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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 PO₂ difference (A-aDO₂) (>25–30 Torr) and inadequate compensatory hyperventilation (arterial PCO₂ >35 Torr) commonly contribute to EIAH, as do acid- and temperature-induced shifts in O₂ dissociation at any given arterial PO₂. 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-aDO₂. 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 PO₂ difference; ventilation-perfusion ratio maldistribution; hyperventilatory compensation; maximal oxygen uptake limitation; airway inflammation

THE PROBLEM OF THE LUNGS’ CAPABILITY for maintaining homeostasis of arterial blood O₂ content and acid-base status during exercise is long-standing in physiology, dating back to before the turn of the 20th century. In the past decade or two, with the development of new approaches to assessing ventilation and perfusion distribution in the lung and with the growing number of observations indicating that gas exchange is far from perfect in the exercising healthy lung, research interest in this problem has intensified. Scientists specializing in respiratory, comparative, environmental, and exercise physiology and in neurophysiology have all been attracted to some aspect of this multifaceted problem, which speaks not only to the intricacies of gas

exchange in the lung but also to the neural, chemical, and mechanical determinants of ventilation and to the broader problem of limitations to exercise performance. Our brief synopsis of this problem attempts first to characterize and also to define exercise-induced arterial hypoxemia (EIAH) in humans and other mammals and then to critically analyze the underlying mechanisms of EIAH and its consequences to maximal O₂ uptake (V_{O₂max}) and exercise performance.

CHARACTERIZING EIAH

The level of oxygenation in arterial blood during exercise is defined by measurements of PO₂, HbO₂

saturation, and O₂ content. Arterial PO₂ (Pa_{O₂}) 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 PO₂ difference (A-aDO₂). Arterial O₂ saturation (Sa_{O₂}) follows Pa_{O₂} but may be modified by O₂ dissociation curve shifts caused by changes in pH, PCO₂, and blood temperature. Arterial O₂ content (Ca_{O₂}) 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 $\dot{V}O_{2\max}$ 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 ($\dot{V}O_2$) [and CO₂ production ($\dot{V}CO_2$)] in moderately heavy through maximum exercise, thereby raising alveolar PO₂ [and reducing arterial PCO₂ (Pa_{CO₂})] 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 Pa_{O₂} is reduced by as much as 30 Torr and Sa_{O₂} 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).

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 Pa_{O₂}, 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 Pa_{O₂} (and thus also in Sa_{O₂}), from a rightward shift of the O₂ dissociation curve without a fall in Pa_{O₂} or from a combination of these processes.

EIAH as a threat to O₂ transport. Reductions in Sa_{O₂} (and, therefore, in Ca_{O₂}), rather than in Pa_{O₂}, better define the consequences of EIAH to systemic O₂ transport and to $\dot{V}O_{2\max}$. As discussed in detail below (see CONSEQUENCES OF EIAH), preventing EIAH by using supplementary inspired O₂ increases $\dot{V}O_{2\max}$ in many subjects (13, 23, 41, 55). The measurable threshold of this effect occurs at a ~3% reduction in Sa_{O₂} from a normal resting value of 98%, and a linear association between ΔSa_{O_2} and $\Delta \dot{V}O_{2\max}$ (where Δ indicates change) is observed beyond this threshold such that each further 1% reduction in Sa_{O₂} (or Ca_{O₂}) causes a ~1–2%

reduction in $\dot{V}O_{2\max}$. Accordingly (until the study of larger groups determines otherwise), we suggest that EIAH be defined so that mild EIAH would correspond to an absolute Sa_{O₂} of 93–95%; moderate EIAH to an absolute Sa_{O₂} in the range of 88–93%; and severe EIAH to Sa_{O₂} values <88%. It is important to keep in mind that Sa_{O₂} may be reduced in heavy exercise, not only because of reductions in Pa_{O₂} 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 Pa_{O₂} vs. pH and

