ARTICLE

Exercise-Induced Intrapulmonary Arteriovenous Shunting and Pulmonary Gas Exchange

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STICKLAND, M.K., and A.T. LOVERING. Exercise-induced intrapulmonary arteriovenous shunting and pulmonary gas exchange. *Exerc. Sport Sci. Rev.*, Vol. 34, No. 3, pp. 99–106, 2006. *Recent research suggests the recruitment of intrapulmonary shunt vessels during exercise, which may contribute to the exercise-induced impairment in pulmonary gas exchange. These findings are consistent with substantial anatomical data demonstrating large-diameter (>25 μm) anatomical shunts in the lung, but are contrary to the considerable functional gas exchange-dependent research that has not detected right-to-left physiological shunt during exercise.*
Key Words: pulmonary circulation, arteriovenous anastomoses, hypoxemia, ventilation/perfusion matching, diffusion

INTRODUCTION

During incremental exercise, most healthy humans develop an impairment in pulmonary gas exchange as quantified by an increase in the alveolar-to-arterial P_{O_2} difference ($AaDO_2$). $AaDO_2$ is a major contributor to exercise-induced arterial hypoxemia, which is characterized by a reduction in arterial oxygen tension (Pa_{O_2}) from rest and a corresponding drop in hemoglobin saturation (Sa_{O_2}) (1). Studies have shown that when Sa_{O_2} is returned to preexercise values, improvements in $\dot{V}_{O_2}max$ and performance are observed, whereas exercise-induced fatigue is reduced, and therefore, a widened $AaDO_2$ and the corresponding drop in Sa_{O_2} can represent an important pulmonary limitation to exercise.

EXERCISE GAS EXCHANGE DETERMINANTS AND TYPICAL METHODS

Much of our understanding of pulmonary gas exchange and exercise has been obtained from the multiple inert gas elimination technique (MIGET), which is the best gas exchange–dependent technique available to functionally evaluate global pulmonary gas exchange (1). The specific methodology is beyond the scope of this article, and the interested reader is directed to previously published reviews; however, a brief introduction of gas exchange, MIGET, and exercise is required. Arterial and exhaled levels of six intravenously infused inert gases, encompassing a wide range of solubility in blood, are used to characterize the distribution of ventilation/perfusion ($\dot{V}_A/\dot{Q}$) ratios within the lung. The computer model that is used to create the $\dot{V}_A/\dot{Q}$ distributions also predicts an $AaDO_2$ based on the recovered distributions, and this estimate typically equates very well with the $AaDO_2$ independently measured from arterial blood gas and respiratory gas exchange data at rest and during moderate exercise (13).

Determinants of $AaDO_2$ include $\dot{V}_A/\dot{Q}$ matching, diffusion limitation, extrapulmonary shunt (*e.g.*, thebesian drainage and bronchial circulation), intracardiac shunt, and/or intrapulmonary (I-P) shunt. Despite a rise in global $\dot{V}_A/\dot{Q}$ ratio, regional $\dot{V}_A/\dot{Q}$ matching within the lung, as calculated by MIGET, deteriorates with incremental exercise, and it has been estimated that $\dot{V}_A/\dot{Q}$ mismatch accounts for virtually all of the increased $AaDO_2$ from rest to moderate exercise (13). During more severe exercise ($\dot{V}_{O_2}$, >2.5 $L \cdot min^{-1}$), a diffusion limitation begins to develop, as measured $AaDO_2$ exceeds the MIGET program–predicted $AaDO_2$ (13). It has been suggested that a diffusion limitation would also impair carbon dioxide exchange, and carbon dioxide retention would itself cause a minor impairment in oxygen equilibration within the lung by preventing the leftward shift in the hemoglobin dissociation curve (Bohr effect). With further increments in

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exercise intensity, diffusion limitation continues to increase, and at maximal exercise, both $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation are said to contribute equally to $AaDO_2$ (1).

Blood that passes through the pulmonary circulation but does not take part in gas exchange is defined as an I-P shunt and would be detected by MIGET through retention of the low-solubility gases, sulfur hexafluoride and ethane, in systemic arterial blood. In addition, a right-to-left intracardiac shunt allows blood to bypass the lungs, increasing $AaDO_2$ and causing retention of inert gases, and thus, MIGET cannot distinguish a right-to-left intracardiac shunt from an I-P shunt. Healthy subjects do not demonstrate right-to-left shunt as measured by MIGET, either at rest or during exercise (1), and therefore, right-to-left shunt is not considered to significantly contribute to the widened $AaDO_2$ with exercise.

Deoxygenated blood returning from the bronchial and thebesian veins is dumped directly into the left atrium, mixing with the newly oxygenated blood from the pulmonary venous circulation, decreasing P_{O2} in the left atrium. The deoxygenated blood bypasses the pulmonary arterial circulation entirely and is therefore considered extrapulmonary shunt. MIGET does not allow for the calculation of extrapulmonary shunt; however, breathing 100% oxygen and examining the change in arterial P_{O2} relative to room air provide an estimate of combined I-P and extrapulmonary shunt. Using the 100% oxygen technique, pulmonary shunt has been estimated to be minimal during exercise (1); however, Wagner *et al.* (13) cautioned that due in part to the well-known difficulties in accurately measuring arterial P_{O2} during 100% oxygen breathing at sea level, postpulmonary shunt cannot be rigorously excluded as a contributing factor at sea level. Nevertheless, based on the considerable amount of data obtained from MIGET and 100% oxygen, it is said that the increased $AaDO_2$ with exercise can be explained by $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation (1), and as a result, research in gas exchange has focused on determining their respective causes.

