Intrapulmonary shunting and pulmonary gas exchange during normoxic and hypoxic exercise in healthy humans

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Intrapulmonary shunting and pulmonary gas exchange during normoxic and hypoxic exercise in healthy humans. J Appl Physiol 104: 1418–1425, 2008. First published February 21, 2008; doi:10.1152/japplphysiol.00208.2007.—Exercise-induced intrapulmonary arteriovenous shunting, as detected by saline contrast echocardiography, has been demonstrated in healthy humans. We have previously suggested that increases in both pulmonary pressures and blood flow associated with exercise are responsible for opening these intrapulmonary arteriovenous pathways. In the present study, we hypothesized that, although cardiac output and pulmonary pressures would be higher in hypoxia, the potent pulmonary vasoconstrictor effect of hypoxia would actually attenuate exercise-induced intrapulmonary shunting. Using saline contrast echocardiography, we examined nine healthy men during incremental (65 W + 30 W/2 min) cycle exercise to exhaustion in normoxia and hypoxia (fraction of inspired O₂ = 0.12). Contrast injections were made into a peripheral vein at rest and during exercise and recovery (3–5 min postexercise) with pulmonary gas exchange measured simultaneously. At rest, no subject demonstrated intrapulmonary shunting in normoxia [arterial Po₂ (Pao₂) = 98 ± 10 Torr], whereas in hypoxia (Pao₂ = 47 ± 5 Torr), intrapulmonary shunting developed in 3/9 subjects. During exercise, ~90% (8/9) of the subjects shunted during normoxia, whereas all subjects shunted during hypoxia. Four of the nine subjects shunted at a lower workload in hypoxia. Furthermore, all subjects continued to shunt at 3 min, and five subjects shunted at 5 min postexercise in hypoxia. Hypoxia has acute effects by inducing intrapulmonary arteriovenous shunt pathways at rest and during exercise and has long-term effects by maintaining patency of these vessels during recovery. Whether oxygen tension specifically regulates these novel pathways or opens them indirectly via effects on the conventional pulmonary vasculature remains unclear.

alveolar-to-arterial oxygen tension difference; contrast echocardiography; pulmonary circulation; exercise-induced arterial hypoxemia

EXERCISE-INDUCED IMPAIRMENT in pulmonary gas exchange is universally observed in healthy humans (6). Indeed, in many endurance-trained athletes, significant gas exchange dysfunction occurs, leading to arterial hypoxemia (6). Diffusion limitation, relative alveolar hypoventilation, unbalanced ventilation-to-perfusion matching, and postpulmonary venous admixture (Thebesian and bronchial venous drainage) are likely contributing factors to the arterial hypoxemia in exercise, but the exact causes of gas exchange inefficiency during exercise in otherwise healthy humans have yet to be entirely elucidated.

Although multiple inert-gas elimination (MIGET) studies have remained unable to demonstrate either significant intracardiac (e.g., patent foramen ovale, atrial septal defect, etc.) or intrapulmonary arteriovenous shunting at rest or during exercise (17), recent studies using saline contrast echocardiography show that with increasing exercise intensity intrapulmonary shunt pathways open in a majority (~90%) of healthy humans (8, 40). Based on the physical principles that govern saline contrast bubble size and survival time (30, 43, 44), Eldridge et al. (8) suggested that these inducible intrapulmonary shunt pathways must be at least 60 μm in diameter. Lovering et al. (25) have confirmed the existence of these large-diameter intrapulmonary arteriovenous pathways by demonstrating transpulmonary passage of 50-μm polymer microspheres under physiological conditions (zones I and II) in isolated, ventilated, and perfused fresh, healthy human lungs. Furthermore, Stickland et al. (39) have directly demonstrated that pathways at least 25 μm in diameter are dormant at rest but are recruited during exercise in healthy dogs. These and the above data suggest that exercise does in fact cause the recruitment of large-diameter arteriovenous intrapulmonary vessels.

