Exercise-induced arterial hypoxemia

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Dempsey, Jerome A., and Peter D. Wagner. Exercise-induced arterial hypoxemia. J. Appl. Physiol. 87(6): 1997–2006, 1999.—Exercise-induced arterial hypoxemia (EIAH) at or near sea level is now recognized to occur in a significant number of fit, healthy subjects of both genders and of varying ages. Our review aims to define EIAH and to critically analyze what we currently understand, and do not understand, about its underlying mechanisms and its consequences to exercise performance. Based on the effects on maximal O₂ uptake of preventing EIAH, we suggest that mild EIAH be defined as an arterial O₂ saturation of 93–95% (or 3–4% <rest), moderate EIAH as 88–93%, and severe EIAH as <88%. Both an excessive alveolar-to-arterial P O₂ difference (A-aD O₂) (>25–30 Torr) and inadequate compensatory hyperventilation (arterial P CO₂ >35 Torr) commonly contribute to EIAH, as do acid- and temperature-induced shifts in O₂ dissociation at any given arterial P O₂. In turn, expiratory flow limitation presents a significant mechanical constraint to exercise hyperpnea, whereas ventilation-perfusion ratio maldistribution and diffusion limitation contribute about equally to the excessive A-aD O₂. Exactly how diffusion limitation is incurred or how ventilation-perfusion ratio becomes maldistributed with heavy exercise remains unknown and controversial. Hypotheses linked to extravascular lung water accumulation or inflammatory changes in the “silent” zone of the lung’s peripheral airways are in the early stages of exploration. Indirect evidence suggests that an inadequate hyperventilatory response is attributable to feedback inhibition triggered by mechanical constraints and/or reduced sensitivity to existing stimuli; but these mechanisms cannot be verified without a sensitive measure of central neural respiratory motor output. Finally, EIAH has detrimental effects on maximal O₂ uptake, but we have not yet determined the cause or even precisely identified which organ system, involved directly or indirectly with O₂ transport to muscle, is responsible for this limitation.

exercise-induced arterial hypoxemia definition; excessive alveolar-to-arterial P O₂ difference; ventilation-perfusion ratio maldistribution; hyperventilatory compensation; maximal oxygen uptake limitation; airway inflammation
saturation, and O₂ content. Arterial P(O₂) (PₐO₂) is determined by the level of alveolar ventilation at any given metabolic demand, together with the efficiency with which O₂ is exchanged between alveolar gas and arterial blood, as indicated by the alveolar-to-arterial P(O₂) difference (A-aDO₂). Arterial O₂ saturation (SₐO₂) follows PₐO₂ but may be modified by O₂ dissociation curve shifts caused by changes in pH, PₐCO₂, and blood temperature. Arterial O₂ content (CₐO₂) follows saturation but will be modified by Hb concentration, which generally increases slightly from rest to heavy exercise. Sufficient data are available over the past half century to define typical changes in these indexes of oxygenation in the young, healthy, habitually inactive or mildly active adult men with V˙O₂max in the 35–55 ml·kg⁻¹·min⁻¹ range. This response typically consists of a gradual widening of the A-aDO₂ from rest (5–10 Torr) to maximal exercise (20–25 Torr), accompanied by a ventilatory response that rises out of proportion to increasing O₂ uptake (V˙O₂) [and CO₂ production (V˙CO₂)] in moderately heavy through maximum exercise, thereby raising alveolar P(O₂) [and reducing arterial PCO₂ (PₐCO₂)] sufficiently to prevent arterial hypoxemia. As highly fit young adult men, and then women and the elderly, were tested in larger numbers beginning in the 1960s, several instances of EIAH have been reported, whereby occasionally PₐO₂ is reduced by as much as 30 Torr and SₐO₂ by as much as 15% below resting levels. We consider it adequately documented that significant EIAH does occur in a significant number of healthy, fit subjects during exercise near sea level (e.g., Refs. 7, 10, 21, 22, 42, 47).

Defining EIAH and Its Components

We propose simple guidelines for defining a significant EIAH, which address two specific purposes: 1) to identify a significant threat to systemic O₂ transport; and 2) to quantify abnormalities in each of the two key determinants of PₐO₂, namely, the ventilatory response and the efficiency of alveolar-to-arterial gas exchange. The choice of EIAH definition will depend on the research question one wishes to address. In this review, we consider EIAH broadly as reduced arterial oxygenation, which may result from a fall in PₐO₂ (and thus also in SₐO₂), from a rightward shift of the O₂ dissociation curve without a fall in PₐO₂, by as much as 15% below resting levels. We consider it adequately documented that significant EIAH does occur in a significant number of healthy, fit subjects during exercise near sea level (e.g., Refs. 7, 10, 21, 22, 42, 47, 48).