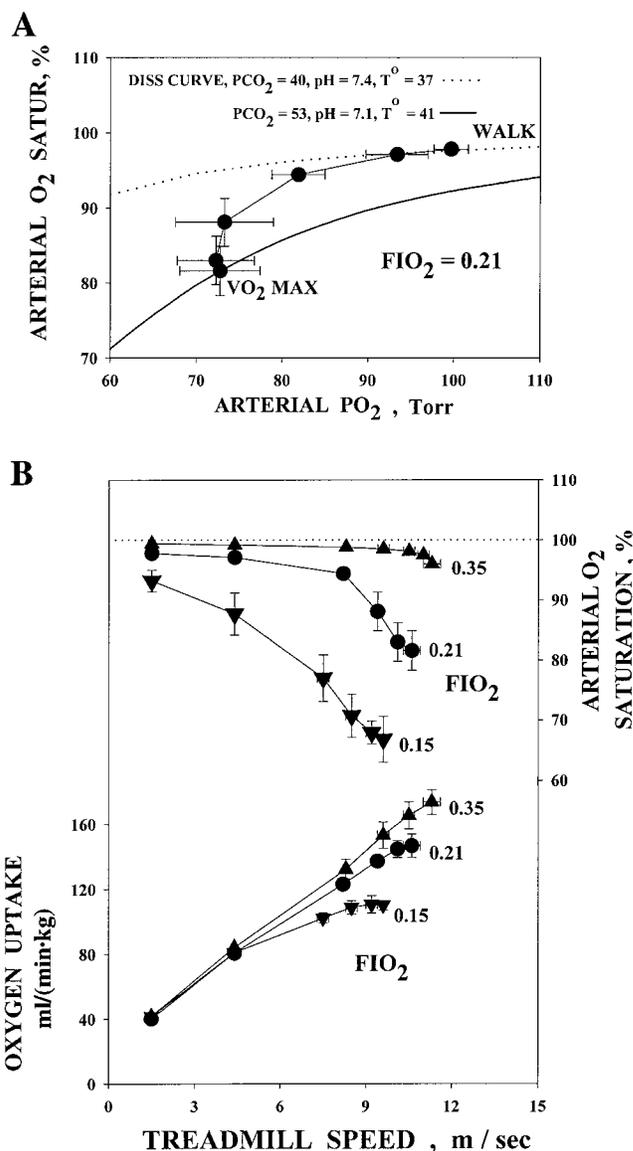


Fig. 1. Exercise-induced hypoxemia in Thoroughbred horses (see Refs. 55, 57). *A*: essentially sequential fall in arterial PO₂ (Pa_{O₂}) and then arterial O₂ saturation (Sa_{O₂}; satur) from rest to gallop. Note large drop in saturation caused by rightward movement of the O₂ dissociation (diss) curve at heavy exercise. *B*: Sa_{O₂} and O₂ uptake ($\dot{V}O_2$) from walk to maximal gallop in the same horses. Data for 3 inspiratory O₂ fractions (F_IO₂) are shown, exemplifying not only sensitivity of Sa_{O₂} to both exercise and F_IO₂ but also dependence of maximal $\dot{V}O_2$ ($\dot{V}O_{2\max}$) on Sa_{O₂}.

temperature effects on Sa_{O_2} by using a standardized HbO_2 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 $\dot{V}O_{2max}$. 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ is usually significant within the various groups studied; however, there are also several instances of weak correlations of EIAH vs. $\dot{V}O_{2max}$ and of subjects (e.g., women) with $\dot{V}O_{2max}$ 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 ($\dot{V}O_{2max}$ 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

¹ At the typical arterial temperature and acid pH achieved at maximal exercise, the suggested guideline of a 3% decrease in SaO₂ to define mild EIAH would require a 10-Torr reduction in PaO₂ below normal resting values. Hence, this reduction in PaO₂ also represents a clearly measurable quantity that signifies a failure of lung function specifically to maintain arterial oxygenation. The problem with using ΔPa_{O_2} is that transient hyperventilation is common at rest, especially in studies where arterial catheterization is new to the subject. Accordingly, the measured resting PaO₂ is often unrepresentative of the subjects' habitual resting blood gases.