ANATOMICAL EVIDENCE FOR INTRAPULMONARY SHUNTING

Our classic understanding of the lungs is that all the blood leaving the right ventricle passes through the pulmonary microcirculation via capillaries before returning to the left heart via pulmonary veins (Fig 1). Despite an absence of right-to-left I-P shunt during exercise as determined by functional gas exchange–dependent techniques (MIGET or 100% oxygen breathing) (1), there is substantial research documenting the existence of anatomical arteriovenous anastomoses in the lung (see Krahl (5) for a list of references). These studies have demonstrated direct vascular anastomoses between pulmonary arteries and veins in many mammals, including rabbit, cat, dog, and healthy human (8,11,15). The diameter of these conduits ranges from 160 μm in the dog up to 390 μm in the cat (8). In humans, vessel diameter has been shown to be up to 55 μm in infants (15) and 200 μm in adults (11).

The structural characteristics of these large-diameter I-P arteriovenous conduits have been described in isolated human lungs. Examining plastic casts of healthy adult human lungs, Tobin (11) found that 47% of the lobules demonstrated secondary glomus-like vessels branching from parent arterioles, with some of these vessels bypassing the capillary network, to terminate in a pulmonary venule or small pulmonary vein (11). Furthermore, Tobin found that glass or resin beads 200 μm ($\pm$25 μm) in diameter were able to bypass the pulmonary microcirculation and subsequently appear in pulmonary veins, prompting him to suggest that these vessels were "functioning as an arteriovenous shunt (11)." Injection pressures were not reported by Tobin (11); however, capillary integrity was maintained, indicating that transpulmonary passage of large-diameter beads was not likely the result of excessive injection pressures. Wilkinson and Fagan (15) examined fresh lungs immediately after sudden death in human infants and found that low injection pressures (<7.5 mm Hg) were sufficient to drive a low-viscosity (2% gelatin) solution across the pulmonary vascular bed in 61% of the lungs. Moreover, they demonstrated that a significant number of 40-μm polymethylmethacrylate beads, with some as large as 55 μm, passed through the pulmonary circulation. The authors stated that it would be "inconceivable" that a pulmonary capillary would stretch to increase its diameter to allow the passage of such large-diameter beads, and they subsequently concluded that "…shunting vessels must be present in the lungs of these children (15)." Despite the typical understanding of the pulmonary circulation, considerable anatomical evidence supports the existence of large-diameter arteriovenous anastomoses within the lung.

EXERCISE-INDUCED ANATOMICAL SHUNTING IN HUMANS

Whyte *et al.* (14) demonstrated evidence for the recruitment of arteriovenous I-P shunts during submaximal exercise in healthy humans. This study was designed to quantify anatomic right-to-left shunt in patients with pulmonary arteriovenous malformations using technetium Tc 99m–labeled albumin microspheres (7–25 μm in diameter). Healthy control subjects were recruited for comparison, and surprisingly, these subjects increased their shunt fraction from 2.9% at rest to 5.1% with exercise (50% of maximal workload; mean power output, 102 W). Arterial blood gases were not obtained, and therefore, $AaDO_2$ could not be calculated. The lower range of the microspheres injected by Whyte *et al.* (14) was within the diameter of a typical pulmonary capillary, which likely explains the larger-than-expected resting shunt of 2.9% in healthy humans. Likewise, at least part of the increased shunt fraction during exercise would be explained by small-diameter microspheres (<11 μm) passing through normal capillaries. Microspheres greater than the diameter of typical pulmonary capillaries in healthy humans would have been preferable because the methods used by Whyte *et al.* (14) do not allow for a differentiation between

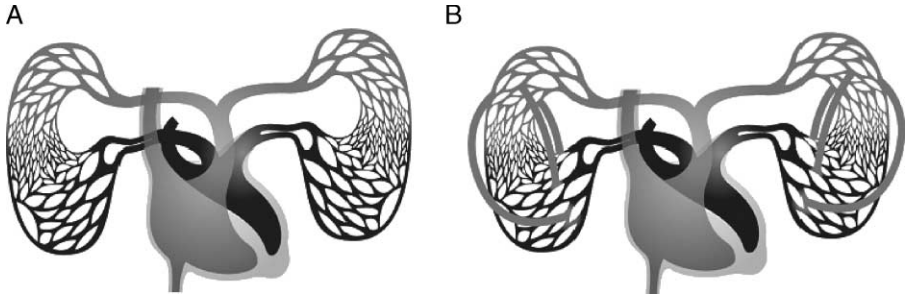

Figure 1. A. Conceptual view of the pulmonary circulation. B. Conceptual view of pulmonary arteriovenous anastomoses.

transpulmonary passage of albumin microspheres via arteriovenous pathways or distended capillaries.

