Exercise-induced intrapulmonary arteriovenous shunting in healthy humans

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Eldridge, Marlowe W., Jerome A. Dempsey, Hans C. Haverkamp, Andrew T. Lovering, and John S. Hokanson. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. J Appl Physiol 97: 797–805, 2004. First published April 23, 2004; 10.1152/japplphysiol.00137.2004.—We hypothesized that increasing exercise intensity recruits dormant arteriovenous intrapulmonary shunts, which may contribute to the widened alveolar-arterial oxygen difference seen with exercise. Twenty-three healthy volunteers (13 men and 10 women, aged 23–48 yr) with normal lung function and a wide range of fitness (mean maximal oxygen uptake = 126% predicted; range = 78–200% predicted) were studied by agitated saline contrast echocardiography (4-chamber apical view). All 23 subjects had normal resting contrast echocardiograms without evidence of intracardiac or intrapulmonary shunting. However, with cycle ergometer exercise, 21 of 23 (91%) of the subjects showed a delayed (>3 cardiac cycles) appearance of contrast bubbles in the left heart. This pattern is consistent with passage of contrast bubbles through the pulmonary circulation. Because the contrast bubbles are known to be significantly larger than pulmonary capillaries, we propose that they are traveling through direct arteriovenous intrapulmonary shunts. In all cases, the intrapulmonary shunting developed at submaximal oxygen uptakes (%maximal oxygen uptake = 59 ± 20 (SD)) and once evident persisted at all subsequent work rates. Within 3 min of exercise termination, the contrast echocardiograms with bubble injection showed no evidence of intrapulmonary shunting. These dynamic shunts will contribute significantly to the widened alveolar-arterial oxygen difference seen with exercise. They may also act as a protective parallel vascular network limiting the rise in regional pulmonary vascular pressure while preserving cardiac output during exercise.

pulmonary circulation; pulmonary gas exchange; exercise-induced hypoxemia

WITH EXERCISE, GAS-EXCHANGE efficiency, as quantified by the difference between the alveolar and the arterial blood oxygen tensions (A-aDO2), progressively worsens in an intensity-dependent manner (1, 10, 53, 60). At maximal exercise, the A-aDO2 reaches values of 20–30 Torr in normal, healthy, untrained subjects and can be as high as 35–50 Torr in some elite athletes (9, 20). In contrast, fixed-workload high-intensity endurance exercise does not result in a time-dependent increasing of gas-exchange efficiency (59), indicating that the magnitude of the A-aDO2 is determined primarily by metabolic rate, rather than exercise duration.

The A-aDO2 is a complex physiological variable and as such is determined by a variety of mechanisms during rest and exercise. Imperfect matching of the distributions of alveolar ventilation (VA) and pulmonary blood flow (Q), otherwise known as the VA/Q ratio, contributes to the A-aDO2 during both rest and exercise (16, 55). With exercise, overall VA/Q nonuniformity increases slightly as estimated by the multiple inert-gas elimination technique (MIGET) (16, 55). It should be stressed that the VA/Q nonuniformity during exercise fails to explain all of the widening of the A-aDO2. Indeed, not all subjects increase VA/Q nonuniformity during exercise (45), whereas a widened A-aDO2 is universally observed. It is argued that any difference between the actual A-aDO2 and that predicted from the measured amount of VA/Q nonuniformity given by MIGET can be attributed to diffusion limitation. With the use of this technique, significant amounts of diffusion limitation, up to two-thirds of the total A-aDO2, have been predicted at metabolic rates as low as 2.0 l/min (19, 55). However, it is unlikely that a diffusion limitation would occur at these moderate metabolic rates when pulmonary capillary blood volume and pulmonary blood flow are submaximal and mean transit time is still >450 ms (56).