Eldridge and associates reported previously that the magnitude of qualitatively measured shunt was greatest at higher exercise intensities (8) and suggested that recruitment of dormant intrapulmonary shunt pathways occurred with increasing pulmonary vascular pressures and flows. For this reason, increased pulmonary artery pressures and cardiac outputs associated by acute exposure to hypoxia could potentially recruit these pathways. However, if intrapulmonary arteriovenous anastomoses are regulated by oxygen tension like conventional pulmonary arterioles, then hypoxia could attenuate or prevent exercise-induced shunting. Accordingly, we postulated that hypoxia [fraction of inspired O₂ (FIO₂) = 0.12] would attenuate recruitment of intrapulmonary shunt pathways during exercise via the potent pulmonary vasoconstrictor response. To test our hypothesis, we performed saline contrast echocardiographic studies during two incremental exercise tests in healthy human subjects breathing ambient air during one test and hypoxia during the other. Preliminary versions of this work have been reported elsewhere (24).

METHODS

The study received approval from the University of Wisconsin-Madison Human Subjects Committee, and each subject gave written informed consent before participation. All studies were performed according to the Declaration of Helsinki.

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Subjects. Fourteen healthy nonsmoking males 18–49 yr of age volunteered to participate in the study. Our previous study (8) showed no difference in either the prevalence or the onset of exercise-induced intrapulmonary shunting between males and females. A screening cardiopulmonary history and physical examination were performed. The screening contrast echocardiogram revealed one subject (~7%) with a contrast bubble echocardiogram consistent with a pulmonary arteriovenous malformation and four subjects (~29%) with a contrast bubble echocardiogram consistent with a patent foramen ovale. These five subjects were excluded from further study. The remaining nine subjects appeared to be free of cardiopulmonary disease.

Pulmonary function and lung diffusion capacity for carbon monoxide testing. Baseline pulmonary function including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), forced midexpiratory flows (FEF25–75), and peak expiratory flow were determined using computerized spirometry (Pulmonizer model PFT 3000, Med Science, St. Louis, MO) according to American Thoracic Society standards (1). Lung diffusion capacity for carbon monoxide (DLCO) was determined by a single-breath breathholding method according to American Thoracic Society standards (2). We used the Jones and Mead method for timing, alveolar sample collection was computer calculated based on subject data and was automatically performed, and CO was measured using an infrared analyzer. Predicted values for pulmonary function and DLCO were calculated as previously described by Knudson et al. (21, 22).

Exercise protocol. The subjects completed two continuous incremental exercise tests (30 W every 2 min starting from 65 W) to volitional exhaustion (subjects could no longer maintain a pedal mental exercise tests (30 W every 2 min starting from 65 W) to previously described by Knudson et al. (21, 22).

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Anthropometric, pulmonary function, and CO was measured using an infrared analyzer. Predicted values for pulmonary function and DLCO were calculated as previously described by Knudson et al. (21, 22).

Exercise protocol. The subjects completed two continuous incremental exercise tests (30 W every 2 min starting from 65 W) to volitional exhaustion (subjects could no longer maintain a pedal mental exercise tests (30 W every 2 min starting from 65 W) to previously described by Knudson et al. (21, 22).

Table 1. Anthropometric, pulmonary function, and VO2max data

<table>
<thead>
<tr>
<th>Value</th>
<th>Value</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>30.1 ± 9.6</td>
<td>Height, cm</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.4 ± 10.8</td>
<td>FVC, liters</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>4.3 ± 0.6 (102.4 ± 11.4%)</td>
<td>FEV1/FVC</td>
</tr>
<tr>
<td>FEF25–75</td>
<td>4.1 ± 1.3 (89.7 ± 25.3%)</td>
<td>DLCO, m·l/min · Torr−1</td>
</tr>
<tr>
<td>VO2max, m·l·kg−1 · min−1</td>
<td>48.1 ± 9.7 (109.8 ± 28.1%)</td>
<td>Normoxia</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>34.3 ± 5.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Values in parentheses are percent predicted. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF25–75, forced midexpiratory flow rate; DLCO, diffusion capacity for carbon monoxide; VO2max, relative maximal oxygen uptake.

SHUNTING AND GAS EXCHANGE DURING NORMOXIC AND HYPOXIC EXERCISE

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Intrathoracic echocardiography has been a very consistent finding so we predicted that the effect of hypoxia would also be consistent. Statistical significance was set to \( P < 0.05 \).