Eldridge *et al.* (2) and Stickland *et al.* (10) examined whether healthy humans recruit anatomical arteriovenous I-P shunts during exercise using the agitated saline contrast echocardiography technique. With this procedure, 10 mL of saline is combined with 0.5 mL of air, and the solution is forcefully agitated to form finely suspended microbubbles, which are generally much larger than the pulmonary capillaries. This solution is then injected into either a peripheral vein or directly into the right atrium, while simultaneously, a four-chamber image of the heart is obtained. The presence of an anatomical I-P shunt is determined by contrast appearance in the left ventricle after at least five heartbeats following the appearance of contrast in the right ventricle (see Fig. 2a and b for examples of a negative- and a positive-contrast echocardiogram). Neither study reported I-P shunting at rest in the upright position; however, most subjects (21/23 in the study of Eldridge *et al.* (2) and 7/8 in the study of Stickland *et al.* (10) developed anatomic I-P shunting with incremental exercise. Furthermore, once I-P shunting developed, all subjects continued to show evidence of shunting with further increases in exercise intensity. The onset of shunting was variable between subjects; however, Stickland *et al.* (10) found that I-P shunting occurred at all work rates with a cardiac output of more than 24 $L \cdot min^{-1}$ (Fig. 3). Correlation analysis found that I-P shunting was strongly correlated with cardiac output ($r = 0.76$) and mean pulmonary artery pressure ($r = 0.73$) (10).

It is important to note that agitated saline contrast echocardiography does not allow for determination of shunt magnitude, and more importantly, the exact size of the contrast bubbles that traverse the pulmonary circulation is unknown. Furthermore, although unlikely, the appearance of saline contrast bubbles in the left ventricle can be due to other factors, including 1) small-diameter (<11 μm) bubbles, which are able to pass through normal capillaries; 2) deformation of larger bubbles and their subsequent transit through the pulmonary capillaries; and/or 3) capillary distention. The estimated survival time for a microbubble small enough to travel through a typical pulmonary capillary

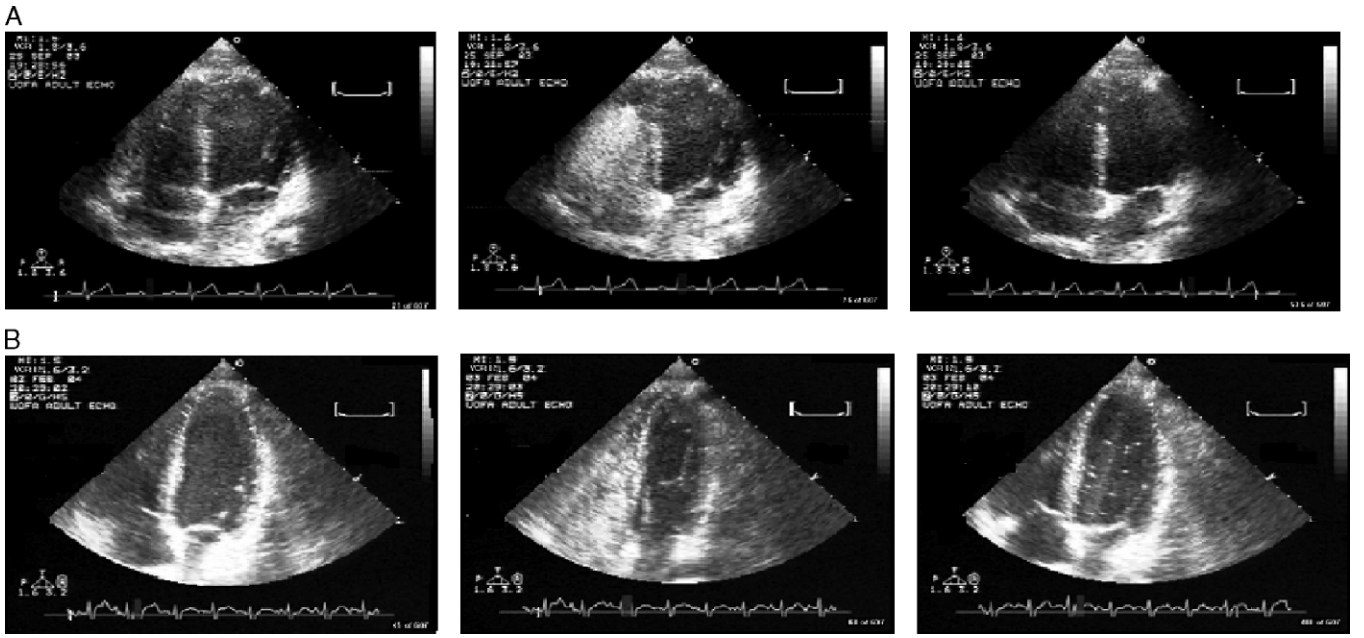

Figure 2. Example of a negative-contrast echocardiogram at rest (A) and a positive-contrast echocardiogram during exercise in two subjects (B). A. Note the contrast entering the right ventricle (seen in the center image on the left); however, contrast does not appear in the left ventricle (right image on the right). B. Note the contrast entering the right ventricle (seen in the center image on the left) and contrast appearing in the left ventricle (right image on the right) (Reprinted from Stickland, M.K., R.C. Welsh, M.J. Haykowsky, S.R. Peterson, W.D. Anderson, D.A. Taylor, M. Bouffard, and R.L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J. Physiol.* 561:321–329, 2004. Copyright © 2004 Blackwell Publishing. Used with permission.)

