Point:Counterpoint: Exercise-induced intrapulmonary shunting is imaginary vs. real

**POINT: EXERCISE-INDUCED INTRAPULMONARY SHUNTING IS IMAGINARY**

Pulmonary gas exchange efficiency deteriorates with exercise in both humans and other species, increasing the alveolar-arterial PO2 difference (AaDO2) (2). The potential contributors to this are ventilation-perfusion inequality, alveolar-capillary diffusion limitation, and shunt (20). These have been well documented under varying exercise conditions including normoxia, hypoxia, and hyperoxia, in particular by the multiple inert gas elimination technique (MIGET) (19). Alveolar, arterial, and mixed venous concentrations of inert gases of differing solubility can be measured and used to quantify ventilation-perfusion inequality, alveolar-capillary diffusion limitation (plus any post-pulmonary venous admixture), and intrapulmonary shunt. From this, their individual contributions to AaDO2 can be determined (4, 19), and intrapulmonary shunt has consistently been the least important of the three.

Recently, intrapulmonary shunting, the passage of mixed venous blood through the pulmonary circulation without contact with ventilated regions of the lung (20), has attracted renewed attention as a potential cause of exercising gas exchange impairment (3, 7, 15). This is because of transpulmonary passage of intravenously injected microbubbles demonstrated by agitated saline contrast echocardiography during exercise, but not at rest (3, 7, 15). The appearance of the microbubbles in the left atrium after three to five cardiac cycles is held as evidence of intrapulmonary shunts. Furthermore, it is suggested that these are important determinants of pulmonary gas exchange during exercise (3, 7, 15). Although we do not think transpulmonary bubble transmission is imaginary, we are reminded of the book *Horton Hears A Who* by Theodore Geisel ("Dr. Seuss"; 14). In this children’s classic, Horton the Elephant hears a sound from a speck of dust, which is home to tiny inhabitants known as Whos. The book reinforces the moral that "a person’s a person, no matter how small." While it can be argued that a “shunt is a shunt, no matter how small,” several important points should be considered, especially when evaluating what microbubble transmission implies for exercising pulmonary gas exchange.

First, the size of transmitted bubbles remains unknown and there are several assumptions that potentially affect the interpretation of the data, reviewed recently in the context of detecting intracardiac shunting via a patent foramen ovale (21). The technique assumes that most bubbles induced by agitating air in saline are larger than pulmonary capillaries and therefore are trapped by the pulmonary circulation. Although the size of the microbubbles is not uniform, the bubbles that are less than the diameter of a pulmonary capillary during exercise (~10 μm) are argued to degrade to such a small size after transit through the pulmonary circulation that they are no longer detectable (21). This was shown experimentally some 28 years ago using M-mode echocardiography (10); however, these experiments have never been repeated using more sensitive modern echo techniques (21). Consequently the size of the bubbles detected in the left heart may be smaller than is assumed, and some bubbles may traverse a normal pulmonary capillary during exercise. In addition, microbubbles are assumed to be rigid, to not deform in the pulmonary circulation, or degrade and then reform with changing gas partial pressures, and that the extent of pulmonary capillary dilation as pulmonary vascular pressures rise during exercise is insufficient to allow passage of bubbles larger than 8–10 μm.

Second, agitated saline contrast echocardiography gives only a qualitative assessment of the presence or absence of microbubbles appearing in the left atrium after a specific delay. It cannot quantify blood flow through the responsible vessels. Where flow in these vessels has been quantified using microspheres of 25 and 50 μm diameter, it has either been zero (9) or very small. In Dr. Stickland, Lovering, and Eldridge’s own data from isolated perfused lungs, such flow averaged 0.01% of cardiac output in baboons, 0.06–0.07% in humans (8), and 0.001–0.05% in dogs. The sole published exception to these observations is in exercising dogs, where microsphere transmission indicated flows <1% of cardiac output (16) in two animals and 3.1% in one. Notably in these animals, there was no evidence of gas exchange impairment and PaO2 was maintained. To explain the average AaDO2 seen during heavy normoxic exercise in man of ~19 Torr (5, 6, 11–13) the shunt would have to be 2.6%, some 37 times greater than the 0.07% value indicated above.