All echocardiograms were digitally recorded by the same echocardiologist and analyzed offline (Camtronics Medical System, Hartford, WI). This system allows for analysis of the echocardiograms at \( \geq 30 \) frames/s. Two cardiologists who were blinded to the conditions under which the echocardiograms were obtained read all echocardiograms independently. There was 100% agreement for the onset of shunting between the two readers. Shunt onset was defined as the appearance of individual bubbles (\( \geq 3 \) bubbles in the left heart after at least three cardiac cycles).

**RESULTS**

**Lung function and maximal oxygen uptake.** Anthropometric, pulmonary function, \( \text{DL}_{CO} \), and exercise data for the nine subjects that completed the exercise protocol are shown in Table 1. All subjects had resting pulmonary function and \( \text{DL}_{CO} \) that were within normal limits.

**Intrapulmonary shunting and gas exchange during normoxic exercise.** Intrapulmonary shunting did not occur at rest in normoxic conditions in any of the subjects. Intrapulmonary shunting occurring in eight of the nine subjects (89%) at submaximal exercise intensities (\( \% \text{VO}_{2\max} = 39 \pm 7 \)) (Tables 2 and 3). Once shunting began, it continued through maximal exercise. Five of the nine subjects (56%) continued to shunt during the recovery period in normoxic conditions (Table 2).

Cardiopulmonary performance data for normoxic rest and exercise are summarized in Table 4. As a group, the \( \text{AAaDO}_{2} \) increased with increasing exercise intensity during normoxic exercise (Fig. 1). Interestingly, the only subject that did not exhibit arteriovenous intrapulmonary shunting during normoxic exercise had an \( \text{AAaDO}_{2} \) that never widened above 10 Torr (Fig. 2). Similar results with respect to the \( \text{AaDO}_{2} \) have been reported by Stickland and associates (40) in a single subject that did not demonstrate exercise-induced intrapulmonary shunting.

**Intrapulmonary shunting and gas exchange during hypoxic exercise.** In contrast to normoxic exercise, three subjects shunted at rest in hypoxia, and all subjects shunted during hypoxic exercise (Table 2). Thus there was an inconsistent effect of hypoxia that caused shunting to occur at lower workloads than that during normoxia in 44% of the subjects (Table 3). The other subjects shunted at the same workload in hypoxic exercise as in normoxic exercise, but no subject shunted at a higher workload (Table 3). During hypoxic exercise, shunting occurred at submaximal exercise intensities (\( \% \text{VO}_{2\max} \) in hypoxia = 45 \pm 28 and \( \% \text{VO}_{2\max} \) in normoxia = 30 \pm 17) (Tables 2 and 3). Once shunting began in hypoxia, it continued through maximal exercise. There was a significant effect of hypoxia on shunting during recovery with all subjects continuing to shunt 3 min after the hypoxic exercise. Furthermore, five subjects continued to shunt at 5 min postexercise in hypoxia (Table 2). In general, left heart contrast was qualitatively denser in hypoxic exercise compared with normoxic exercise at identical workloads (Fig. 3).

Cardiopulmonary performance data for hypoxic rest and exercise are summarized in Table 5. As a group, the \( \text{AAaDO}_{2} \) increased with increasing exercise intensity during hypoxic exercise (Fig. 1). The \( \text{AAaDO}_{2} \) during hypoxic exercise was significantly greater than the respective normoxic \( \text{AAaDO}_{2} \) up to a workload of 229 W (Fig. 1, Tables 4 and 5). Oxygen consumption (\( \text{VO}_{2} \)) was not significantly different between normoxia and hypoxia up to 196 W. At 229 W, \( \text{VO}_{2} \) was significantly less in hypoxia. Above 229 W we had an insufficient number of subjects (Tables 4 and 5) to make statistical comparisons, and data in Fig. 1 are graphed accordingly. When the \( \text{AAaDO}_{2} \) values in normoxia and hypoxia were compared at relative exercise intensities, we found that mean \( \text{AAaDO}_{2} \) remained greater in hypoxia (Fig. 4).