EIAH as a threat to O₂ transport. Reductions in SₐO₂ (and, therefore, in CₐO₂), rather than in PₐO₂, better define the consequences of EIAH to systemic O₂ transport and to V˙O₂max. As discussed in detail below (see Consequences of EIAH), preventing EIAH by using supplementary inspired O₂ increases V˙O₂max in many subjects (13, 23, 41, 55). The measurable threshold of this effect occurs at a ~3% reduction in SₐO₂, from a normal resting value of 98%, and a linear association between ∆SₐO₂ and ∆V˙O₂max (where ∆ indicates change) is observed beyond this threshold such that each further 1% reduction in SₐO₂ (or CₐO₂) causes a ~1–2% reduction in V˙O₂max. Accordingly (until the study of larger groups determines otherwise), we suggest that EIAH be defined so that mild EIAH would correspond to an absolute SₐO₂ of 93–95%; moderate EIAH to an absolute SₐO₂ in the range of 88–93%; and severe EIAH to SₐO₂ values <88%. It is important to keep in mind that SₐO₂ may be reduced in heavy exercise, not only because of reductions in PₐO₂ but also (and often to an equal extent) by a pH- and temperature-induced rightward shift of the HbO₂ dissociation curve (see Figs. 1 and 2). It is advisable then to distinguish (and to report) the independent effects of a reduced PₐO₂ vs. pH and...
temperature effects on \( \text{SaO}_2 \) by using a standardized HbO2 dissociation curve.1

EIAH as an indicator of inadequacies in ventilation and gas exchange. It is also important to identify and quantify the key components of abnormal gas exchange, as defined by excessive widening of A-aDO2 and/or insufficient alveolar hyperventilation during exercise. Essentially, all normal subjects develop an increased A-aDO2 with exercise, and values of 15–25 Torr are common at \( \text{VO}_{2\max} \). Arterial Pco2 usually falls to 30–35 Torr. Based on such responses, we suggest that an A-aDO2 in the 25–30 Torr range is excessive and that if A-aDO2 exceeds 35–40 Torr, severe inefficiencies in gas exchange are present. Correspondingly, PaCO2 in the 35–38 Torr range indicates a borderline effective alveolar hyperventilation, and PaCO2 > 38 Torr suggests the absence of a compensatory hyperventilatory response. The use of these criteria may serve as a guide in identifying the key potential determinants of EIAH; however, it is important to recognize that one of these two criteria may be abnormal during exercise without actually resulting in significant reductions in PaO2 or SaO2, underlining the need to separately consider EIAH in terms of its effects on O2 transport and its relationship to pulmonary gas exchange and ventilation.

Relationship of EIAH to \( \text{VO}_{2\max} \) and Habitual Activity Levels

Habitually active subjects are the only healthy subjects thus far to demonstrate EIAH in appreciable numbers. The correlation of EIAH to \( \text{VO}_{2\max} \) is usually significant within the various groups studied; however, there are also several instances of weak correlations of EIAH vs. \( \text{VO}_{2\max} \) and of subjects (e.g., women) with \( \text{VO}_{2\max} \) within 20% of normal predicted values who experienced significant EIAH. Equally impressive and mysterious are the large numbers of highly fit male and female endurance athletes of all ages (\( \text{VO}_{2\max} \) 150–200% of predicted normal), who do not experience significant EIAH, even at their very high peak work rates (7, 14, 21, 42, 50).

Prevalence of EIAH. The prevalence of EIAH near sea level has been estimated at ~50% of young, adult, highly fit male athletes (40), but this estimate is at best a guess, because insufficient numbers of subjects have been tested by using direct measurements of arterial blood gases. Furthermore, the prevalence of EIAH will likely vary with such factors as age and gender, and certainly the numbers studied to date within each of these basic categories are woefully small.

EIAH and Exercise Intensity

When EIAH is present, it usually peaks at or near maximal exercise intensity. In many cases, a consistent fall in PaO2 is not obvious until very heavy or maximum exercise. On the other hand, in many trained subjects, the trend toward EIAH clearly begins at moderate intensity workloads, as A-aDO2 widens with little or no accompanying hyperventilatory compensation (7, 14, 46). In such subjects, as exercise intensity further increases, PaO2 and SaO2 continue to fall as A-aDO2 widens further, compensatory hyperventilation is minimal, and metabolic acidosis ensues. This ten-
dency toward developing EIAH in submaximal exercise has not been emphasized sufficiently in studies to date. Its occurrence may have significant implications for deciphering the causes of EIAH (see below).