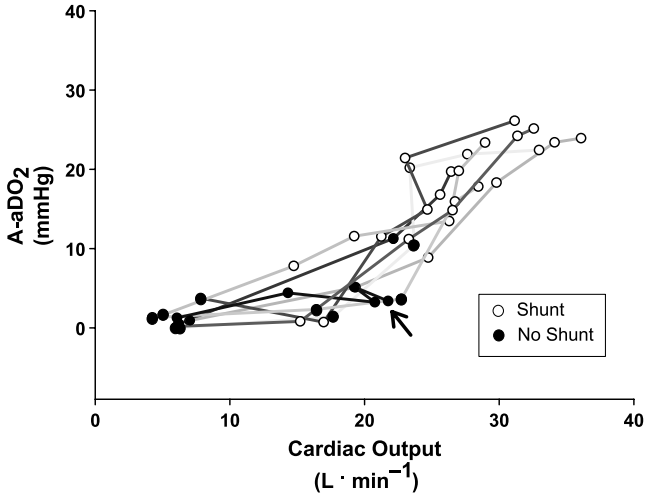

Figure 3. Individual relationships during upright rest and graded exercise between cardiac output and $AaDO_2$ difference. Note that $AaDO_2$ is the alveolar-arterial P_{O_2} difference. *Arrow* denotes peak work rate for the subject who did not develop I-P shunt during exercise (Reprinted from Stickland, M.K., R.C. Welsh, M.J. Haykowsky, S.R. Peterson, W.D. Anderson, D.A. Taylor, M. Bouffard, and R.L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J. Physiol.* 561:321–329, 2004. Copyright © 2004 Blackwell Publishing. Used with permission.)

is 190–550 ms in static fluid; however, microbubble dissolution is rapidly accelerated with increased fluid velocity and hydrostatic pressure (see Refs. (2) and (10) for further discussion). Thus, the fourfold to fivefold increase in cardiac output combined with the onefold to twofold increase in pulmonary artery/pulmonary venous pressure typically observed with incremental exercise would greatly reduce survival time of small-diameter bubbles. Moreover, I-P shunt is detected by appearance of contrast in the left ventricle after a minimum of five heartbeats after appearance in the right ventricle, which represents at least a 1-s delay even at maximal exercise. Therefore, it is unlikely that microbubbles entering the left ventricle during exercise would be the result of small-diameter bubbles passing through normal or distended pulmonary capillaries.

ANATOMICAL EVIDENCE AGAINST EXERCISE-INDUCED SHUNTING IN HORSES

Recently, Manohar and Goetz (6) investigated whether similar I-P arteriovenous shunts are recruited in the exercising thoroughbred horse, an animal well known for a large $AaDO_2$ during exercise. Arteriovenous shunting was studied by rapidly injecting 15-μm, stable, isotope-labeled, neutron-activated microspheres into the right atrium, while blood was simultaneously withdrawn at a constant rate from the aorta. Despite a widened $AaDO_2$ at maximal exercise, no microspheres were detected in the aortic blood samples, indicating no exercise-induced arteriovenous shunts in these animals. This observation may not be surprising because thoroughbred horses are unique in that they are the only mammal that consistently demonstrates exercise-induced pulmonary hemorrhage, and contrary to humans (10,13), thoroughbred horses do not demonstrate a reduction in pulmonary vascular resistance above moderate-intensity exercise (7). It is important to note that the estimated peak cardiac output in the maximally exercising horses examined by Manohar and Goetz (6) would have been ~332 L ·min^{-1}, and thus, their aortic sampling rate of 25 mL · min^{-1} represents 0.008% of cardiac output. Manohar and Goetz (6) injected 20 million microspheres into the right ventricle during maximal exercise, which, assuming a 2% anatomical shunt, would result in 400,000 microspheres getting across the pulmonary circulation. Under ideal conditions, sampling 0.008% of cardiac output would retrieve ~30 microspheres in the aortic arterial sample. The neutron-activated procedure is said to be sensitive enough to detect as little as one microsphere in a sample, although the manufacturers of the microspheres (Biopal, Worcester, MA) recommended a minimum of 400 microspheres per sample for accurate blood flow measurement. Therefore, based on their published data, Manohar and Goetz (6) may have lacked the sensitivity necessary to accurately and reliably detect a small shunt fraction in these animals.