**DISCUSSION**

The purpose of this study was to determine whether hypoxia (\( \text{FiO}_{2} = 0.12 \)) attenuates or exacerbates exercise-induced intrapulmonary shunting. At this level of hypoxia, there is an acute, but inconsistent, effect on the pulmonary vasculature indicated by the opening intrapulmonary arteriovenous shunt pathways at lower workloads (i.e., at rest and during exercise). Longer term, this level of hypoxia had a significant effect on the pulmonary vasculature, as it induced shunting during recovery from exercise in all subjects at 3 min postexercise and in the majority of subjects up to 5 min postexercise. Whether low oxygen tension specifically regulates these novel shunt pathways or opens them indirectly via effects on the conventional pulmonary vasculature remains unclear.
Table 4. Cardiopulmonary performance at rest and during normoxic exercise

<table>
<thead>
<tr>
<th>Workload (Watts)</th>
<th>V̇E, l/min</th>
<th>HR, beats/min</th>
<th>V̇O2, l/min</th>
<th>V̇CO2, l/min</th>
<th>RER</th>
<th>SaO2, %</th>
<th>PaO2, Torr</th>
<th>PaCO2, Torr</th>
<th>HCO3⁻, mM</th>
<th>pH</th>
<th>Temperature, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 W</td>
<td>13.3 ± 4.5</td>
<td>62 ± 7</td>
<td>0.43 ± 0.16</td>
<td>0.34 ± 0.13</td>
<td>0.79</td>
<td>99 ± 1</td>
<td>98 ± 12</td>
<td>98 ± 10</td>
<td>36 ± 6</td>
<td>10.7</td>
<td>37 ± 0.2</td>
</tr>
<tr>
<td>65 W</td>
<td>30.1 ± 6.1</td>
<td>101 ± 11</td>
<td>1.47 ± 0.35</td>
<td>1.36 ± 0.35</td>
<td>0.88</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>36 ± 3</td>
<td>89</td>
<td>36.9 ± 0.2</td>
</tr>
<tr>
<td>98 W</td>
<td>37.4 ± 8.6</td>
<td>111 ± 15</td>
<td>1.75 ± 0.39</td>
<td>1.8 ± 0.39</td>
<td>0.91</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
<td>40 ± 3</td>
<td>1.5</td>
<td>37 ± 0.3</td>
</tr>
<tr>
<td>131 W</td>
<td>47.3 ± 9.8</td>
<td>122 ± 16</td>
<td>2.1 ± 0.34</td>
<td>2.0 ± 0.51</td>
<td>0.97</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>39 ± 3</td>
<td>1.9</td>
<td>37 ± 0.2</td>
</tr>
<tr>
<td>196 W</td>
<td>56.7 ± 10.7</td>
<td>133 ± 17</td>
<td>2.3 ± 0.67</td>
<td>2.6 ± 0.51</td>
<td>1.01</td>
<td>92 ± 10</td>
<td>92 ± 9</td>
<td>92 ± 9</td>
<td>38 ± 4</td>
<td>2.4</td>
<td>37 ± 0.3</td>
</tr>
<tr>
<td>229 W</td>
<td>72.2 ± 14.7</td>
<td>147 ± 16</td>
<td>2.75 ± 0.39</td>
<td>3.14 ± 0.43</td>
<td>1.10</td>
<td>96 ± 1</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>38 ± 4</td>
<td>2.8</td>
<td>37 ± 0.4</td>
</tr>
<tr>
<td>261 W</td>
<td>88.6 ± 20.5</td>
<td>157 ± 15</td>
<td>3.11 ± 0.42</td>
<td>3.74 ± 0.53</td>
<td>1.14</td>
<td>96 ± 1</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>38 ± 4</td>
<td>3.2</td>
<td>37 ± 0.5</td>
</tr>
<tr>
<td>294 W</td>
<td>113.1 ± 31.1</td>
<td>167 ± 13</td>
<td>3.47 ± 0.52</td>
<td>4.13 ± 0.36</td>
<td>1.13</td>
<td>96 ± 1</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>38 ± 4</td>
<td>3.2</td>
<td>37 ± 0.5</td>
</tr>
<tr>
<td>327 W</td>
<td>132.9 ± 23.7</td>
<td>173 ± 12</td>
<td>3.64 ± 0.25</td>
<td>4.58 ± 0.3</td>
<td>1.13</td>
<td>96 ± 1</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>38 ± 4</td>
<td>3.2</td>
<td>37 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. V̇E, minute ventilation; HR, heart rate; V̇O2, oxygen consumption; V̇CO2, carbon dioxide production; RER, respiratory exchange ratio; SaO2, arterial oxygen saturation; PaO2, arterial PO2; PaCO2, arterial PCO2; pH, arterial pH; AaDO2, alveolar-to-arterial difference in oxygen tension.