The mode and duration of exercise. The mode and duration of exercise will affect EIAH. EIAH commonly occurs only transiently with very brief progressive exercise because of ventilatory lag, and then \( P_aO_2 \) increases over time with increasing ventilation. On the other hand, in fit subjects susceptible to EIAH who undergo 4–5 min of heavy-intensity, constant-load exercise, \( P_aO_2 \) falls within the initial 30–60 s of exercise and is maintained at this reduced level throughout the ensuing 3–4 min (7). Even if \( P_aO_2 \) stays level, \( SaO_2 \) may continue to fall further as \( pH \) falls. The general impression is that treadmill running and walking cause greater and more consistent EIAH than does cycle ergometry, in part because of a greater ventilatory response to cycling. However, there is also evidence of a larger \( A-aDO_2 \) in running than cycling in the same subjects at the same \( Vo_2 \). Upright and supine cycle exercise causes similar levels of EIAH as do running and grade walking at similar \( Vo_2 \). Prolonged exercise at moderate exercise intensities (<80% \( Vo_2\text{max} \)) only very rarely causes EIAH, even in subjects who experience significant EIAH in short-term maximal exercise (12, 17). A major protective mechanism in long-term exercise may be the greater hyperventilatory response.

Methods of Quantifying EIAH

EIAH must be identified by direct measurements of arterial blood gases, and these measurements should be corrected to the in vivo arterial blood temperature. Arterial blood temperature is commonly measured directly or estimated from esophageal temperature. The correction factor for \( P_o2 \) and \( P_co2 \) is very important, because the temperature correction is very important, because the temperature commonly increases ~1.5–2°C over the course of a standard progressive exercise test and even more in heavy constant-load endurance exercise. The correction factor for \( P_o2 \) and \( P_co2 \) is ~5% per 1°C. This means that without temperature correction we can underestimate the true in vivo \( P_o2 \) by 10 Torr or more during progressive exercise of brief duration and by much more during heavy endurance exercise. These errors are equal to the suggested minimum decrements in \( P_aO_2 \) for defining EIAH; and failure to temperature-correct \( P_co2 \) would correspondingly overestimate ideal alveolar \( O_2 \) and, therefore, the \( A-aDO_2 \). Noninvasive ear oximetry is commonly used in exercise studies in healthy subjects who would not be expected to desaturate >10%. Thus the great majority of these changes lie on the relatively flat portion of the \( HbO_2 \) dissociation curve, and it is very difficult to accurately quantify changes in \( SaO_2 \), and especially in \( P_aO_2 \), with this indirect measurement. Furthermore, since the only readily measured variable is \( SaO_2 \), one cannot even begin to identify the potential causes of EIAH.

EIAH IN ANIMALS

EIAH is not confined to humans. Across a number of species, data show changes generally similar to those in humans. Whereas less athletic species (goat, calf, rat) show little gas-exchange inefficiency at peak exercise, highly athletic species (dog, horse) develop a large \( A-aDO_2 \) at maximal effort. Just as for humans, the degree of hyperventilation during exercise is variable, and, as a result, \( P_aO_2 \) and \( P_co2 \) change in ways reflecting both the ventilatory response and the gas-exchange inefficiencies.

Table 1 shows typical data from a number of animal studies and indicates the range of responses. It is evident that, except for the Thoroughbred racehorse (55), \( P_aCO_2 \) is reduced by hyperventilation during exercise. In the goat, calf (52), and rat (9), the \( A-aDO_2 \) is slightly excessive, but their considerable hyperventilation keeps \( P_aO_2 \) high. In more aerobic species, e.g., pig (18), dog (20), and fox (30), \( A-aDO_2 \) begins to rise to a greater degree, but \( P_aO_2 \) is maintained near resting levels by hyperventilation. In still more athletic animals [pony (52)], \( P_aO_2 \) cannot be maintained despite hyperventilation. Finally, in the trained Thoroughbred horse (55), \( A-aDO_2 \) is high, alveolar hypoventilation occurs, and there is considerable EIAH. The horse thus represents an extreme, which may reflect selective breeding by humans that has focused on enhancing cardiovascular and not pulmonary function. Interpretation of these data is facilitated by noting that \( Vo_2\text{max} \) scales to body size (log/log plot) with a slope of only 0.81 (53), accounting for the higher specific \( Vo_2\text{max} \) in smaller animals. Species that can reach a \( Vo_2\text{max} \) greater than expected from Taylor’s scaling relationship (horse and

Table 1. Interspecies comparison of gas-exchange responses to exercise

| Species | Ref. No. | \( P_o2 \), Torr | \( P_co2 \), Torr | \( A-aDO_2 \), Torr | \( P_o2 \), Torr | \( P_co2 \), Torr | \( A-aDO_2 \), Torr | \( SaO_2 \), % | \( Vo_2\text{max} \), ml kg\(^{-1}\) min\(^{-1} \)
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<td>105</td>
<td>37</td>
<td>2</td>
<td>123</td>
<td>26</td>
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<td>95.0</td>
<td>57</td>
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<td>52</td>
<td>108</td>
<td>39</td>
<td>0</td>
<td>114</td>
<td>29</td>
<td>9</td>
<td>100.0</td>
<td>37</td>
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<td>9</td>
<td>95</td>
<td>36</td>
<td>14</td>
<td>108</td>
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<td>17</td>
<td>104</td>
<td>43</td>
<td>0</td>
<td>99</td>
<td>37</td>
<td>14</td>
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<td>68</td>
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<td></td>
<td></td>
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<td>120</td>
<td>19</td>
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<td>4</td>
<td>77</td>
<td>50</td>
<td>28</td>
<td>81.6</td>
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\( A-aDO_2 \), alveolar-to-arterial \( O_2 \) difference; \( SaO_2 \), arterial \( O_2 \) saturation; \( Vo_2\text{max} \), maximal \( O_2 \) uptake.
dog) are those with the greatest inefficiencies in pulmonary gas exchange.