SHUNT CONSEQUENCE

If these vessels, detected in humans with either albumin microspheres (14) or saline contrast echocardiography (2,10), are similar to the vessels documented by Tobin (11), they are unlikely to be capillaries and, therefore, can contribute to the exercise-induced impairment in gas exchange. Indeed, a shunt of pure mixed venous blood of ~3% would account for all of the increased $AaDO_2$ during exercise. Moreover, because wall thickness of pulmonary vessels increases with increasing diameter, 200-μm arteriovenous anastomoses would have a medial wall thickness of ~2.5 μm, which would not participate in gas exchange to

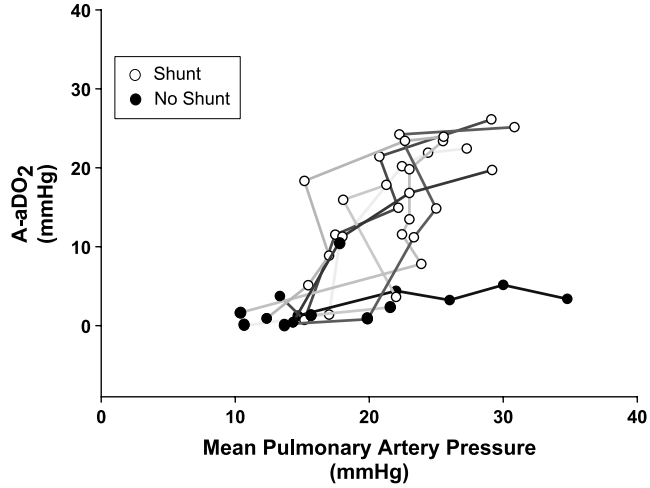

Figure 4. Individual relationships during upright rest and graded exercise between mean pulmonary artery pressure and $AaDO_2$. Note that $AaDO_2$ is the alveolar-arterial P_{O_2} difference (Reprinted from Stickland, M.K., R.C. Welsh, M.J. Haykowsky, S.R. Peterson, W.D. Anderson, D.A. Taylor, M. Bouffard, and R.L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J. Physiol.* 561:321–329, 2004. Copyright © 2004 Blackwell Publishing. Used with permission.)

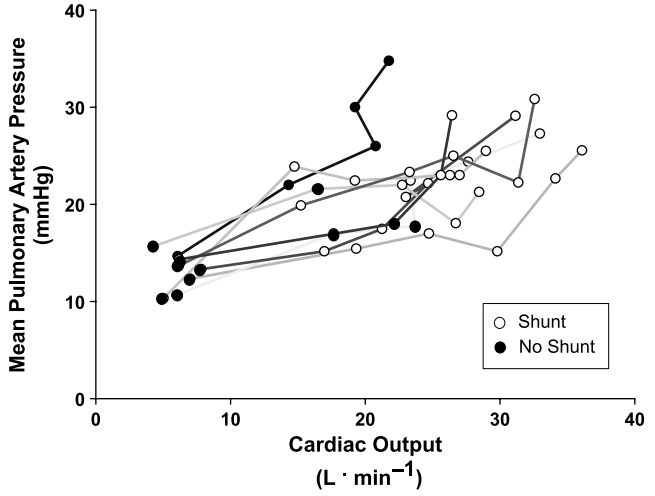

Figure 5. Individual relationships during upright rest and graded exercise between cardiac output and mean pulmonary artery pressure (Reprinted from Stickland, M.K., R.C. Welsh, M.J. Haykowsky, S.R. Peterson, W.D. Anderson, D.A. Taylor, M. Bouffard, and R.L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J. Physiol.* 561:321–329, 2004. Copyright © 2004 Blackwell Publishing. Used with permission.)

the same extent as a capillary with a medial wall thickness of only 0.2 μm. Stickland *et al.* (10) found that anatomic I-P shunt recruitment was correlated with $AaDO_2$ (r = 0.68), and I-P shunting always occurred at an $AaDO_2$ of more than 12 mm Hg (Figs. 3, 4). Interestingly, Stickland *et al.* (10) found that the one subject who did not develop anatomic I-P shunts with exercise had the lowest $\dot{V}_{O_2}max$, peak cardiac output, and $AaDO_2$, despite peak exercise pulmonary artery pressures in excess of 30 mm Hg (Figs. 3–5).

In addition to the impact on gas exchange, shunt recruitment can have other important cardiopulmonary consequences. Based on Poiseuille's law, an increase in vessel diameter would decrease the driving pressure needed to maintain flow. These vessels can act as "pop-off valves" in response to increases in flow and pressure and, therefore, represent an adaptive mechanism to reduce the potential damaging effects of high regional perfusion pressures during exercise. The recruitment of I-P shunts would also limit the increase in right ventricular afterload. Mean pulmonary artery pressure increases approximately 116% from upright rest to peak exercise in healthy humans, whereas mean systemic arterial pressure increases only approximately 28% (data from Stickland *et al.* (10)). Consequently, the increase in right ventricular stroke work is considerably greater with exercise as compared with the thicker, stronger left ventricle. Thus, these shunt vessels can help to limit the exercise-induced increase in pulmonary vascular pressures, reducing the potential for edema/damage and improving right ventricular/pulmonary vascular coupling.