Fig. 1. Pulmonary gas exchange during normoxic and hypoxic exercise vs. absolute workload. All data points are means ± SE, n = 9 unless otherwise specified. AaDO2, alveolar-to-arterial oxygen tension difference; ns, not significantly different from normoxia. *Significantly different from normoxia, P < 0.05; n was insufficient above 229 W to make statistical comparisons.

Fig. 2. Gas exchange during normoxic and hypoxic exercise in a single subject without shunting during normoxic exercise. Closed symbols indicate no shunting. Open symbols indicate shunting.

Methodological considerations. Saline contrast echocardiography as a method to detect arteriovenous intrapulmonary shunt at rest and during exercise requires that saline contrast bubbles traverse the pulmonary circulation via large-diameter pathways as opposed to distended capillaries. Glazier et al. examined capillary distension in rapidly frozen greyhound lungs, demonstrating that the mean capillary width under physiological perfusion pressures of 37–74 mmHg was 6.5 μm with the largest measured capillary not exceeding 13 μm (11), suggesting that capillaries do not distend beyond 15 μm. Because the size distribution of the contrast bubbles that we inject is unknown, there may be bubbles small enough (<15 μm) to travel through pulmonary capillaries created in our suspensions.

The viability of saline contrast bubbles is limited by time, blood flow, and pressure. Because we have defined the presence of an intrapulmonary shunt as bubbles appearing in the left heart after >3 cardiac cycles, even with a heart rate of 180 beats/min at maximal exercise the total transit time from the right heart to the left heart would be 1 s. It has been previously demonstrated that an 8-μm bubble has a survival time <190 ms, which makes the appearance of a bubble in the left heart 1,000 ms, or three cardiac cycles later, virtually impossible (30, 43, 45). Furthermore, pulmonary blood flow and pressures are increased during exercise, and contrast bubble dissolution (i.e., viability) is rapidly accelerated as flow velocity (43–45) and pressure increase (28). Accordingly, in healthy human subjects, contrast bubbles are filtered and eliminated by the pulmonary circulation. This transpulmonary passage of contrast bubbles is indicative that the bubbles are traveling through large-diameter vessels. There is direct evidence that these large-diameter (>25–50 μm) intrapulmonary arteriovenous anastomoses exist in healthy human, baboon (25), and dog (39) lungs. Furthermore, Stickland et al. (39) have directly demonstrated that these pathways are dormant at rest in healthy dogs but open up during exercise.

In our previous studies, we used only air and sterile saline to create suspensions of microbubbles (8). In the present study, we used 1 ml of the subject’s blood in addition to air and sterile saline. The addition of the blood was used to create more stable suspensions, anastomoses exist in healthy human, baboon (25), and dog (39) lungs. Furthermore, Stickland et al. (39) have directly demonstrated that these pathways are dormant at rest in healthy dogs but open up during exercise.
A significant number of corner vessels were 20 μm in diameter and enter into the systemic circulation during hypoxic conditions, whereas microspheres do not bypass the pulmonary circulation and enter the systemic circulation in normoxia (26). Manohar and Goetz (35) have shown the existence of pulmonary arteriovenous shunts in fetal lambs. They demonstrated further that these shunt pathways become nonfunctional at rest postnatally in lambs and sheep (27). These data suggest that the intrapulmonary arteriovenous vessels that allow for the transpulmonary passage of saline contrast bubbles during normoxic and hypoxic exercise in adult humans may be remnant fetal pathways that, advantageously, allowed for blood to be diverted away from nonfunctional gas exchange units of the fetal lung.

