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 intrapulmonary shunt (3, 17) by MIGET. This is because change occurring by diffusion may result in an underestimation 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.

REFERENCES


COUNTERPOINT: EXERCISE-INDUCED INTRAPULMONARY SHUNTING IS REAL

The conventional pulmonary circulation 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 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-
Arteriovenous anastomoses (i.e., shunts) were first described 129 years ago (19) and these pathways allow for arterial blood to bypass the capillary beds and join up with postcapillary venous blood. Large diameter intrapulmonary arteriovenous pathways (or shunts) are known to exist in many species including humans (25, 27), dogs (16), cats (17), and rabbits (17). A critique of previous anatomic work is that the methods used were not physiological. Recently we documented intrapulmonary arteriovenous pathways using 50 and 25 μm solid microspheres in healthy human, baboon, and dog lungs, which were isolated, ventilated, and perfused at physiological pressures (14, 22). These studies established the patency and functional diameter of some of these intrapulmonary arteriovenous shunt
vessels under conditions that more closely replicate physiological conditions.

Using all anatomic based approaches, there is a significant amount of evidence that intrapulmonary arteriovenous shunting during exercise is indeed real. In healthy humans we have demonstrated transpulmonary passage of saline contrast bubbles during submaximal through maximal exercise, but not during upright normoxic rest (6, 12, 13, 23, 24). With the use of saline contrast echocardiography, intrapulmonary shunt is defined as the presence of saline contrast bubbles in the left heart three or more cardiac cycles after appearance of contrast bubbles in the right heart (6, 9, 12, 23). Because saline contrast bubbles small enough to travel through even the largest pulmonary capillaries (<13 μm) have a life span less than three cardiac cycles (even at maximal exercise), transpulmonary passage of these bubbles must occur via large diameter intrapulmonary arteriovenous shunt pathways (2, 15, 18, 28, 29).

Of note, saline contrast bubbles can be forced through the normal pulmonary microcirculation using a firmly wedged pulmonary artery catheter with a perfusion pressure of 300 Torr. However, these extreme pulmonary driving pressures do not occur in healthy exercising humans making this an unlikely explanation for the transpulmonary passage of saline contrast bubbles (15).

Consistent with the human, intrapulmonary arteriovenous shunting occurs in dogs. Intravenously injected 25 μm microspheres were found in the tissue and arterial blood of the systemic circulation during exercise but not at rest (22). Dogs were confirmed not to have intracardiac shunts and with an established diameter of 25 μm, these microspheres bypassed the pulmonary capillaries via arteriovenous vessels at least 25 μm in diameter.

Arteriovenous vessels would divert deoxygenated blood away from pulmonary capillaries. If a significant amount of cardiac output was diverted through these pathways when mixed venous partial pressure of oxygen is reduced, such as during exercise, then pulmonary gas exchange as evaluated by the alveolar to arterial oxygen difference (AaDO2) would be impaired. With the use of the Bergman equation, only a 2% shunt of cardiac output would be required to increase AaDO2 during exercise (11). Indeed, a 1.4 ± 0.8% shunt has been calculated in exercising dogs (22) and exercise-induced intrapulmonary arteriovenous shunting is correlated to AaDO2 in healthy humans (23), suggesting these vessels may play an important role in pulmonary gas exchange impairment during exercise.

Based on the amount of morphological and functional anatomic-based data supporting the existence of inducible intrapulmonary shunts, it may be somewhat surprising that work using the 100% O2 technique or the multiple inert gas elimination technique (MIGET) has not detected these pathways in healthy humans during exercise (see Ref. 5 for complete list of references), suggesting that shunts are imaginary. However, this discrepancy may be explained by precapillary gas exchange and the vasomotor effect of O2 on the pulmonary circulation, both of which are critically dependent on concentration gradient and physical properties of the gas (Fig. 1, B and C).