Third, the magnitude of the intrapulmonary shunt measured using MIGET in a large number of human subjects during exercise is consistent with the quantitative intrapulmonary shunt data. Although the statement is made that intrapulmonary shunting measured by the MIGET is not observed during exercise in healthy subjects, this is not strictly true. Intrapulmonary shunts are sometimes observed, but they are so small as to be physiologically insignificant. Table 1 shows summarized data from MIGET studies during heavy cycle exercise (90% of V̇O2 max) in both normoxia and hypoxia published by our laboratory since 1996 (5, 6, 11–13). In these studies, where V̇O2 max ranged from 2,000 to 6,000 ml/min, intrapulmonary shunt was always less than 1% of the cardiac output, averaging just 0.2% in normoxia and 0.1% in hypoxia. Importantly, the effect of this level of shunt on gas exchange is minimal, increasing the AaDO2 by less than 2 Torr (Table 1). As a percentage of the total AaDO2, intrapulmonary shunt explains only 7% in normoxia and much less (<1%) in hypoxia.

<table>
<thead>
<tr>
<th></th>
<th>Normoxia (21%)</th>
<th>Hypoxia (12.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇O2, ml/min, STPD</td>
<td>3.685 (728)</td>
<td>2.893 (630)</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>24.9 (5.1)</td>
<td>24.6 (5.4)</td>
</tr>
<tr>
<td>Intrapulmonary shunt, %</td>
<td>0.2 (0.7)</td>
<td>0.1 (0.3)</td>
</tr>
<tr>
<td>AaDO2, Torr</td>
<td>19 (10)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>AaDO2 from Shunt, Torr</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>% of AaDO2 from shunt</td>
<td>7.4</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values in parentheses are SD. Metabolic and gas exchange data during very heavy exercise in normoxia (n = 64) and hypoxia (n = 57) from previously published studies (5, 6, 11–13). In all cases the measured intrapulmonary shunt measured by the multiple inert gas technique was less than 1% of cardiac output and had a minimal effect on pulmonary gas exchange.

http://www.jap.org
That intrapulmonary shunt is miniscule is further confirmed by a recent study reporting venous admixture in very fit athletes during exercise breathing pure O₂ (18). During 100% oxygen breathing, alveolar PO₂ is elevated to such an extent that ventilation-perfusion inequality and diffusion limitation no longer contribute to the AaDO₂—it can be explained only by right to left shunting (18). In this study (16), venous admixture during 100% oxygen averaged 0.5%, a value also consistent with the previously reported microsphere and inert gas data.

Fourth, it has never been shown that oxygen exchange across the vessels responsible for microbubble transmission is impaired. It is entirely possible that oxygen exchange is normal, and indeed, as stated above in exercising dogs (14), arterial oxygenation was not impaired, suggesting this to be the case.

Finally, it has been argued by Drs. Stickland, Lovering, and Eldridge that proximal vessel (precapillary) gas inert gas exchange occurring by diffusion may result in an underestimation of the proximal vessel gas inert gas exchange occurring by diffusion may result in an underestimation of the intrapulmonary shunt (3, 17) by MIGET. This is because diffusion equilibration of inert gases is much faster than for O₂. However, were that the case, the problem for O₂ exchange becomes one of diffusion limitation and not shunt. But even here, there is spectrophotometric evidence (1) that O₂ can also take part in precapillary exchange, casting doubt on this explanation.

In summary, flow through vessels responsible for microbubble transmission in exercising humans has never been shown to impair gas exchange and should not be equated to a shunt, which implies an absence of gas exchange. Furthermore, when intrapulmonary shunts have been quantified, irrespective of technique, they are tiny, like the Whos that Horton the Elephant heard, and can account for no more than 1.4 mmHg, or 7%, of the total AaDO₂ of 19 mmHg. We leave it to the reader to decide if microbubble transmission really implies a shunt, whether a “shunt is a shunt no matter how small,” and if the effect of intrapulmonary shunt on pulmonary gas exchange is significant.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grant HL-081171, American Heart Association Grant 055002N, and the Parker B. Francis Foundation.

REFERENCES


Susan R. Hopkins1,2 I. Mark Offert1 Peter D. Wagner1 Departments of 1Medicine and 2Radiology University of California San Diego La Jolla, California e-mail: shopkins@ucsd.edu

COUNTERPOINT: EXERCISE-INDUCED INTRAPULMONARY SHUNTING IS REAL

The conventional pulmonary circulatory route begins with the pulmonary artery that travels in parallel with the airway, dividing with the airway, until finally reaching the capillary bed within the alveolus (4; Fig. 1A). The capillary bed consists of vessels 7 to 10 μm in diameter, never exceeding 13 μm even under very high, non-physiological perfusion pressures (8). The conventional veins then collect blood from capillaries, combining to form progressively larger vessels. Despite this traditional view of the pulmonary vascular circuit, there is substantial anatomic evidence of large-diameter arteriovenous anastomoses in the lung that bypass the traditional blood flow circuit (Fig. 1B).

A shunt can be defined as “a vascular passage by which blood is diverted from its usual or normal path (arterio-