Modulation of intrapulmonary arteriovenous pathways by oxygen tension. There may be many mechanisms responsible for the modulation of intrapulmonary arteriovenous pathways, including direct modulation by alveolar or mixed venous PO2 and/or indirect recruitment by increased regional pulmonary vascular pressures and flows, increased shear stress, and/or flow-mediated processes. If intrapulmonary arteriovenous anastomoses simply responded to oxygen tension in a manner consistent with the majority of the pulmonary circulation, then hypoxia would constrict these vessels and reduce or prevent the transpulmonary passage of saline contrast bubbles. However, we found the opposite such that low inspired oxygen tension resulted in left heart contrast that was qualitatively greater in hypoxic exercise than in normoxic exercise.

One possible reason for this apparent discrepancy is that both increased regional pulmonary pressures and flows during hypoxia indirectly modulate intrapulmonary shunting. With acute hypoxia, both pulmonary blood flow and pulmonary vascular pressures are increased at rest and during submaximal exercise (9, 19, 20), and the heterogeneous vasoconstriction that occurs in response to hypoxia would likely result in markedly increased regional pressures and flows (16), as opposed to global increases in pressure and flow. Under similar conditions of exercise and hypoxic stress as those cited above and thus presumably similar increases in pulmonary blood flow and pressure, we observed a consistent effect on intrapulmonary shunting during recovery and induced shunting in a subject who did not shunt under normoxic conditions. Therefore, both regional high flows and pressures observed in hypoxic conditions may also regulate these pathways indirectly via regional mechanical forces in addition to, or instead of, a direct effect of oxygen tension on these vessels. However, when the data were analyzed for relative exercise intensities, when cardiac output, and therefore pulmonary blood flow, would be relatively similar in each condition (14, 37), we found that the AaDO2 was greater with hypoxia than with normoxia.

who shunted had done so at ~40% of V̇O2max in normoxia and ~30% of V̇O2max in hypoxia. Whether the lack of variability in shunt onset was caused by stable bubbles or was the result of the subjects’ anatomy and physiology is unknown.

Which pulmonary vessels could allow for the transpulmonary passage of saline contrast bubbles? One alternative explanation for our results could be that the saline contrast bubbles traveled through corner vessels. Although corner capillaries as large as 20 μm in diameter have been measured in greyhound lungs (35), recent work by Manohar and Goetz (26) reported that 15-μm microspheres do not bypass the pulmonary circulation and enter into the systemic circulation during maximal exercise in the thoroughbred horse. Clearly, if a significant number of corner vessels were 20 μm in diameter or if a significant number of capillaries could distend above 10 μm, then at least some 15-μm microspheres would have passed through the pulmonary circulation and been detected in the systemic circulation of the maximally exercising thoroughbred horse whose capillary pressures have been estimated to be as high as 95 mmHg (41). These pressures are much greater than those pressures achieved in the maximally exercising human. Accordingly, saline contrast bubbles smaller than capillaries (<15 μm) and corner vessels (<20 μm) are not likely to survive long enough to reach the left heart because of the increased pulmonary pressures, flows, and shear stresses associated with exercise (28–30, 34, 43–45), making transpulmonary passage via either normal and distended capillaries or corner vessels highly unlikely (see Methodological considerations). In the absence of gross capillary distension and passage via corner vessels, inducible arteriovenous anastomoses remain as the only reasonable explanation for our results.

Although the origin of these inducible intrapulmonary arteriovenous anastomoses is unknown, they may be remnant fetal vessels. Wilkinson and Fagan (42) have demonstrated the existence of intrapulmonary arteriovenous pathways in newborn human lungs, and recently McMullan et al. (27) demonstrated the existence of pulmonary arteriovenous shunts in fetal lambs. They demonstrated further that these shunt pathways become nonfunctional at rest postnatally in lambs and sheep (27). These data suggest that the intrapulmonary arteriovenous vessels that allow for the transpulmonary passage of saline contrast bubbles during normoxic and hypoxic exercise in adult humans may be remnant fetal pathways that, advantageously, allowed for blood to be diverted away from nonfunctional gas exchange units of the fetal lung.