Lastly, an important secondary role of the lungs is to act as a biological sieve, filtering particles/various emboli returning from the peripheral venous circulation that are greater than 7–11 μm (the typical size of a pulmonary capillary). The recruitment of arteriovenous vessels can have an additional consequence in that the lung's role as a biological filter of particles greater than 11 μm would be compromised, increasing the risk for particles bypassing the lungs, resulting in peripheral embolization.

MECHANISM FOR SHUNT RECRUITMENT

Stickland *et al.* (10) suggested that the increase in microvascular pressure, secondary to the rise in cardiac output with incremental exercise, is the likely mechanism to open these shunt vessels. Furthermore, some subjects shunted at rest when supine (10), providing additional evidence for pressure-induced shunt recruitment. In the same subjects, Stickland *et al.* (9) found that when mean pulmonary artery and pulmonary artery wedge pressures were acutely increased in parallel during exercise by lower-body positive pressure (mean increase, 3.7–4.0 mm Hg), shunt recruitment and, correspondingly, $AaDO_2$ were not consistently affected. Stickland *et al.* (9) noted that, whereas mean pulmonary artery pressure at shunt onset was consistent within subjects, pulmonary hemodynamics at shunt onset was highly variable between subjects, suggesting that the sensitivity of these vessels may be variable between subjects, or alternately, other factors such as driving pressure, tidal volume, shear stress, and/or mixed venous P_{O_2} may play a role in recruiting shunt vessels.

RESOLVING THE DISPARITY BETWEEN FUNCTIONAL GAS EXCHANGE–DEPENDENT DATA AND ANATOMICAL DATA

The disparity between shunt calculated with functional gas exchange–dependent techniques versus anatomical techniques is not without precedent (3, 12) and may be because of gas exchange occurring proximal to or within arteriovenous anastomoses. Our classic understanding of the lungs is that gas exchange occurs only between alveoli and pulmonary capillaries. However, early empirical human data would indicate that this is perhaps an oversimplification. Jameson (4) is one of several studies documenting rapid gas exchange between alveoli or airways and pulmonary arteries. Healthy and diseased subjects were instrumented with a 2.5-mm pulmonary artery catheter, which contained a platinum electrode proximal to the tip, allowing for rapid sensing of oxygen or hydrogen. At rest, the catheter was advanced such that it was wedged into a main pulmonary artery. Subjects then breathed either room air, 100% oxygen, or 100% hydrogen. As illustrated in Figure 6, an inhalation of room air results in a rapid (<5 s) increase in oxygen signal, whereas an inhalation of 100% oxygen produced a larger faster (<3 s) response. These responses began less than 1 s after the gas entered the nose and paralleled the change in alveolar gas tension. The sensing of the wedged catheter preceded the response of a catheter positioned in the aorta, providing strong evidence against the possibility of a bronchial arterial source for the increased pulmonary artery gas concentration. Withdrawal of the catheter up to 3 cm from the wedge position still produced identical results in most subjects. Moreover, the

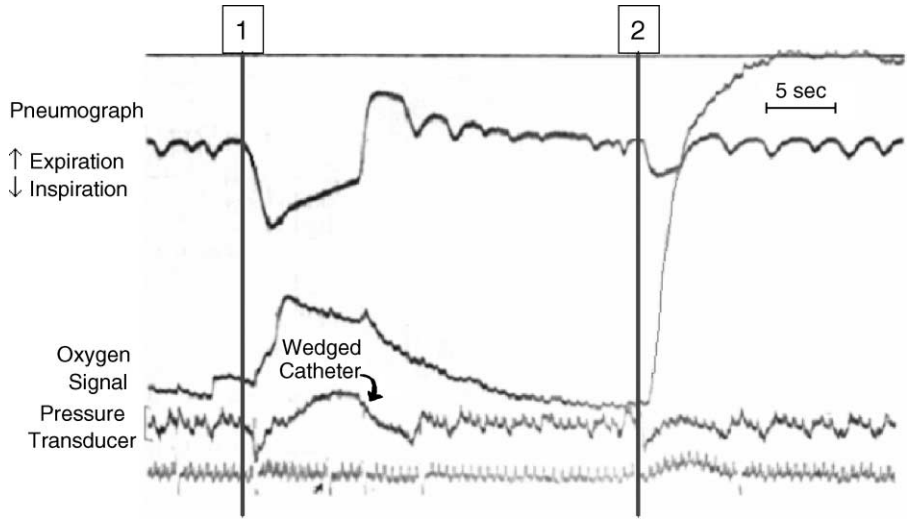

Figure 6. Recording of pneumograph, oxygen signal from wedged platinum electrode, wedge pressure, and electrocardiogram when patient inhaled deeply room air (1) and took a small breath of 100% oxygen (2). Note the small response of oxygen signal after the deep breath of air and the large response of the oxygen signal after a small breath of 100% oxygen. Patient had no shunt (Reprinted from Jameson, A.G. Gaseous diffusion from alveoli into pulmonary arteries. *J. Appl. Physiol.* 19:448–456, 1964. Copyright © 1964 The American Physiological Society. Used with permission.)