Another potential contributor to the widened A-aDO2 with exercise is venous admixture from intrapulmonary arteriovenous shunts. Wagner and colleagues (55) used 100% oxygen breathing and MIGET to test for shunt during exercise. By using the 100% oxygen test, the calculated shunt fractions were found to be ~2%. The authors suggested that this represented postpulmonary shunt because the MIGET did not detect intrapulmonary shunting. However, the validity of these standard tests for detecting intrapulmonary shunts may be questionable because significant prepulmonary capillary gas exchange may occur and its magnitude is critically dependent on the gas concentration gradient (6, 11, 24, 49). Therefore, intrapulmonary arteriovenous connections that act as shunts at low or normal oxygen tensions may participate in gas exchange at high inspired oxygen fraction, leading to an underestimation of shunted blood. Furthermore, when a high inspired oxygen fraction is used, measurements of blood oxygen tension are not sufficiently accurate to distinguish shunts <10% of the cardiac output. Similarly, MIGET may underestimate intrapulmonary shunting because the detection of shunting is dependent on retention of sulfur hexafluoride, an inert gas with a very low solubility in blood. The very low solubility and the large concentration gradient may allow for precapillary elimination of sulfur hexafluoride, like that which occurs with the 100% oxygen technique, thus underestimating intrapulmonary shunting. The MIGET is also prone to spurious and even impossible results as evidenced by findings of a wider predicted (from VA/Q estimates) than actually measured A-aDO2 (19).

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Morphological studies demonstrate the existence of direct vascular conduits between pulmonary arteries and veins in both dog (4, 5, 34, 36, 37) and human lungs (51, 52, 62). Furthermore, increases in the fraction of intrapulmonary shunting in these animal models appear to occur with increasing pulmonary arterial pressure and flow (5). Thus it is reasonable to postulate that even moderate-intensity exercise may augment this shunt fraction. Because the shunted blood is deoxygenated and becomes more so as oxygen extraction by the contracting muscles increases, only a small fraction of the cardiac output as shunt is necessary to widen the A-aD O 2 .

We hypothesized that intrapulmonary arteriovenous shunts are recruited in healthy humans during exercise. To test our hypothesis, we performed agitated saline contrast bubble echocardiography at rest and during progressive exercise in healthy individuals with a wide continuum of maximal oxygen uptake.

METHODS

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

Subjects. Twenty-six healthy, nonsmoking volunteers (15 men and 11 women), aged 18–49 yr were recruited and, after written, informed consent was given, agreed to further study. A screening cardiopulmonary history and physical examination were performed, and all subjects appeared to be free of cardiopulmonary disease. The resting contrast echocardiograms performed just before the exercise protocol revealed a previously unrecognized patent foramen ovale in two subjects, and a third subject had a contrast bubble echocardiogram consistent with a pulmonary arteriovenous malformation. These three subjects were excluded from the exercise studies.

Pulmonary function and lung diffusion capacity for carbon monoxide testing. Baseline pulmonary function (Pulmonizer model PFT 3000, Med Science, St. Louis, MO) including forced vital capacity, forced expiratory volume in 1 s, forced mid-expiratory flow, and peak expiratory flow were determined as described previously (50). Lung diffusion capacity for carbon monoxide (DL CO ) was determined by a single-breath breath-holding method (35).

Exercise protocol. Twenty-three subjects (13 men and 10 women) completed a progressive incremental exercise test to exhaustion on a magnetically braked cycle ergometer. After a 2 min warm-up with the nose clip in place, 136% during his progressive exercise study. The images presented are typical of those obtained from all 23 subjects studied. In all cases the quality of the images was good. With digital image recording and a frame rate of 30 images/s, we were often able to see bubbles emerging from the pulmonary veins and then track these bubbles as they passed through the left heart after a delay of at least three cardiac cycles. The delayed appearance of bubbles in the left heart indicates transpulmonary passage of contrast bubbles either through abnormally dilated capillaries (43) or through intrapulmonary arteriovenous shunts (2, 18, 21, 27, 48). Harmonic imaging enhances detection of the nonlinear backscatter from the contrast bubbles, thus improving signal-to-noise and greatly improving visualization of bubble contrast in the cardiac chambers. All of the contrast echocardiograms were performed with the subject seated on the cycle ergometer with the mouthpiece and nose clip in place.

Data analysis. Descriptive and physiological data are presented as means ± SD (Sigma Stat 2.03, Aspire Software International, Leesburg, VA). All of the echocardiograms were digitally recorded and analyzed offline (Camtronic Medical System, Hartland, WI). This system allows for analysis of the echocardiograms at 30 frames/s.