Fig. 3. Representative contrast echocardiograms in one subject during normoxic and hypoxic exercise. A: echocardiogram in normoxic exercise (196 W). B: echocardiogram in hypoxic exercise (196 W). RA, right atrium; LV, left ventricle; RV, right ventricle. Note almost complete opacification of the LV during exercise in hypoxia, indicating a greater number of saline contrast bubbles compared with that in normoxic exercise.
Gas exchange efficiency mechanisms responsible for opening these dynamic pathways. Clearly, more work is needed to determine the mechanisms responsible for opening these dynamic pathways.

What are the physiological consequences of increased intrapulmonary shunting in hypoxia? Gas exchange efficiency determined by the difference between the alveolar and the arterial blood oxygen tension (AaDO₂) worsens in an intensity-dependent manner during exercise (6). It is generally agreed that ventilation to perfusion heterogeneity and extrapulmonary shunt play a role in this gas exchange inefficiency, but the roles of intrapulmonary shunting, intracardiac shunting, and diffusion limitation are not well defined. If inducible large-diameter intrapulmonary arteriovenous pathways do not participate in gas exchange, then they have the capacity to act as an anatomical shunt. In the present study, we found that intrapulmonary shunting occurred at rest and lower workloads in hypoxia than in normoxia and that qualitatively, shunting was greater in hypoxia. Gas exchange was significantly worse at most submaximal exercise intensities, and there was a tendency for it to be worse at rest in hypoxia. These data suggest that the change in onset of shunting and the qualitative increase in shunting intensity are playing some role in gas exchange efficiency at rest and during exercise in hypoxic conditions. Alternatively, blood traveling through these large-diameter intrapulmonary arteriovenous vessels during exercise may be diffusion limited, thereby preventing complete equilibration of blood gases and worsening gas exchange as a result (10, 38), an effect further exacerbated by hypoxic conditions.

Possible non-gas exchange related sequellae of increased intrapulmonary shunting in hypoxia. We hypothesized in our previous report that arteriovenous intrapulmonary pathways may provide a parallel vascular pathway that would allow for the protection of the pulmonary capillaries from damaging increases in vascular pressure (8). We found that intrapulmonary shunting occurred at lower workloads (i.e., at rest and during exercise) in hypoxia, and the magnitude of the shunt was qualitatively greater. This would mean that during conditions of high pressures and flows, such as exercise and hypoxic exercise, recruitable intrapulmonary arteriovenous pathways do in fact provide a parallel pathway to divert potentially damaging pressures from reaching pulmonary capillaries in the majority of healthy humans. Consequently, those few human subjects that demonstrate exercise-induced pulmonary hemorrhaging (7, 18) may either not have intrapulmonary arteriovenous pathways or have fewer of these pathways than the normoxia. This would suggest that increased pressure, rather than flow, may be responsible for recruiting the shunt pathways. Clearly, more work is needed to determine the mechanisms responsible for opening these dynamic pathways.