CAUSES OF EIAH

In humans, EIAH severity correlates most consistently and inversely with A-aDO2. Interindividual differences in PaCO2 or the ventilatory equivalent for VO2 (or VCO2) are also commonly found to correlate significantly with EIAH; however, there are many exceptions, especially in mild EIAH, and thus the degree of hyperventilation accounts for less of the variance in PaO2 in most studies. Those men and women, in both young and old age groups, who experience severe EIAH have almost equal contributions from the absence of hyper- old age groups, who experience severe EIAH have almost equal contributions from the absence of hyperventilation and widened A-aDO2 to their hypoxemia, compared with nonhypoxic subjects at comparable VO2max. For combined human and animal group mean data (Table 1), variations in O2 saturation at maximum exercise are best predicted from a multiple linear-regression model (r = 0.93)2, where ventilation (as reflected by PaCO2) explains ~60% of the variance in SaO2. VO2max accounts for 25% of it, and A-aDO2 for the remainder.

Why Inadequate Hyperventilatory Compensation?

The answer to this question is complex and begins with an appreciation of the multiple factors that determine the ventilatory response to heavy exercise. First, the level of ventilatory stimuli (including circulating H+ concentration, K+ concentration, O2, and catecholamines plus powerful neural feedforward and feedback influences) is an important consideration. However, stimulus levels are, if anything, greater in subjects with EIAH and, therefore, could not explain the accompanying inadequate hyperventilatory response. Second, the mechanical influences of airway diameter and respiratory muscle force production may prevent expression of the full ventilatory response to existing stimuli. Evidence favoring a role for mechanical constraint includes observations that the gains of the ventilatory and tidal volume (VT) responses to added chemoreceptor stimuli are reduced during heavy and maximal workloads relative to those obtained during mild and moderate exercise intensities (5, 22, 32, 33). A third factor, often invoked to explain differences in ventilatory responses to exercise, is the interindividual difference in sensitivity to both existing stimuli and to mechanical constraints.

Much of the mechanical constraint on minute ventilation (VE) appears to be imposed by the airways that have an upper limit to flow rate, especially on expiration, as defined by the maximum volitional flow-volume envelope. Partial encroachment of the VT on the maximum flow-volume envelope is experienced by most trained subjects during heavy to maximum exercise. In many very fit young men, and especially in women and older fit adults, almost all of the flow-volume envelope may be utilized during maximal exercise (21, 22, 31). These groups are especially vulnerable to expiratory flow limitation during maximum exercise because of their high metabolic and, therefore, ventilatory requirements, combined with 1) a normal maximum flow-volume envelope in the young men; 2) a smaller envelope in the women (relative to men of similar height); and 3) a substantial age-dependent reduction in lung elastic recoil and expiratory flow reserve in the 65- to 75-year-old endurance athletes. That this flow limitation may constrain V̇e is demonstrable experimentally by the increase in VT and V̇E (and reduction in the end-expiratory lung volume (EELV)) and increased gain of the ventilatory response to CO2, which occurs when low-density He-O2 mixtures are inspired to expand the maximum flow-volume loop and to eliminate expiratory flow limitation (32). These data also suggest that <50% of the VT needs to encroach on the maximum expiratory flow-volume envelope to cause EELV to rise and VT and V̇E to be constrained. Perhaps then even minimal amounts of airway narrowing initiate, reflexly, termination of expiratory effort; as EELV increases, inspiratory motor output would be inhibited via increased vagal feedback from lung stretch at high end-inspiratory lung volume (2, 38). However, this is speculation. We do not even know if a true reflex inhibition actually occurs with the onset of (impending) flow limitation. Valid, artifact-free methods for measuring central neural respiratory motor output in the exercising human are needed so that we can even begin to understand ventilatory control during heavy-intensity exercise.

Another potential mechanical limit to V̇E is the pressure or force developed by inspiratory muscles, which may approach 90% of their capacity at peak exercise in fit subjects (22, 29). However, when a proportional-assist ventilator was used to unload the respiratory muscles under these conditions, changes in V̇E were variable and often insignificant, indicating that the respiratory muscle load, per se, was not an important constraint to V̇E or that behavioral responses to positive-pressure mechanical ventilation became a dominant factor in controlling V̇E during exercise (27).