almost identical response from a rapid inhalation with the simultaneous infusion of dextrose solution through the catheter indicates that the signal is not because of retrograde flow from the pulmonary veins (see Fig. 5 from the original article). These findings demonstrate directly that gas can diffuse rapidly from alveoli or airways into pulmonary arteries of approximately 2.5 mm in diameter in healthy and diseased subjects. Indeed, some have suggested that this precapillary gas exchange explains the pulmonary vascular vasoconstrictor response to hypoxia because the rapid increase in pulmonary vascular resistance precedes a drop in P_{O_2} measured at the aorta. Based on the results of his study, Jameson (4) suggested that the traditional view of the area within the pulmonary vascular bed where gas exchange occurs requires revision. Specifically, that diffusion is not localized to only the capillary beds, but rather, diffusion is a more general process, occurring through the wall of the pulmonary arteries and increasing as the capillaries are approached.

Evidence for precapillary gas exchange occurring within the pulmonary vasculature is important in reconciling the anatomical versus physiological evidence for I-P shunts. Precapillary gas exchange would have the effect of shifting the constructed $\dot{V}_A/\dot{Q}$ distribution to the right (*i.e.*, toward higher $\dot{V}_A/\dot{Q}$ ratios) compared with gas exchange occurring only within the capillaries. Moreover, precapillary gas exchange would affect inert gases more than oxygen or carbon dioxide because the rate of equilibration for inert gases is much faster in comparison to that of oxygen and carbon dioxide. Thus, blood can actually bypass the pulmonary capillaries via arteriovenous anastomoses, but would not be recorded with techniques such as MIGET as a functional or physiological I-P shunt, because lower-solubility gases would have diffused out of the lung upstream within the pulmonary arteries.

We do not know the origin, size, or makeup of these arteriovenous connections within the lung. If the intact human lung has arteriovenous vessels up to the 200-μm diameter, as described by Tobin in the isolated human lung, this can result in substantial intravessel diffusion limitation for oxygen. Genovesi *et al.* (3) proposed incomplete gas exchange within arteriovenous shunts as an explanation for why anatomical shunt calculated with radionuclide particles (42%) was much greater than shunt calculated with oxygen breathing (13%) in a patient with large-diameter pulmonary telangiectases. Hereditary hemorrhagic telangiectasia is characterized by the substantial dilation of pulmonary capillaries, which causes hypoxemia and increases the risk for stroke. Although these vessels may be of different origin, the example illustrated by Genovesi *et al.* (3) would apply to arteriovenous shunts recruited during exercise in health. Figure 7a illustrates gas exchange between alveoli and a normal (7–11 μm) capillary, resulting in almost perfect gas exchange ($AaDO_2$, 5–10 mm Hg). Figure 7b demonstrates limited gas exchange between alveoli and an arteriovenous anastomosis during room air breathing. Here, despite a similar precapillary P_{O_2} gradient, a diffusion limitation develops within the vessel because of the large vessel diameter, resulting in a large alveolar–pulmonary venous P_{O_2} difference (~50 mm Hg). The blood from anastomosis units would be combined with blood from more normal alveolar capillary units in the pulmonary vein, resulting in the reduction of $AaDO_2$ toward a more typical exercise value (~20–35 mm Hg). Genovesi *et al.* rationalized that breathing 100% oxygen would reduce the diffusion limitation by increasing the precapillary P_{O_2} gradient, allowing oxygen to diffuse across the enlarged distance to reach the center of the vessel (Fig. 7c). As illustrated by Genovesi *et al.* (3), arteriovenous anastomoses would allow the passage of labeled microspheres (or microbubbles), but because these arteriovenous anastomoses take part in limited gas exchange, they would not be detected as a functional I-P shunt by gas exchange–dependent methods with a large diffusion gradient such as 100% oxygen breathing or MIGET (Fig. 7).