### Table 5. Cardiopulmonary performance at rest and during hypoxic exercise

| W | V̇E, l/min | HR, beats/min | V̇CO₂, l/min | RER | AaDO₂, mmHg | SaCO₂, % | PaCO₂, Torr | pH | HCO₃⁻ | pHa | Arterial lactate, mM | Temperature, °C | n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 16.2 ± 3.8 | 77 ± 15 | 0.4 ± 0.14 | 1.03 ± 0.18 | 86 ± 7 | 47 ± 5 | 32 ± 3 | 36.9 ± 0.2 | 0.9 ± 0.3 | 24.4 ± 1.6 | 0.18% | 5.6 ± 1.4 | 9 |
| 65 | 39.4 ± 10 | 122 ± 18 | 1.31 ± 0.28 | 0.9 ± 0.17 | 79 ± 5 | 38 ± 6 | 31 ± 3 | 36.8 ± 0.3 | 1.2 ± 0.4 | 23.8 ± 1.5 | 0.2% | 23.3 ± 1.9 | 9 |
| 98 | 51 ± 11.6 | 136 ± 17 | 1.6 ± 0.28 | 0.97 ± 0.15 | 76 ± 6 | 36 ± 5 | 32 ± 3 | 36.9 ± 0.4 | 1.8 ± 0.8 | 23.4 ± 1.9 | 0.4% | 27.6 ± 1.3 | 9 |
| 131 | 67.6 ± 14.4 | 148 ± 15 | 1.95 ± 0.36 | 1.03 ± 0.14 | 74 ± 6 | 35 ± 6 | 32 ± 4 | 37 ± 0.4 | 2.7 ± 1.3 | 22.3 ± 2.2 | 0.1% | 42.2 ± 1.8 | 9 |
| 163 | 84.5 ± 15.8 | 158 ± 14 | 2.24 ± 0.53 | 1.11 ± 0.16 | 74 ± 6 | 36 ± 6 | 31 ± 3 | 37.1 ± 0.6 | 6.2 ± 2.3 | 20.5 ± 2.8 | 0.0% | 6.2 ± 2.3 | 9 |
| 196 | 104.9 ± 15.8 | 167 ± 13 | 2.47 ± 0.55 | 1.17 ± 0.15 | 73 ± 5 | 37 ± 5 | 29 ± 2 | 37.2 ± 0.6 | 8.2 ± 2.7 | 20.2 ± 5.8 | 0.9% | 8.2 ± 2.7 | 9 |
| 229 | 119.5 ± 19.5 | 170 ± 13 | 2.57 ± 0.34 | 1.23 ± 0.11 | 72 ± 4 | 37 ± 4 | 28 ± 2 | 37.4 ± 0.8 | 7.6 ± 1.7 | 21.8 ± 4.6 | 0.0% | 7.6 ± 1.7 | 9 |
| 261 | 146.9 ± 16.1 | 179 ± 6 | 2.96 ± 0.29 | 1.19 ± 0.08 | 76 ± 4 | 40 ± 0 | 27 ± 1 | 38.1 ± 0.4 | 15.1 ± 0.6 | 18.7 ± 1.4 | 0.0% | 15.1 ± 0.6 | 9 |

Values are means ± SD. *V̇O₂ was significantly less in hypoxia at 229 W.

**Fig. 4.** Pulmonary gas exchange during normoxic and hypoxic exercise vs. relative exercise intensities. Values plotted are for each individual in normoxia and hypoxia. Slopes are linear regressions drawn for each group data set, normoxia (dashed line) or hypoxia (solid line). The y-intercept in hypoxia was significantly greater than in normoxia, indicating greater gas exchange inefficiency during hypoxic exercise at relative exercise intensity (P = 0.04, paired t-test). %V̇O₂max, percent of predicted maximal oxygen uptake.
majority (~90%) of healthy humans who do demonstrate exercise-induced intrapulmonary shunting and who also do not demonstrate exercise-induced pulmonary hemorrhage. Likewise, Manohar and Goetz (26) have demonstrated that exercise-induced intrapulmonary shunting does not occur in thoroughbred race horses during exercise. Not surprisingly, these horses always demonstrate exercise-induced pulmonary hemorrhaging. However, considering the excessive pulmonary blood flows and pressures generated by these animals during maximal exercise, a 2% intrapulmonary shunt may not be enough to attenuate the microvascular injury and prevent the pulmonary hemorrhage. The reasons thoroughbred horses do not have or fail to open these postulated parallel pathways are unclear, but the answers may lie in the differences in criteria for natural and artificial selection.

Summary. We have demonstrated that intrapulmonary shunting at rest and during exercise and recovery from exercise can be modulated by hypoxia in some, but not all, individuals. The mechanism by which oxygen tension directly or indirectly regulates these intrapulmonary arteriovenous pathways remains unclear. The vessels may be directly modulated by oxygen tension in a manner similar to some components of the fetal circulation or they may be controlled indirectly by regional pressures and flows. Regardless, that these vessels can be modulated by lowering inspired oxygen tension suggests that these vessels likely participate in multiple roles related to the control of blood flow through the lung. In addition to playing a negative role in gas exchange by acting as an anatomical shunt or a diffusion-limited vessel, these pathways may also play an adaptive role in the pulmonary circulation by acting as a parallel pathway during conditions of regional high pressure and flows, thereby reducing or preventing these potentially detrimental pressures and flow from damaging fragile pulmonary microvessels.

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