RESULTS

Lung function and maximal oxygen uptake data. Anthropometric, pulmonary function, DL CO , and exercise data for the 23 subjects that completed the exercise protocol are shown in Table 1. All of these subjects had resting pulmonary function and DL CO that were within normal values. There was a wide continuum in fitness level with predicted maximal oxygen uptake (V O 2max ) ranging from 78 to 200%.

Contrast echocardiography during progressive exercise. Shown in Figs. 1, 2, and 3 are contrast echocardiograms obtained from a 48-yr-old male subject (%predicted V O 2 max = 136%) during his progressive exercise study. The images presented are typical of those obtained from all 23 subjects studied. In all cases the quality of the images was good. With digital image recording and a frame rate of 30 images/s, we were often able to see bubbles emerging from the pulmonary veins and then track these bubbles as they passed through the left heart chambers.

Table 1. Subject characteristics and resting lung function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (n = 13)</th>
<th>Women (n = 10)</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>32.2±8.0</td>
<td>27.2±7.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.6±8.0</td>
<td>165.1±2.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.2±11.9</td>
<td>58.8±3.0</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.3±0.6 (100.9±11.7)</td>
<td>4.1±0.4 (112.1±10.2)</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>4.3±0.5 (98.5±11.7)</td>
<td>3.6±0.4 (115.0±9.9)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.81±0.08</td>
<td>0.88±0.06</td>
</tr>
<tr>
<td>FEF 25–75 l/s</td>
<td>4.4±1.6 (93.7±31.1)</td>
<td>4.2±0.8 (115.0±21.7)</td>
</tr>
<tr>
<td>DL CO , ml·min⁻¹·Torr⁻¹</td>
<td>38.8±4.3 (89.9±10.4)</td>
<td>26.7±4.7 (86.0±12.8)</td>
</tr>
<tr>
<td>VO2max, ml·kg⁻¹·min⁻¹</td>
<td>51.9±10.1 (120.0±24.6)</td>
<td>41.7±8.2 (132.5±33.1)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Values in parentheses are percent predicted (3, 25, 26). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF25–75 forced expiratory flow of midexpiratory volume; DL CO , diffusion capacity for carbon monoxide; VO2max, relative maximal oxygen uptake.
Figure 1 shows the apical four-chamber contrast echocardiograms obtained at rest. The subject is seated on the cycle ergometer with the mouthpiece and nose clip in place. Immediately after injection of contrast bubbles, both the right atrium (RA) and right ventricle (RV) are densely opacified with contrast bubbles. The left heart is free of contrast consistent with the absence of intracardiac shunts. After several cardiac cycles the left heart remains free of contrast, indicating that the pulmonary circulation has effectively trapped and eliminated the contrast bubbles.

Figure 2 shows contrast echocardiograms obtained at exercise intensities of 100, 230, and 260 W. At 100 W (%VO2max = 40%), immediately after contrast bubble injection, the RA and RV are densely opacified, whereas the left heart is free of contrast indicating no intracardiac shunting. Five cardiac cycles later the left heart remains clear, with no evidence of transpulmonary passage of contrast bubbles. In this subject, transpulmonary passage of contrast bubbles occurred at 230 W (%VO2max = 84%). Again, immediately after contrast injection the RA and RV are densely opacified, whereas the left heart remains clear. Five seconds (or 10 cardiac cycles) later, contrast bubbles are clearly seen in the left heart. The delayed arrival of contrast in the left ventricle indicates passage of bubbles through the pulmonary circulation (also see Fig. 4). A similar pattern with a delayed appearance of contrast is seen at 260 W (%VO2max = 94%). Note that the density of contrast bubbles appearing in the left ventricle is qualitatively greater at 260 W than at 230 W.

Figure 3 shows the contrast echocardiograms obtained 3 min after termination of the exercise bout. The subject remained on the cycle ergometer in the riding position. After contrast injection, there was no evidence of intracardiac shunting or transpulmonary passage of contrast bubbles.