An important but poorly understood factor determining the ventilatory response to heavy exercise is the marked interindividual differences in ventilatory responsiveness or receptor sensitivity, either to the available neurohumoral stimuli or to the inhibitory feedback.3

\[2 \text{SaO}_2(\%) = 110.4 - 0.38 \cdot \text{PaCO}_2 - 0.80 \cdot \text{A-aDO}_2 - 0.51 \cdot \dot{V}_{O2\text{max/\text{kg}}}\]
influences from mechanoreceptors. For example, there are subjects who show a sluggish ventilatory response to heavy exercise with little or no obvious mechanical constraint via flow limitation (21, 22). On the other end of the spectrum are those subjects who show significant expiratory flow limitation but continue to increase their respiratory motor output and ventilation right to the very limits of their flow-volume envelope, despite the production of extremely negative inspiratory and positive expiratory pleural pressures. Furthermore, several subjects with EIAH will underventilate during even mild and moderate exercise intensity, i.e., in the absence of significant flow limitation or of high loads on the respiratory muscles (7, 14, 15, 28, 46). So, blunted stimulus responsiveness likely contributes significantly to the reduced ventilatory response to exercise. Unfortunately, these characteristics are not consistently predictable from conventional (resting) hypoxic or hypercapnic ventilatory response tests, and the popular generalization that highly trained endurance athletes all have blunted chemoreceptor responses has many exceptions.

We emphasize that EIAH is not completely preventable by improving $V_A$, at least within realistic limits. For example, in very fit subjects with the most severe EIAH and with $A-aD_o_2 > 35$ Torr, $P_{A CO_2}$ in the 36–39 Torr range, and $V_E$ at 85% of ventilatory capacity, it may be predicted (by using the alveolar air equation) that $V_E$ would need to increase by >50 l/min or by 35–50% and $P_{A CO_2}$ to fall below 25 Torr to maintain $P_{A O_2} > 85$ Torr at $V_O^{2max}$. Interestingly, similar increases in $V_A$ would be required to drive $P_{A CO_2}$ low enough so as to completely compensate arterial pH in the face of the accompanying metabolic acidosis. This degree of h yperventilation is not possible mechanically, because these ventilatory requirements far surpass the maximum ventilatory capacity—as estimated from the maximum voluntary ventilation or from the maximum flow-volume loop and breathing frequency at maximal exercise. Experimentally, removal of expiratory flow limitation via He-O2 breathing resulted in only a 15–20% increase in $V_E$, a reduction in $P_{A CO_2}$ of 5–7 Torr, and prevention of 30–40% of the EIAH (7, 31, 32).

Why an Increase in $A-aD_o_2$ with Exercise?

The classically described causes of an increased $A-aD_o_2$ include 1) ventilation-perfusion ($V_A/Q$) inequality; 2) failure of alveolar-end capillary diffusion equilibrium; and 3) right-to-left shunt. Shunts may occur 1) within the lungs or between atria, ventricles, or great vessels; and 2) in a postpulmonary setting, due to venous admixture of arterial blood with blood from bronchial and thebesian veins. Determining which of these alone or in combination are responsible for any increase in $A-aD_o_2$ with exercise is difficult, and most such information has come from using the multiple inert-gas-elimination technique (MIGET).

At rest, it is clear that the entire $A-aD_o_2$ is accounted for by $V_A/Q$ inequality in normal subjects (humans and other mammals). There is no evidence for diffusion limitation or measurable contributions from intrapulmonary or extrapulmonary shunts (56). During heavy exercise, $V_A/Q$ inequality still accounts for much, and sometimes all, of the $A-aD_o_2$, at least at sea level (56). It is of considerable interest that the severity of $V_A/Q$ mismatching is greater during heavy exercise than at rest (8, 56), but the effect of this increase in inequality on $P_{A O_2}$ is mitigated by the well-known increase in overall lung $V_A/Q$ ratio. Thus, because alveolar ventilation increases relatively more than does cardiac output (Q) during exercise, the $V_A/Q$ distribution is shifted to a higher range of $V_A/Q$ ratios, thereby raising alveolar and thus arterial $P_{A O_2}$. Consequently, the magnitude of the $A-aD_o_2$ component attributable to $V_A/Q$ inequality remains essentially constant from rest to exercise (56). Why $V_A/Q$ mismatch increases with exercise is addressed below.

At or near $V_O^{2max}$ diffusion limitation appears to develop. Whereas this is not uniformly observed, it is more common in subjects with greater levels of fitness and in athletic species such as horse and dog (20, 55). Application of the MIGET is the clearest way of detecting the presence of diffusion limitation, since the inert gases used in the method are invulnerable to variable degrees of diffusion limitation. They can, therefore, be used to predict the $P_{A O_2}$ that would be expected if only $V_A/Q$ inequality and intrapulmonary shunts existed. If this prediction statistically matches measured values for $P_{A O_2}$, one concludes that there is no diffusion limitation present. On the other hand, diffusion limitation would lead to a lower value for actual $P_{A O_2}$ than predicted by MIGET (11), whether or not $V_A/Q$ inequality and/or shunts were also present. Whereas this difference in $P_{O_2}$ is usually attributed to diffusion limitation, it is true that bronchial and thebesian venous admixture would lead to a similar difference between the measured and MIGET-predicted $P_{A O_2}$, and this cannot be strictly separated from diffusion limitation. The magnitude of the postpulmonary shunt in exercising humans is not known precisely. During exercise in normoxia, a shunt as small as 1–2% of the cardiac output may account for a substantial portion of the difference between predicted and measured $A-aD_o_2$ (8), whereas in hypoxia unreasonably high amounts of shunt in the range of 10–20% of the cardiac output are required to account for the predicted to measured $A-aD_o_2$ (36).