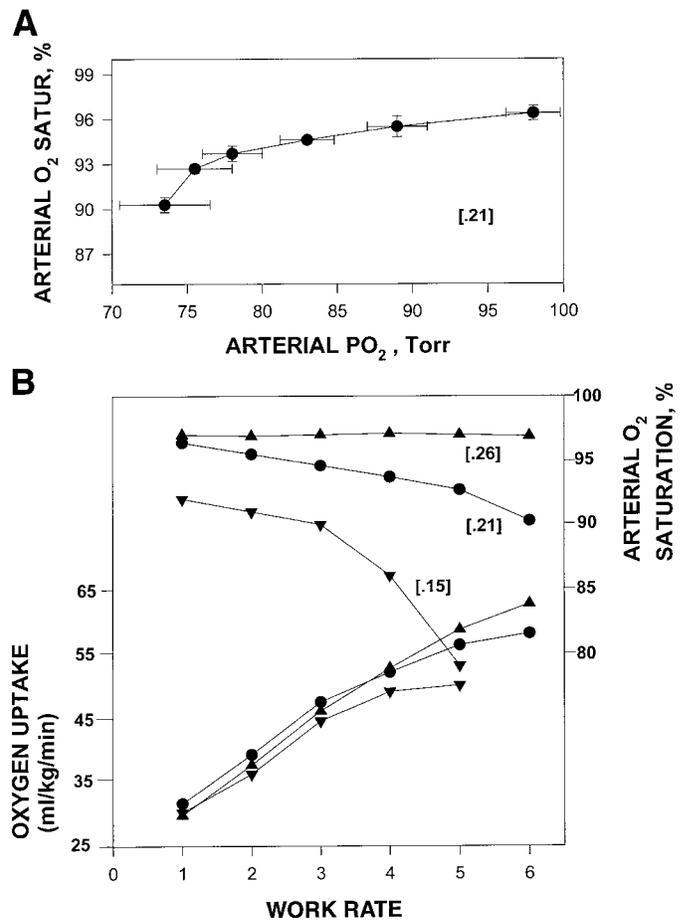


Fig. 2. Exercise-induced arterial hypoxemia in fit humans ($n = 15$ young women) during treadmill running. "Work rates" refer to an increasing treadmill grade of 2% every 2.5 min while speed is maintained at 6–10 miles/h. *A*: exercise-induced arterial O₂ desaturation at maximal exercise due almost equally to a reduction in PaO₂ and a rightward shift in the HbO₂ dissociation curve (acidic pH = 7.29; temperature = 38.2°C). Also, note reduction in PaO₂ beginning at submaximal work rates and progressing to maximum. *B*: effect of preventing exercise-induced arterial hypoxemia (EIAH) (via FI_{O₂} of 0.26) and of acute hypoxia (FI_{O₂} of 0.15) on SaO₂ and $\dot{V}O_2$. Note that changes in SaO₂ do not affect $\dot{V}O_2$ at submaximal work rates but do change the plateau effect at and near peak work rates. The 0.21 and 0.26 FI_{O₂} data are from Refs. 13 and 14, and effects of 0.15 FI_{O₂} were estimated from data in Refs. 7 and 28.

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 abnormally 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, S_{aO_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-aDO₂ in running than cycling in the same subjects at the same $\dot{V}O_2$. Upright and supine cycle exercise causes similar levels of EIAH as do running and grade walking at similar $\dot{V}O_2$. Prolonged exercise at moderate exercise intensities (<80% $\dot{V}O_{2max}$) 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 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_{aO_2} and P_{aCO_2} is ~5% per 1°C. This means that without temperature correction we can underestimate the true in vivo P_{aO_2} 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_{aCO_2} would correspondingly overestimate ideal alveolar PO_2 and, therefore, the A-aDO₂. 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 HbO₂ dissociation curve, and it is very difficult to accurately quantify changes in S_{aO_2} , and especially in P_{aO_2} , with this indirect measurement. Furthermore, since the only measured variable is S_{aO_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-aDO₂ at maximal effort. Just as for humans, the degree of hyperventilation during exercise is variable, and, as a result, P_{aO_2} and P_{aCO_2} 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-aDO₂ 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-aDO₂ 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-aDO₂ 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 $\dot{V}O_{2max}$ scales to body size (log/log plot) with a slope of only 0.81 (53), accounting for the higher specific $\dot{V}O_{2max}$ in smaller animals. Species that can reach a $\dot{V}O_{2max}$ greater than expected from Taylor's scaling relationship (horse and

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

Species	Ref. No.	Rest			Maximal Exercise				$\dot{V}O_{2max}$, ml·kg ⁻¹ ·min ⁻¹
		PO_2 , Torr	PCO_2 , Torr	A-aDO ₂ , Torr	PO_2 , Torr	PCO_2 , Torr	A-aDO ₂ , Torr	S_{aO_2} , %	
Goat	52	105	37	2	123	26	4	95.0	57
Calf	52	108	39	0	114	29	9	100.0	37
Rat	9	95	36	14	108	29	11	93.9	74
Pig	17	104	43	0	99	37	14	89.7	68
Fox	17				120	19	12	92.0	216
Dog	52	97	34	13	101	25	26	92.6	137
Pony	52	107	37	0	95	25	32	90.3	89
Horse	55	105	41	4	77	50	28	81.6	144

