2 |
| Mixed venous PO\textsubscript{2}, Torr | 41.9±0.7 | 43.4±1.8 | 30.7±1.1 | 28.3±1.5 | 27.8±1.6 | 26.9±1.7 | 24.8±1.2 |
| Blood lactate, mM | 0.7±0.0 | 0.8±0.0 | 1.3±0.3 | 3.0±0.7 | 6.7±0.6* | 9.8±0.7* | 12.4±0.8 |

Values are means ± SE. LBPP, lower-body positive pressure; SUP, supine; UP, upright; 1–5, exercise load; V\textsubscript{E}, minute ventilation. *P < 0.05 vs. control condition at same intensity.
an increase in microvascular pressure secondary to the increase in Q with incremental exercise opens shunt vessels and reduces vascular resistance (and potentially PAP) (27), explaining the stronger relationship between Q, IP shunt recruitment, and A-aDO2. Examination of Fig. 6 indicates that, although critical opening pressure is somewhat consistent within subjects, considerable between-subject variability exists. The individual variability in critical opening pressure, combined with the relatively small increase in PAP with LBPP, likely explains why LBPP failed to substantially affect IP shunt recruitment.

In the resting upright position, 52-mmHg LBPP did not affect A-aDO2; however, one subject developed shunt. From our supine and upright data, it is evident that IP shunt recruitment is variable between subjects and is not consistently explained by the pulmonary hemodynamics measurements we made. Further research is needed using more sensitive techniques to determine what factors may explain the between-subject variability in IP shunt recruitment both at rest and during exercise.

### Ventilation

Despite increased pulmonary vascular pressures, arterial PCO2, VE/VCO2, tidal volume, and breathing frequency were not consistently affected by LBPP. Some have suggested that the increases in pulmonary vascular pressures during exercise may stimulate pulmonary juxtacapillary receptors, which have some
ventilatory control and partially explain exercise hyperpnea (17, 18). Accordingly, we expected a consistent decrease in arterial PCO2 and an increase in V˙E/V˙CO2 with LBPP. We did observe elevated V˙E and breathing frequency with LBPP at workloads 1 and 3. However, this hyperpnea with LBPP was likely due to peripheral chemoreceptor stimulation secondary to changes in limb blood flow (25), since V˙CO2 was elevated at both workloads, whereas blood lactate and epinephrine were higher at workload 3. Robertson et al. (22) demonstrated an increase in V˙E/V˙CO2 during exercise in response to rapid intravenous saline infusion and attributed this response to either mild acidosis from the infusion or afferent signals for the lung or muscle. Our data do not support a significant role for pulmonary juxtacapillary receptors in exercise hyperpnea in health.

Pulmonary Edema/Lung Damage

In the present paper, we took a “black-box” approach to examine the potential impact of pulmonary vascular pressures on gas exchange. It is possible that pulmonary pressures were not sufficiently elevated with LBPP to negatively impact gas exchange as measured by A-aDO2. In addition, we did not evaluate capillary recruitment, V/Q matching, or diffusion limitation, and therefore we can only speculate on how LBPP may have affected these determinants of gas exchange. It is generally assumed that full pulmonary capillary recruitment occurs above an oxygen uptake of 3.5 l/min (31), and based on our data full-capillary recruitment likely occurred after level 3 (oxygen uptake = 3.2 l/min, Q = 25.1 l/min) due to the rapid increase in PAP and PAWP. Above this intensity, capillary recruitment should not have been affected by LBPP, and based on previous studies (11, 30) we would expect both V/Q matching and diffusion limitation to have deteriorated with edema development secondary to acute increases in pulmonary vascular pressures. Therefore, if edema developed with LBPP, it was insufficient to impair gas exchange as evaluated by A-aDO2. There is a large body of research suggesting pulmonary edema/damage development with exercise (4, 10, 12, 15, 26, 38); however, recent work by Zavorsky et al. (39) failed to find a relationship between postexercise radiographic evidence of edema and exercise A-aDO2. A-aDO2 may lack sensitivity as a marker of edema in healthy exercising humans, which would also explain why no relationship has been observed between exercise A-aDO2 and postexercise diffusion impairment (21).

We cannot confirm that the increase in large-vessel pressure from LBPP resulted in parallel increases in microcirculation pressure. The increased PAWP would suggest that pulmonary venous pressure was also increased, and therefore pressure should have been elevated throughout the microcirculation; however, this cannot be established without direct measurement. An acute increase in pulmonary vascular pressures of 5–10 mmHg with LBPP may have had a greater effect on gas exchange and shunt recruitment, although we suggest that these values are well above those typically seen during normoxic exercise. Ongoing research using isolated lungs should provide a better understanding of arteriovenous shunt size as well as critical opening pressures needed for shunt recruitment. Different results may have been observed had we recruited athletes with a high V˙O2 max who show a pronounced exercise-induced impairment in pulmonary gas exchange. Some would suggest that these athletes would have greater PAP pressures during exercise because of their elevated Q and, therefore, would be more likely to develop greater edema and a larger impairment in gas exchange. However, Reeves and Taylor (19) demonstrated that ~86% of the variance in PAP during upright exercise can be explained by PAWP (which is said to reflect left-ventricular end-diastolic filling pressure), and Levine et al. (14) demonstrated that endurance-trained athletes have better...
left-ventricular compliance compared with nonathletes. Indeed, in a companion paper (28), we found that PAWP at peak exercise was lower in subjects with a high vs. low VO2max, whereas no difference was observed in PAP. These results indicate that, to achieve greater pulmonary flow rates (i.e., Q˙), fitter subjects accomplish the increased driving pressure not through higher PAP but by having better cardiac compliance and therefore lower pulmonary venous pressures compared with less-fit subjects.

In conclusion, this paper examined the effect of acute increases in pulmonary vascular pressures on pulmonary gas exchange, IP shunt, and ventilation at rest and during exercise in normal healthy men. Although it is acknowledged that flow and pressure in the pulmonary vascular system of a human are highly interrelated, data presented indicate that exercise A-aDO2 is not affected by small, acute increases in both PAP and PAWP. Consistent with a coupling to A-aDO2, the frequency of IP shunt was not typically affected by LBPP. Finally, ventilation at rest and during exercise was also unaffected by increasing pulmonary vascular pressure.

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