Significant intrapulmonary shunts cannot be identified in the majority of cases, either at rest or during exercise, in normal subjects or animals. Even when present, they usually amount to <1% of the Q and have little impact on $P_{A O_2}$.

There is some evidence that incomplete gas mixing in the alveoli or airways confers a small degree of gas-exchange inefficiency. This may cause $P_{A O_2}$ to fall perhaps 12 Torr (16). Again, this is, by and large, an essentially negligible factor in arterial oxygenation, and there is little evidence for this in humans.

Finally, no matter what the physiological basis may be for an increased $A-aD_o_2$, the reduction in mixed venous $P_{O_2}$ that normally accompanies exercise acts to further lower $P_{A O_2}$. Mixed venous $P_{O_2}$ falls because...
VO₂ increases relatively more than Q from rest to exercise. The effect is to cause more diffusion limitation and also to reduce end-capillary PO₂ in regions of the lung where low Vₐ/Q ratios exist (59). Because mixed venous PO₂ commonly drops from ~40 Torr at rest to 20 Torr during heavy exercise, the effect is considerable.

In summary, both diffusion limitation and greater VA/Q mismatch contribute to the increased A-aDO₂ during exercise. The contribution of VA/Q inequality to the A-aDO₂ is generally constant from rest to VO₂max, whereas that of diffusion limitation is not seen until heavy or even maximal exercise is undertaken. Current data suggest that, on average, these two processes contribute similarly to the A-aDO₂ at or near VO₂max (52). The reduced mixed venous PO₂ further reduces PAO₂, but both intrapulmonary and extrapulmonary shunts appear to be negligible.

Mechanism of Increase in VA/ Q Inequality With Exercise

Why VA/Q mismatch worsens remains an unresolved issue. There are several candidate mechanisms: 1) normal minor structural differences in airways and/or blood vessels throughout the lungs that would cause no significant variation in airways or vascular resistance at rest could become significant on exercise because of the increase in gas and blood flow rates; 2) bronchoconstriction, even at subclinical levels, could alter ventilation distribution; 3) secretions from airways irritated by high air flow rates of sometimes cold, dry air could affect ventilation distribution; 4) modulators of airway and vascular tone in the lung could be affected, in turn altering ventilation or blood flow distribution; 5) mild interstitial edema could develop and, through changes in local compliance (alveolar wall edema) or resistance (perivascular or bronchial edema), affect the distribution of ventilation or blood flow. Of these candidates, 1 cannot be currently excluded, and direct evidence is impossible to obtain. However, the persistence of VA/Q mismatch beyond the time required for ventilation and Q to return to resting levels postexercise (50) does not support this mechanism; 2 is not the explanation for the majority of subjects, i.e., those who do not suffer from exercise-induced bronchoconstriction; 3 also cannot be positively excluded at the present time, nor can 4. Indeed, there are data suggesting a role for histamine in the development of EIAH (44). However, there is a body of largely indirect evidence that supports the development of transient interstitial edema (1, 3, 44, 45). The problem is clearly yet unresolved.

Mechanism of Increase in Diffusion Limitation With Exercise

The degree of diffusion limitation expected in any given lung is elegantly explained by Piiper and Scheid (39) in terms of their compound variable D/(βQ), where D is lung diffusing capacity and β is the mean slope of the conceptually linear O₂-Hb dissociation curve in the physiological range. With D in ml·min⁻¹·Torr⁻¹, β in ml O₂·l·blood⁻¹·Torr⁻¹, and Q in l/min, when D/(βQ) is 4.6, diffusion equilibration would be 99% complete; D/(βQ) = 3.0 allows 95% equilibration; and D/(βQ) = 1.0 allows only 63% equilibration. Whereas all three components (D, β, and Q) increase on exercise, D/(βQ) falls. This fall can be accentuated by limited gains in overall D (possibly from VA/Q mismatching or from alveolar interstitial edema) or by greater than average increases in β and Q. Athletes typically exhibit a high Q and also high O₂ extraction from blood perfusing muscles. Because high O₂ extraction increases β by increasing the average slope of the O₂-Hb curve in the working range, athletes in particular are subject to greater reduction in D/(βQ) than are sedentary subjects. Consequently, it is no surprise that, as discussed earlier, the most athletic subjects and species are those most subject to diffusion limitation, particularly due to high Q. Recent evidence suggests that subjects with more exercise-induced hypoxemia at a given VCO₂ also have a lower D (47). Thus diffusion limitation is dictated by the summed effects of an intrinsically low D, potentially limited increases in D with exercise, high O₂ extraction, and high Q because of training state or intrinsic athleticism.