Detection of intracardiac vs. intrapulmonary right-to-left shunts with contrast echocardiography. Time of the appearance of contrast bubbles in the left heart after right heart filling is used to distinguish intracardiac from intrapulmonary shunts. If intracardiac right-to-left shunting exists, contrast bubbles will rapidly fill the left heart (44). If the contrast bubbles pass through the lungs, they will appear in the left heart after a delay of at least three cardiac cycles. Figure 4 shows six sequential apical four-chamber contrast echocardiograms obtained from a 28-yr-old female subject during submaximal exercise (%VO2max = 40). The first image shows the peripheral contrast injection with contrast bubbles filling the right heart. Each subsequent image is separated in time by 1 s. There is no evidence of contrast bubbles in the left heart until the fifth image, which is eight cardiac cycles after the contrast injection. The delayed appearance of bubbles in the left heart indicates transpulmonary passage of contrast bubbles either through abnormally dilated capillaries (43) or through intrapulmonary arteriovenous shunts (2, 18, 21, 27, 48). We found that with submaximal exercise 91% (21 of 23) of the subjects showed a delayed (>3 cardiac cycles) appearance of contrast bubbles in the left heart. However, no shunting was seen after termination of exercise.

Intersubject variability. Table 2 shows the cardiopulmonary measures at the onset of intrapulmonary arteriovenous shunting. In all cases, the intrapulmonary shunting developed at submaximal exercise levels (13–84%VO2max) and, once present, persisted with each subsequent work rate. Shown in Fig. 5 is the frequency distribution, among the 23 subjects, of the exercise intensity at the onset of shunting. The %VO2max at the onset of shunting was broadly distributed, with the distribution skewed toward the higher exercise intensities. Two male subjects did not develop intrapulmonary arteriovenous shunting at any exercise intensity. Otherwise, these subjects were not different from the subjects that demonstrated exercise-induced shunting.

DISCUSSION

The goal of this study was to determine whether intrapulmonary arteriovenous shunts develop in healthy humans during exercise. We used agitated saline contrast echocardiography during exercise and found that contrast bubbles traversed the pulmonary circulation and appeared in the left heart in 91% (21 of 23) of subjects tested. The transpulmonary passage of contrast bubbles was not evident at rest but developed at submaximal oxygen consumptions and persisted with each subsequent work rate. However, the shunting was not seen 3 min after the termination of maximal exercise. We believe our
Fig. 2. Contrast echocardiograms during exercise. At 100 W, there is no evidence of intracardiac or intrapulmonary shunting, as the left heart remains free of contrast bubbles. In this subject, the first evidence of intrapulmonary shunting is seen at 230 W (percent maximal oxygen uptake (% $\text{VO}_2\text{max}$) = 84%). Note the delayed appearance of contrast bubbles in the left heart. The same pattern is seen at 260 W. Again all images are apical 4-chamber views.

Fig. 3. Contrast echocardiograms 3 min after the termination of maximal exercise. Note that there is no evidence of intracardiac or intrapulmonary shunting, as the left heart remains free of contrast bubbles. All images are apical 4-chamber views.
Findings provide good evidence for the recruitment of arteriovenous intrapulmonary shunts with exercise.

Is contrast echocardiography valid for detecting intrapulmonary arteriovenous shunting during exercise? Contrast echocardiography is a standard clinical method for detecting anatomic intrapulmonary shunts at rest (2, 18, 21, 48). Recently, Lee and colleagues (27) showed that contrast echocardiography was 100% sensitive compared with pulmonary angiography for detecting pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. However, the specificity of contrast echocardiography for detecting intrapulmonary arteriovenous shunts has not been carefully examined. Confidence in contrast echocardiography for detecting anatomic intrapulmonary shunts during exercise is dependent on adequately addressing several concerns involving contrast bubbles and pulmonary capillary morphology.

What are the effects of exercise on bubble survival during passage through the pulmonary circulation? A possible explanation for our findings is that, with the shortened pulmonary circulation time during exercise, small contrast bubbles (<10 μm) may survive long enough to pass through pulmonary capillaries and appear in the left heart chambers. The injected saline contrast bubbles have a wide spectrum of diameters. However, the small-diameter (<10 μm) contrast bubbles that could pass through normal pulmonary capillaries collapse rapidly (29, 31, 32, 38). The remaining larger bubbles are filtered and eliminated by the pulmonary microcirculation (4, 31, 32, 44). Meltzer and colleagues (32) calculated survival times of contrast bubbles in degassed stationary whole blood by applying the theoretical principles of bubble behavior in fluids (14).