A-aDO₂, alveolar-to-arterial PO_2 difference; S_{aO_2} , arterial O₂ saturation; $\dot{V}O_{2max}$, maximal O₂ 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 \dot{V}_{O_2} (or \dot{V}_{CO_2}) 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 hyperventilation and widened A-aDO₂ to their hypoxemia, compared with nonhypoxemic subjects at comparable $\dot{V}_{O_{2max}}$. 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, $\dot{V}_{O_{2max}}$ 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 (V_T) 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 (\dot{V}_E) 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 V_T on the maximum flow-volume envelope is experienced by most

trained subjects during heavy to maximum exercise.³ 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 \dot{V}_E is demonstrable experimentally by the increase in V_T and \dot{V}_E [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 V_T needs to encroach on the maximum expiratory flow-volume envelope to cause EELV to rise and V_T and \dot{V}_E to be constrained. Perhaps then even minimal amounts of airway narrowing initiate, reflexively, 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 \dot{V}_E 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 \dot{V}_E were variable and often insignificant, indicating either that the respiratory muscle load, per se, was not an important constraint to \dot{V}_E or that behavioral responses to positive-pressure mechanical ventilation became a dominant factor in controlling \dot{V}_E 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

² SaO₂ (%) = 110.4 - 0.38 · PaCO₂ - 0.80 · A-aDO₂ - 0.51 · $\dot{V}_{O_{2max}}$ /kg.

³ The proximity of the tidal to the maximum flow-volume envelope during exercise correlates with simultaneous measures of the proximity of tidal expiratory pressures to maximum effective transpulmonary pressure (P_{max}) (21, 37). However, in most instances, truly maximum effective flow and pressure are only achieved over a portion of the V_T at low lung volumes. Thus "complete" flow limitation is usually not achieved in the sense that further imposed changes in transpulmonary pressure would not increase expiratory flow rate over some lung volumes (34).

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 \dot{V}_A , at least within realistic limits. For example, in very fit subjects with the most severe EIAH and with $A\text{-}a\text{D}O_2 > 35$ Torr, P_{aCO_2} in the 36–39 Torr range, and \dot{V}_E at 85% of ventilatory capacity, it may be predicted (by using the alveolar air equation) that \dot{V}_E would need to increase by > 50 l/min or by 35–50% and P_{aCO_2} to fall below 25 Torr to maintain $P_{aO_2} > 85$ Torr at $\dot{V}_{O_{2max}}$. Interestingly, similar increases in \dot{V}_A would be required to drive P_{aCO_2} low enough so as to completely compensate arterial pH in the face of the accompanying metabolic acidosis. This degree of hyperventilation 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- O_2 breathing resulted in only a 15–20% increase in \dot{V}_E , a reduction in P_{aCO_2} of 5–7 Torr, and prevention of 30–40% of the EIAH (7, 31, 32).

Why an Increase in A-aDO₂ with Exercise?

The classically described causes of an increased $A\text{-}a\text{D}O_2$ include 1) ventilation-perfusion (\dot{V}_A/\dot{Q}) inequality; 2) failure of alveolar-end capillary diffusion equilibration; 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 $A\text{-}a\text{D}O_2$ 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 $A\text{-}a\text{D}O_2$ is accounted for by \dot{V}_A/\dot{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, \dot{V}_A/\dot{Q} inequality still accounts for much, and sometimes all, of the $A\text{-}a\text{D}O_2$, at least at sea level (56). It is of considerable interest that the severity of \dot{V}_A/\dot{Q} mismatching is greater during heavy exercise than at rest (8, 56), but the effect of this increase in inequality on P_{aO_2} is mitigated by the well-known increase in overall lung \dot{V}_A/\dot{Q} ratio. Thus, because alveolar ventilation increases relatively more than does cardiac output (\dot{Q}) during exercise, the \dot{V}_A/\dot{Q} distribution is shifted to a higher range of \dot{V}_A/\dot{Q} ratios, thereby raising alveolar and thus arterial P_{O_2} . Consequently, the magnitude of the $A\text{-}a\text{D}O_2$ component attributable to \dot{V}_A/\dot{Q} inequality remains essentially constant from rest to exercise (56). Why \dot{V}_A/\dot{Q} mismatch increases with exercise is addressed below.

At or near $\dot{V}_{O_{2max}}$, 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_{aO_2} that would be expected if only \dot{V}_A/\dot{Q} inequality and intrapulmonary shunts existed. If this prediction statistically matches measured values for P_{aO_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_{aO_2} than predicted by MIGET (11), whether or not \dot{V}_A/\dot{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_{aO_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 $A\text{-}a\text{D}O_2$ (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 $A\text{-}a\text{D}O_2$ (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 \dot{Q} and have little impact on P_{aO_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_{aO_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 $A\text{-}a\text{D}O_2$, the reduction in mixed venous P_{O_2} that normally accompanies exercise acts to further lower P_{aO_2} . Mixed venous P_{O_2} falls because

\dot{V}_{O_2} increases relatively more than \dot{Q} from rest to exercise. The effect is to cause more diffusion limitation and also to reduce end-capillary PO_2 in regions of the lung where low \dot{V}_A/\dot{Q} ratios exist (59). Because mixed venous PO_2 commonly drops from ~ 40 Torr at rest to 20 Torr during heavy exercise, the effect is considerable.

