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 1.

<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.
However, were that the case, the problem for O2 exchange Eldridge that proximal vessel (precapillary) gas inert gas ex-
as stated above in exercising dogs (14), arterial oxygenation was
It is entirely possible that oxygen exchange is normal, and indeed,
the vessels responsible for microbubble transmission is impaired. 
Fourth, it has never been shown that oxygen exchange across the 
vehicles responsible for microbubble transmission is impaired. 
It is entirely possible that oxygen exchange is normal, and indeed, 
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 ex-
change occurring by diffusion may result in an underestimation 
of 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 ex-
planation. 
In summary, flow through vessels responsible for micro-
bubble 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 ex-
change is significant.

REFERENCES

1. Conhaim RL, Staub NC. Reflection spectrophotometric measurement of 
O2 uptake in pulmonary arterioles of cats. J Appl Physiol 48: 848–856, 
1980.


3. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokan-
sron JS. Exercise-induced intrapulmonary arteriovenous shunting in 

4. Hlastala MP, Robertson HT. Inert gas elimination characteristics of the 

5. Hopkins SR, Gavin TP, Siafakas NM, Haseler LJ, Offert IM, Wagner 
H, Wagner PD. Effect of prolonged, heavy exercise on pulmonary gas 

SR, Wagner PD. Effect of acetazolamide on pulmonary and muscle gas 
exchange during normoxic and hypoxic exercise. J Physiol 579: 909–921, 
2007.

7. Lovering AT, Romer LM, Haverkamp HC, Pegelow DF, Hokanson 
JS, Eldridge MW. Intrapulmonary shunting and pulmonary gas exchange 
during normoxic and hypoxic exercise in healthy humans. J Appl Physiol 

8. Lovering AT, Stickland MK, Kelso AJ, Eldridge MW. Direct demon-
stration of 25- and 50-μm arteriovenous pathways in healthy human and 

9. Manohar M, Goetz TE. Intrapulmonary arteriovenous shunts of >15 
μm in diameter probably do not contribute to arterial hypoxemia in 
229, 2005.

10. Meltzer RS, Tickner EG, Popp RL. Why do the lungs clear ultrasonic 

PD, Hopkins SR. Does gender affect human pulmonary gas exchange 

12. Podolsky A, Eldridge MW, Richardson RS, Knight DR, Johnson EC, 
Hopkins SR, Johnson DH, Michimata H, Grussl B, Feiner J, Kurfak 
SS, Bickler PE, Severinghaus JW, Wagner PD. Exercise-induced VA/Q 
inequality in subjects with prior high-altitude pulmonary edema. J Appl 

H, Wagner PD, Hopkins SR. Pulmonary gas exchange during exercise in 
highly trained cyclists with arterial hypoxemia. J Appl Physiol 87: 1802– 
1812, 1999.

for Young Readers, 1962.

15. Stickland MK, Lovering AT. Exercise-induced intrapulmonary arterio-
venous shunting and pulmonary gas exchange. Exerc Sport Sci Rev 34: 

16. Stickland MK, Lovering AT, Eldridge MW. Exercise-induced arterio-
venous intrapulmonary shunting in dogs. Am J Respir Crit Care Med 

WD, Taylor DA, Bouffard M, Jones RL. Intrapulmonary shunt and 
pulmonary gas exchange during exercise in humans. J Physiol 561: 

18. Vogiatzis I, Zakynthinos S, Boushell R, Athanasopoulos D, Guenette 
JA, Wagner H, Roussos C, Wagner PD. The contribution of intrapul-
monary shunts to the alveolar-to-arterial oxygen difference during exercise 

19. Wagner PD, Saltzman HA, West JB. Measurement of continuous 
distributions of ventilation-perfusion ratio: theory. J Appl Physiol 36: 

20. West JB. Respiratory Physiology: The Essentials. Baltimore, MD: Lip-
pincott, Williams & Wilkins, 2005.

21. Woods TD, Patel A. A critical review of patent foramen ovale detection 
using saline contrast echocardiography: when bubbles lie. J Am Soc 

GRANTS

This work was supported by National Heart, Lung, and Blood Institute 
Grant HL-081171, American Heart Association Grant 054002N, and 
the Parker B. Francis Foundation.

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 acinus (4; Fig. 1A). The capillary bed consists of 
vessels 7 to 10 μm in diameter, never exceeding 13 μm even 
der 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-