Table 2. Physiological data at the onset of transpulmonary passage of contrast

<table>
<thead>
<tr>
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<th>Men (n = 11)</th>
<th>Women (n = 10)</th>
<th>All Subjects (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>124±19 (102–154)</td>
<td>133±23 (111–178)</td>
<td>128±21 (102–178)</td>
</tr>
<tr>
<td>V̇E, l/min</td>
<td>56.4±20.1 (33–96)</td>
<td>35.5±15.3 (11–62)</td>
<td>46.4±20.6 (11–96)</td>
</tr>
<tr>
<td>%V̇O₂max, %</td>
<td>61±18 (30–84)</td>
<td>56±23 (13–85)</td>
<td>59±20 (13–85)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Values in parentheses are ranges. HR, heart rate; V̇E, expiratory ventilation; V̇O₂, oxygen uptake; %V̇O₂max, percent of relative maximum oxygen uptake.
 unlikely to exceed 15 μm. Thus, during exercise, increased vascular pressures and blood flow velocity, contrast bubble survival times would likely be even shorter than at rest. The mean pulmonary capillary transit time is ~750 ms at rest and decreases during exercise. However, even in well-trained athletes, with cardiac outputs as high as 30 l/min, mean pulmonary transit time does not fall below 450 ms at maximal exercise (56). Thus it is highly unlikely that survival of contrast bubbles able to pass through normal pulmonary capillaries during exercise explains our findings.

The contrast bubble diameters in vivo are not known precisely. However, given the inherent instability of small bubbles in the circulation (see above), it is estimated that the size distribution of peripherally injected contrast bubbles entering the pulmonary microcirculation is in the range of 60–90 μm (43).

What is the relationship between pulmonary capillary distention and bubble size during exercise? Contrast echocardiography cannot distinguish between distinct anatomic intrapulmonary arteriovenous shunts and dilated pulmonary capillaries. Structural derangements of the pulmonary microcirculation, including intrapulmonary arteriovenous shunts and capillary distention with capillary diameters of 60–80 μm, are reported in hepatopulmonary syndrome (8, 43). These patients have a widened A-aDO₂ and a positive contrast echocardiogram. However, there are no data to support this magnitude of capillary distention in the normal lung at rest or during exercise.

With progressive exercise, pulmonary vascular pressures and flow increase. These forces act to recruit and distend the pulmonary microcirculation (41). The true extent to which the pulmonary capillaries distend in humans during exercise is not known. Morphological studies in isolated perfused greyhound lungs suggest that capillary distensibility is limited and is unlikely to exceed 15 μm despite distending pressures as high as 73 Torr (15). Reeves and Taylor (41) applied a distensibility model for the pulmonary microcirculation (28) to pulmonary hemodynamic data obtained in healthy humans during both supine and upright exercise. They estimated the distensibility coefficient (defined as the percent change in capillary diameter per unit change in pressure) for human pulmonary microcirculation to be 1.35% per Torr. In humans, during peak exercise, the mean pulmonary capillary distending pressure in zone III has been estimated to be 36 Torr (58). Thus these calculations suggest that pulmonary capillary distension would not exceed 20 μm, even at peak exercise intensity. Pulmonary capillary disruption, not excessive distention, has been suggested as the more likely result with such high pulmonary vascular pressures (57). Thus our findings are not explained by passage of contrast bubbles through distended pulmonary capillaries.

During exercise with increased pulmonary vascular driving pressures (pulmonary artery pressure minus left atrial pressure), it is conceivable that contrast bubbles larger than pulmonary capillaries could be forced through the pulmonary microcirculation. In humans, rapid, forceful injection of agitated saline contrast bubbles through a tightly wedged pulmonary artery catheter forced contrast bubbles through the normal pulmonary microcirculation (31). This required a firm occlusive wedge position and an injection pressure of 300 Torr (44). In humans at maximal exercise, pulmonary vascular driving pressure remains relatively low, never exceeding 20 Torr (40). With these low driving pressures it is unlikely that trapped contrast bubbles are being forced through the pulmonary microcirculation even at the highest exercise levels.