Conhaim and Staub (3) demonstrated precapillary O2 exchange in rapidly frozen cat lungs. In these studies, oxyhemoglobin saturation in 500 μm pulmonary arteries from lungs ventilated with room air were as high as 77% at the perimeter of the blood vessel, while blood at the core of the vessel was as low as 47% saturated with oxygen (3). The size of the perimeter of the blood vessel becoming oxygenated increased from 62 μm in normoxia to 401 μm in lungs ventilated with 100% O2. The authors calculated that in normoxia, mixed venous blood may be as much as 15% oxygenated by the time it reaches the alveolar capillary, while blood would be fully oxygenated before reaching the capillary when breathing 100% O2. Importantly, precapillary gas exchange of both O2 and N2 have also been demonstrated in humans (10, 20). These studies demonstrated that precapillary O2 exchange occurs in normoxia, with a greater O2 exchange occurring in larger vessels with an increased fraction of inspired oxygen. Accordingly, in subjects breathing 100% O2 during exercise, O2 exchange would occur proximal to the intrapulmonary arteriovenous pathways (3, 10, 20), and thus these vessels would not be “seen” as true shunt, as the calculated venous admixture (Qs/Qt) would be minimal (Fig. 1C).

Furthermore, a fundamental assumption of the 100% O2 technique is that the elevated level of inspired oxygen does not have an effect on the pulmonary microcirculation. This does not appear correct, as we recently demonstrated that exercise-induced intrapulmonary arteriovenous shunting can be eliminated in subjects within 2 min of breathing 100% O2 (13). These findings raise a concern for the use of the 100% O2 technique as a valid method for assessing exercise-induced arteriovenous shunt in normoxia and may explain why venous admixture decreases from 3.5% to 0.5% of cardiac output when subjects breathe 100% O2 during exercise (26).

With respect to the MIGET, even a small degree of precapillary gas exchange (i.e., restricted to the perimeter blood of a 500 μm vessel) would allow elimination of low-soluble inert gas within the arteries/arterioles. Therefore, if low-solubility gases are exiting the blood within the pulmonary artery upstream of the capillary beds, then these inert gases would never even reach smaller functional arteriovenous shunt vessels (>25 to 50 μm), and thus these anatomical shunts would appear imaginary to those using the MIGET. In addition, intrapulmonary arteriovenous pathways themselves may participate in limited gas exchange restricted to their perimeter blood, which would allow some deoxygenated core blood to bypass the pulmonary capillary bed in normoxia, but not be recorded as true mixed venous shunt for the same reasons detailed above (7, 21).

More than 100 years of anatomic data document large diameter arteriovenous pathways in the lung. Recent work has simply demonstrated that these vessels are not always open but become functional under specific conditions, such as during exercise. Is exercise-induced intrapulmonary shunting real? When using anatomic-based techniques (microbubbles and microspheres) they are indeed real.

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Andrew T. Lovering1
Marlowe W. Eldridge2
Michael K. Stickland3
1University of Oregon
Department of Human Physiology
Eugene, Oregon
e-mail: lovering@uoregon.edu
2Department of Population Health Sciences
Department of Biomedical Engineering
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
3Division of Pulmonary Medicine
Department of Medicine
University of Alberta
and Centre for Lung Health (Covenant Health)
Edmonton, Alberta, Canada

REBUTTAL FROM HOPKINS, OLFERT, AND WAGNER

Our colleagues suggest that transpulmonary microbubble passage demonstrates shunting important for gas exchange during exercise (5). However, they themselves show that flow through vessels allowing 25 μm microsphere transmission is generally very small and have not demonstrated any associated gas exchange effect. They are trying to elevate the status of miniscule intrapulmonary arteriovenous pathways into elephant-sized shunts.

They demonstrate microsphere transmission of only 0.001–0.05% of cardiac output at resting flows (6, 8), less than the small ~0.2% found with the multiple inert gas technique (MIGET). During exercise, MIGET-detected shunt in humans (3) and dogs (4) averages 0.1%. In exercising dogs (8), our colleagues report pulmonary microsphere transmission of 1.42%, which they interpret as a 1.42% shunt. In pulmonary gas exchange, shunt has only one definition—blood not exposed to ventilated alveoli during passage through the lungs. Shunted blood does not participate in gas exchange and arterial PO2 thus falls. Importantly in their dogs, PaO2 increased with exercise (from 99 to 106 Torr) while estimated AaDO2 was unchanged at 10 Torr. First, PaO2 increasing to 106 Torr contradicts the assertion that “shunts” are important during exercise. Second, a 10 Torr AaDO2 is entirely accounted for by venous shunting and pulmonary gas exchange.

Our colleagues find that microbubble transmission correlates with the AaDO2 during exercise (9), but many variables correlate without any cause-and-effect relationship. They also argue that precapillary gas exchange impairs the ability of MIGET to detect shunts, as low-solubility gases are eliminated upstream of shunt vessels. However, where pathologic intrapulmonary shunt and hypoxemia are expected (e.g., hepa-