Demand vs. Capacity as an Explanation for EIAH?

Does EIAH occur because the highly trained human or animal has undergone adaptation in nonpulmonary (i.e., cardiovascular and metabolic) determinants of maximum O₂ transport and VO₂max, but not at the level of the lung and airways (6)? On the one hand, this idea seems reasonable because of many findings showing that—with few exceptions—the lung in physically trained humans or in athletic animals differs not at all or very little from the sedentary animal; and that physical training sufficient to increase VO₂max has no measurable effects on lung function or structure. On the other hand, evidence against this concept as the sole explanation for EIAH are some reports that the onset of excessive widening of the A-aDO₂ and, therefore, EIAH can be shown to occur in many cases, even in submaximal exercise, (see Figs. 1 and 2) and in rare cases EIAH can be equally severe in submaximal and maximal exercise (7, 14, 46). The occurrence of EIAH in submaximal exercise has not received sufficient emphasis. It may have significant implications for how we view EIAH as predominantly a result of an “underbuilt” lung in athletes, relative only to their extraordinary demand for maximum O₂ transport or whether in some cases the stresses associated with training may actually have effects on structural or secretory characteristics in the lung's parenchyma and peripheral airways that would predispose to an excessive maldistribution of VA and/or Q during exercise.

CONSEQUENCES OF EIAH

EIAH Effects on VO₂max

The effect of EIAH on VO₂max has been demonstrated in a limited number of studies in fit humans and horses by adding sufficient O₂ to the inspired air to prevent the EIAH (13, 23, 41, 55) (see Figs. 1 and 2). Note that this approach, which aims to maintain SaO₂ and CaO₂ at resting levels, differs substantially from the more common use of much higher concentrations of inspiratory
The critical dependence of V\(\dot{O}_2\)\text{max} on O2 transport may only be met with SaO2 (and CaO2) such that V\(\dot{O}_2\)\text{max} is affected by this threshold of desaturation changes linearly. This phenomenon has been observed in various species and is a significant finding that has implications for understanding the limits of aerobic exercise.

For example, in the Thoroughbred horse, which normally reaches 85–90% SaO2 at V\(\dot{O}_2\)\text{max} (see Fig. 2), the further reduction of V\(\dot{O}_2\)\text{max} beyond these levels is substantial. These threshold values are similar to those found when arterial hypoxemia was caused experimentally via increased inspiratory CO fraction or reduced F\text{I}_O2 (19, 28, 57). The further reduction of V\(\dot{O}_2\)\text{max} beyond this threshold of desaturation changes linearly with SaO2 (and CaO2) such that V\(\dot{O}_2\)\text{max} is affected by 20% in the Thoroughbred horse, which normally has a maximum of 85–90% SaO2 at V\(\dot{O}_2\)\text{max} (see Fig. 2). The majority of the effect of preventing EIAH on V\(\dot{O}_2\)\text{max} occurs because V\(\dot{O}_2\) is increased at a given high-intensity work rate. Thus preventing EIAH removes the plateau effect of V\(\dot{O}_2\) vs. work rate and delays it until a higher work rate is reached (see Figs. 1 and 2). These data add to the substantial findings already available that have documented that O2 transport to the working tissue, as determined by blood flow, CaO2, and O2 extraction, is the important limiting factor to V\(\dot{O}_2\)\text{max} in healthy subjects, as opposed to the metabolic capacity of the muscle mitochondria (see Ref. 57 for review). This critical dependence of V\(\dot{O}_2\)\text{max} on O2 transport may only apply to normal or highly trained subjects, whereas the V\(\dot{O}_2\)\text{max} in the extremely sedentary subject or animal may not be O2 supply dependent (4, 23).

EIAH becomes an especially important determinant of V\(\dot{O}_2\)\text{max} in hypoxic environments, particularly in the highly trained athlete, who usually suffers the greatest decrement in V\(\dot{O}_2\)\text{max} at high altitudes (10, 28). Thus even relatively small decrements in inspired P\text{O}_2 (for example to 120–130 Torr or ~1,000 m altitude), which would not be expected to influence SaO2 or V\(\dot{O}_2\)\text{max} appreciably in the untrained, have been shown to precipitate substantial EIAH at the high work rates achieved in the highly fit, with marked decrements in V\(\dot{O}_2\)\text{max} and endurance exercise performance. Even trained subjects with mild or even no discernable EIAH at sea level may experience moderate-to-severe EIAH in the face of only modest decrements in inspiratory P\text{O}_2 (7, 10). Diffusion limitation at these high work rates in hypoxic environments is a likely cause of EIAH in the athlete (see above), along with limited room within the maximum flow-volume envelope to further increase alveolar ventilation in response to hypoxic chemoreceptor stimulation during heavy exercise (22).