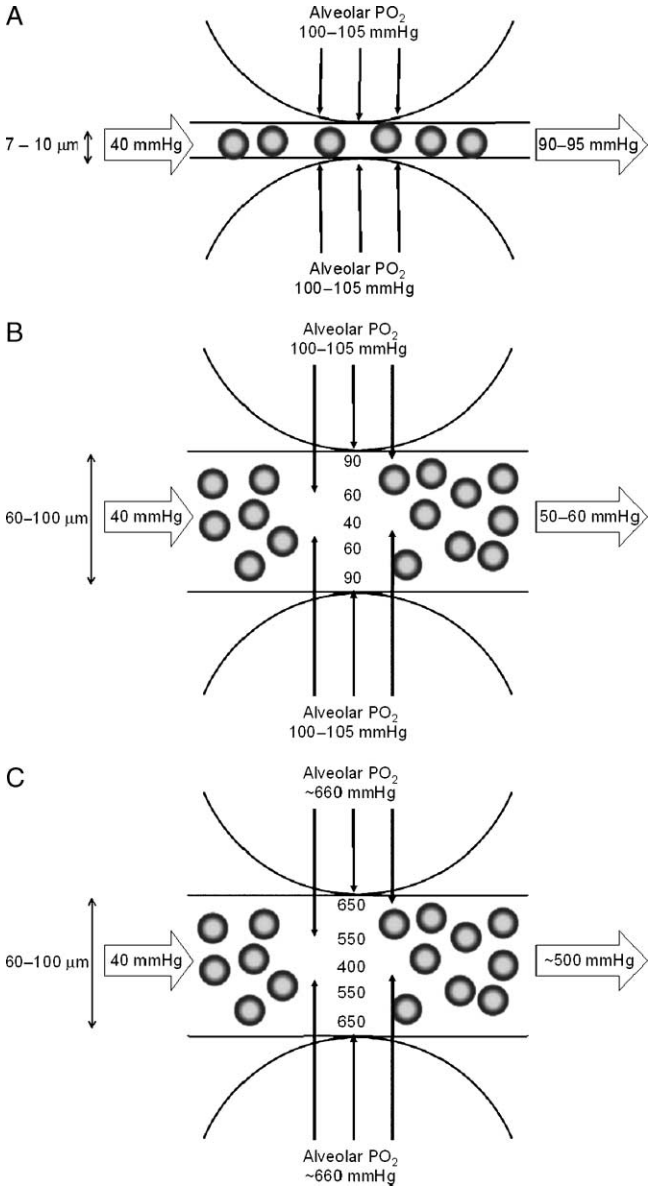

Figure 7. Illustration of gas exchange within a normal pulmonary capillary (A), within an arteriovenous anastomoses (B), and within an arteriovenous anastomoses while breathing 100% oxygen (C). A. Blood in the normal pulmonary capillary equilibrates with the alveolar gas before entering the pulmonary veins. The small alveolar-arterial P_{O_2} gradient ($AaDO_2$) is probably due, in part, to ventilation-perfusion inequalities. B. When arteriovenous anastomoses are present, some oxygen will enter the blood, but the blood flow through these vessels is not in balance with the amount of oxygen that can pass through the vessel wall at this alveolar P_{O_2}. C. When the alveolar P_{O_2} is increased by breathing pure oxygen, the quantity of oxygen that can diffuse through the vessel wall may increase severalfold, and the calculated shunt is less than that obtained while breathing room air [Adapted from Genovesi, M.G., D.F. Tierney, G.V. Taplin, and H. Eisenberg. An intravenous radionuclide method to evaluate hypoxemia caused by abnormal alveolar vessels. Limitation of conventional techniques. *Am. Rev. Respir. Dis.* 114:59–65, 1976. Copyright © 1976 American Thoracic Society. Used with permission.]

Data from Jameson (4) and Genovesi *et al.* (3) provide two explanations as to why gas exchange-dependent techniques, which measure functional (or physiological) shunt, differ from anatomical evidence. With precapillary gas exchange (4), arteriovenous anatomic I-P shunts, which bypass capillaries, may exist; however, they are not "seen" through gas exchange-dependent techniques because of diffusion, which has occurred proximal to the alveoli. Alternately, or in addition, although arteriovenous conduits can be considered anatomical shunts because they permit the passage of larger particles, they also represent a diffusion limitation for oxygen because of incomplete gas exchange, which is overcome when the diffusion gradient is elevated, as in the case of 100% (3). Indeed, both gas exchange-dependent and anatomical shunt exercise data can be accurate because they are "looking" at the lung from two different viewpoints (functional vs anatomical). Importantly, diffusion is reduced with decreasing transit time. Therefore, these arteriovenous conduits, which are recruited during exercise, may not represent a substantial impairment to gas exchange until they occur in combination with reduced pulmonary transit time and/or low mixed venous P_{O_2}. Notably, diffusion limitation as measured by MIGET typically develops at an oxygen consumption of more than 2.5 $L \cdot min^{-1}$ (1), and anatomic I-P shunting is most common above this intensity (10).

FURTHER QUESTIONS/PROBLEMS

As illustrated in Figures 3 and 4, I-P shunts developed in some subjects without an immediate effect on $AaDO_2$, whereas in others, $AaDO_2$ widened slightly without evidence for shunt recruitment. This variability could be due to the inability of contrast echocardiography to quantify shunt and/or the contribution of $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation to $AaDO_2$ irrespective of anatomical shunt. Indeed, further work is needed in examining the relationship between functional pulmonary gas exchange and anatomical shunt. Moreover, neither contrast echocardiography nor radiolabeled albumin microspheres with a variable size distribution allow for precise determination of arteriovenous vessel diameter. Clearly, studies using precisely sized microspheres designed to accurately quantify and determine the size distribution of these vessels under physiological conditions are needed. Unfortunately, many of these questions are unlikely to be investigated in humans because of the lack of commercially available large-diameter (>11 μm) biodegradable microspheres.

CONCLUSION

Previous research has demonstrated anatomic arteriovenous shunts in the lung, and recent human data suggest that these vessels are recruited during exercise and contribute to the exercise-induced impairment in gas exchange. The recruitment of anatomical arteriovenous shunts during exercise is rather controversial, and thus, we balanced these findings with a discussion regarding why shunt vessels would not be recorded using traditional, functional gas exchange–dependent techniques. Arteriovenous shunting may have an important

physiological role both in health and disease, although further work is needed to better characterize these vessels.

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