Spontaneous echo formation has been reported in the literature but tends to occur in structures prone to blood stasis, such as the inferior vena cava (30) and left atrium (7). Red blood cell clumping and rouleaux are believed to be the most likely source of the spontaneous echoes (39). Because increased blood flow and shear stress abrogate these spontaneous echoes, they are extremely unlikely during exercise and should not create ambiguity in our study.

In summary, our findings in combination with published theoretical and experimental data suggest that the contrast bubbles are passing through distinct intrapulmonary arteriovenous shunts. However, our findings using saline contrast echocardiography are qualitative. Furthermore, contrast echocardiography is limited to detecting anatomic intrapulmonary shunts and thus is blind to intrapulmonary shunting due to atelectasis and alveolar flooding. In addition, contrast echocardiography will not detect postpulmonary shunting. Further studies are needed to define shunt vessel diameters and to quantify the shunt fraction.

What is the anatomic basis for intrapulmonary arteriovenous shunts? Intrapulmonary arteriovenous shunts have been demonstrated in human lungs (51, 52, 62). Wilkinson and Fagan (62) examined the lungs of 49 infants (<44 wk old) who died suddenly. They showed that very low injection pressures <7.5 Torr were required to drive a 2% gelatin solution across the pulmonary vascular bed in 61% (30 of 49) of the lungs. Furthermore, they found that 50–μm polymethylmethacrylate beads also passed through the pulmonary circulation. The authors suggested that the gelatin and beads were flowing through a distinct low-resistance vascular network and that these large-diameter conduits were remnant intrapulmonary arteriovenous shunts. Tobin (51) examined plastic casts of normal human lungs prepared specifically to preserve the microcirculation. As expected, he found that the alveoli within a primary lobule are supplied by a single branch of the arteriole accompanying the bronchiule into the lobule. However, in 47% of the lobules examined he found secondary glomuslike vessels that branch from the parent arterioles at right angles. Some of these vessels bypassed the capillary network, to terminate in a pulmonary venule. Furthermore, infusion of glass or resin beads, 50–200 μm in diameter, into the pulmonary artery or inferior vena cava bypassed the pulmonary microcirculation and subsequently appeared in the pulmonary veins (51, 52). The authors suggested that these vessels may function as intrapulmonary arteriovenous shunts.

Elliott and Reid (13) described, in human lungs, a network of small muscular arteries that branch from the conventional pulmonary arteries at right angles and, because they have no accompanying airways, are referred to as supernumerary arteries. Conventional pulmonary arteries accompany the airway to supply the alveolar capillary from within the lobule. The supernumerary arteries rapidly divide and enter the lobule at its edge (42). Interestingly, Elliott and Reid (13) could not identify supernumerary arteries in pulmonary angiograms performed in humans at rest. At their origin, supernumerary arteries have a
sphincter (13) or muscular baffle valve (47) that appears to regulate blood entry. The baffle valve is situated such that parent artery dynamics determine whether the valve is opened or closed. Under low-flow conditions or active vasoconstriction of the parent artery, the baffle valve is pulled closed. However, as pulmonary blood flow increases, the parent artery is distended and the baffle valve opens to allow blood to enter the supernumerary artery (47). We believe that the supernumerary arteries may be the same vessels described by Tobin and colleague (51, 52) (see above). Furthermore, a supernumerary-like vessel with a baffle valve could explain our findings that recruitment of intrapulmonary arteriovenous shunts during exercise appear to be regulated, in part, by pulmonary vascular pressures and flow. Clearly, further investigation is needed to better define the structural characteristics and functional regulation of these dynamic intrapulmonary arteriovenous conduits.