Mechanisms of EIAH Effects on V\(\dot{O}_2\)\text{max}

The effect of EIAH on V\(\dot{O}_2\)\text{max} is fairly predictable based solely on the reduction in SaO2 and CaO2 and therefore, in turn, on the limits placed on the widening of the maximal arterial-to-venous O2 content difference across the working muscle. This change in the maximum arterial-to-venous O2 difference in proportion to the change in CaO2 has not been documented directly with studies that have prevented EIAH but has been shown when CaO2 was increased to above-normal levels during exercise either with hyperoxia (25) or via increased Hb concentration (54). The major consequence of EIAH is probably its effect on convective O2 delivery to the working muscles. Theoretically, EIAH may also affect the unloading of O2 from muscle microcirculatory red blood cells and its subsequent diffusive movement into the myocytes. This is because the diffusion process depends on the P\text{O}_2 difference between red blood cells and mitochondria. EIAH will lower microvascular P\text{O}_2 and, therefore, impede diffusion movement of O2 into muscle. However, this diffusive effect is likely minor unless arterial hypoxemia is severe.

The theories outlined above attribute the detrimental effects of EIAH on V\(\dot{O}_2\)\text{max} directly to an impairment of O2 delivery to the working locomotor muscles because of reduced CaO2; however, there are alternative explanations based on studies conducted in acute environmental hypoxia, suggesting that systemic hypoxemia may (indirectly) cause feedback inhibition of limb locomotor muscle force output in order to spare the function and/or oxygenation of more vital organ systems. Perhaps, then, it is the prevention of inadequate myocardial O2 supply (36), or excessive respiratory muscle work (24), or even central nervous system hypoxia (51) which limits the peak work rate of locomotor muscles in the presence of arterial hypoxemia. For example, the idea that EIAH means reduced O2 transport to the myocardium (as well as to the limbs) also leaves open the option that the release of this hypoxemia may increase myocardial O2 supply, force of ventricular contraction, and Q (36). A companion concept requiring further testing is that changes in CaO2 affect limb blood flow inversely with the change in P\text{A}_2, thereby resulting in no net change in O2 transport to the working limb (58). Any resulting change in V\(\dot{O}_2\)\text{max} is attributable, then, to differences in the V\(\dot{O}_2\) of nonexercising tissue, such as hyperperfused splanchnic tissue. Finally, an important related question concerns the effect of EIAH on exercise performance per se, rather than on V\(\dot{O}_2\)\text{max}, two outcome measurements that are sometimes (but not always) closely related (35, 36). Hypoxic O2 supplementation studies usually show a concomitant effect on exercise performance, but these effects may be substantially less than on V\(\dot{O}_2\)\text{max} (26, 35).

Summary: Unresolved Questions

Significant advances have been made, especially over the past decade, in describing EIAH and in understanding some of its causes and consequences to O2 transport and exercise performance; however, several fundamental problems remain unresolved, in many cases because we are unable to apply definitive measurements to the complex in vivo conditions present during maximum exercise. We have not yet accumulated sufficient defini-
tive descriptive data to know the true prevalence of EIAH and the effects of fitness level, gender, and/or healthy aging. How significant and widespread is the occurrence of excessive A-aDo2 and EIAH during submaximal exercise and does this imply that EIAH results from a negative effect of training on lung structure, rather than merely a marked discrepancy between the adaptability of pulmonary vs. cardiovascular determinants of O2 transport? Our techniques have as yet failed to provide a sufficiently clear window on lung function during heavy exercise so as to permit precise quantitation of extravascular lung water, or of morphological changes in the diffusion pathway or in the uniformity of red blood cell transit time distribution, or of inflammatory changes in the so-called “silent zone” of the lung’s peripheral airways. Accordingly, even the basic causes of VA/Q maldistribution and of diffusion limitation during exercise remain a mystery as do the reasons underlying the marked interindividual differences in propensity toward EIAH among athletes of similar levels of supranormal VO2max. Similarly, without a valid measure of central neural respiratory motor output during exercise we are unable to explore whether, or under what specific conditions, feedback inhibition actually occurs or how true interindividual differences in ventilatory sensitivity may be assessed. Finally, and of appeal to scientists concerned with broader questions of exercise physiology, a century of research has left us still mystified by exactly how exercise-induced arterial hypoxaemia limits VO2max or exercise performance. Is the elusive concept of a “critical Po2” in the muscle capillary or mitochondria for ATP generation valid or worthwhile?...and, specifically, what organ system involved directly or indirectly with O2 transport is most vulnerable and, therefore, primarily responsible for the limitation of VO2max in the presence of EIAH?

The authors thank Susan Hopkins and Thomas Wetter for critical review of the manuscript and Patricia Kalscheur for manuscript preparation.

Original research of the authors reported in the review was supported by National Heart, Lung, and Blood Institute Grant HL-17731 for P. D. Wagner and HL-15469 for J. A. Dempsey.

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