What is the physiological relevance of intrapulmonary arteriovenous shunting during exercise? Intrapulmonary shunting through arteriovenous conduits will contribute to venous admixture and widen the A-aDO₂. Because shunted blood is deoxygenated and becomes more so with exercise as oxygen extraction increases, only a small fraction of the cardiac output as shunt is necessary to widen the A-aDO₂ significantly. Indeed, during moderate-intensity exercise an assumed 2% shunt of mixed venous blood can account for one-half of the widened A-aDO₂, with increased V̇O₂/Q nonuniformity as measured, with MIGET accounting for the remainder (16). During maximal exercise, Wagner and colleagues (55) also used MIGET to determine that one-third of the measured A-aDO₂ of 25 Torr was due to V̇A/Q nonuniformities. Using data from Wagner et al. and the measured mixed venous oxygen content of 5.2 ml O₂/100 ml, we calculated that the remaining A-aDO₂ could be accounted for by a shunt fraction of 2.2% of the cardiac output. In well-trained endurance athletes with high V̇O₂ max, some develop excessive A-aDO₂ widening during both moderate- and high-intensity exercise, whereas others do not (9, 20, 22). Perhaps a significant source of this intersubject variability lies in small interindividual differences in exercise effects on intrapulmonary shunts or variability in shunt vessels between subjects.

The pulmonary vascular bed is unique. Being in series with the left heart and the systemic circulation, the pulmonary vascular bed must accommodate the entire cardiac output, which will increase four- to sixfold from rest to exercise in healthy humans. Local recruitment of arteriovenous intrapulmonary shunts, as exercise intensity increases, may help to maintain low regional pulmonary vascular resistance. This may allow for small increases in cardiac output after maximal pulmonary capillary recruitment and distention has occurred. With shunting, the arterial blood oxygen content will fall. However, an increased cardiac output would at least partially compensate for the fall in oxygen content and potentially preserve systemic oxygen transport. There is a paucity of studies examining the impact of intrapulmonary right-to-left shunting on exercise. An extreme example is the work of Whyte and colleagues (61), who investigated the effects of intrapulmonary right-to-left shunting on pulmonary hemodynamics and gas exchange during exercise in patients with substantial pulmonary arteriovenous malformations. These patients had surprisingly good maximal exercise capacity (>70% predicted) despite profound arterial oxygen desaturation. During progressive exercise, these individuals generate higher than normal cardiac outputs, which serve to prevent large decrements in systemic oxygen delivery.

Local recruitment of intrapulmonary shunts may also act as a parallel vascular network that opens to divert potentially damaging hydrodynamic energy away from fragile pulmonary capillaries. Without these shunts, some regions of the lung may see high pressures and flow with resultant vascular and capillary injury. Indeed, some elite athletes develop exercise-induced pulmonary hemorrhage during very intense exercise (23). In addition, some individuals develop capillary-leaf pulmonary edema with rapid ascent to altitude (46). A postulated mechanism for high-altitude pulmonary edema is capillary stress failure (57). With increasing exercise intensity, individuals prone to high-altitude pulmonary edema have higher pulmonary vascular pressures and resistance than matched controls (12). Are these individuals more susceptible to pulmonary vascular injury because they do not have or fail to open arteriovenous intrapulmonary shunts under these hyperdynamic conditions?

In summary, we have discovered what we believe to be intrapulmonary arteriovenous shunts that are recruited during exercise in healthy humans. The intrapulmonary shunts appear to be distinct vascular conduits that open as pulmonary blood flow and vascular pressures climb with increasing exercise intensity. These intrapulmonary shunts will contribute to the widened A-aDO₂ seen with exercise. To a much lesser extent, they may act as a protective parallel circuit limiting the rise in pulmonary vascular pressure while preserving cardiac output during exercise. In our study, only 2 of the 23 subjects did not demonstrate intrapulmonary shunting. Are these individuals at higher risk for pulmonary capillary injury during heavy exercise at high cardiac output but less prone to excessive widening of the A-aDO₂? Clearly, the existence of these dynamically controlled intrapulmonary shunts has far-reaching impact on how we view the pulmonary circulation in both health and disease. Further investigations are needed to quantify these exercise-induced shunts and to define their anatomical characteristics.

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804 INTRAPULMONARY ARTERIOVENOUS SHUNTING DURING EXERCISE