In summary, both diffusion limitation and greater \dot{V}_A/\dot{Q} mismatch contribute to the increased A-a $\dot{D}O_2$ during exercise. The contribution of \dot{V}_A/\dot{Q} inequality to the A-a $\dot{D}O_2$ is generally constant from rest to $\dot{V}O_{2max}$, 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-a $\dot{D}O_2$ at or near $\dot{V}O_{2max}$ (52). The reduced mixed venous PO_2 further reduces Pa_{O_2} , but both intrapulmonary and extrapulmonary shunts appear to be negligible.

Mechanism of Increase in \dot{V}_A/\dot{Q} Inequality With Exercise

Why \dot{V}_A/\dot{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 \dot{V}_A/\dot{Q} mismatch beyond the time required for ventilation and \dot{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 $D/(\beta\dot{Q})$, where D is lung diffusing capacity and β is the mean slope of the conceptually linear O_2 -Hb dissociation curve in the physiological range. With D in $ml \cdot min^{-1} \cdot Torr^{-1}$, β in $ml O_2 \cdot l \text{ blood}^{-1} \cdot Torr^{-1}$, and \dot{Q} in l/min , when $D/(\beta\dot{Q})$ is 4.6, diffusion equilibration would be 99% complete; $D/(\beta\dot{Q}) = 3.0$ allows 95% equilibration; and $D/(\beta\dot{Q}) =$

1.0 allows only 63% equilibration. Whereas all three components (D , β , and \dot{Q}) increase on exercise, $D/(\beta\dot{Q})$ falls. This fall can be accentuated by limited gains in overall D (possibly from \dot{V}_A/\dot{Q} mismatching or from alveolar interstitial edema) or by greater than average increases in β and \dot{Q} . Athletes typically exhibit a high \dot{Q} and also high O_2 extraction from blood perfusing muscles. Because high O_2 extraction increases β by increasing the average slope of the O_2 -Hb curve in the working range, athletes in particular are subject to greater reduction in $D/(\beta\dot{Q})$ 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 \dot{Q} . Recent evidence suggests that subjects with more exercise-induced hypoxemia at a given $\dot{V}CO_2$ 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 O_2 extraction, and high \dot{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 O_2 transport and $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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-a $\dot{D}O_2$ 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 O_2 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 \dot{V}_A and/or \dot{Q} during exercise.

CONSEQUENCES OF EIAH

EIAH Effects on $\dot{V}O_{2max}$

The effect of EIAH on $\dot{V}O_{2max}$ has been demonstrated in a limited number of studies in fit humans and horses by adding sufficient O_2 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 Sa_{O_2} and Ca_{O_2} at resting levels, differs substantially from the more common use of much higher concentrations of inspiratory

O₂ fraction (F_IO₂; >0.50), because at Pa_{O₂} >500 Torr Ca_{O₂} is actually increased 15% or more above resting levels, rather than being maintained, so that a nonphysiological hyperoxia rather than normoxic condition is sustained throughout exercise. The results of the EIAH prevention studies in humans are consistent in showing that EIAH will reduce $\dot{V}O_{2\max}$, at least in trained subjects. The threshold of desaturation at which this effect is measurable is somewhat variable among subjects, but a consistent effect appears to be initiated at ~3–4% O₂ desaturation below resting levels. These threshold values are similar to those found when arterial hypoxemia was caused experimentally via increased inspiratory CO fraction or reduced F_IO₂ (19, 28, 57). The further reduction of $\dot{V}O_{2\max}$ beyond this threshold of desaturation changes linearly with Sa_{O₂} (and Ca_{O₂}) such that $\dot{V}O_{2\max}$ is affected by >20% in the Thoroughbred horse, which normally desaturates to 80% Sa_{O₂} or below (Fig. 1), and up to ~15% in the human, who desaturates to a maximum of 85–90% Sa_{O₂} at $\dot{V}O_{2\max}$ (see Fig. 2). The majority of the effect of preventing EIAH on $\dot{V}O_{2\max}$ occurs because $\dot{V}O_2$ is increased at a given high-intensity work rate. Thus preventing EIAH removes the plateau effect of $\dot{V}O_2$ 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, Ca_{O₂}, and O₂ extraction, is the important limiting factor to $\dot{V}O_{2\max}$ in healthy subjects, as opposed to the metabolic capacity of the muscle mitochondria (see Ref. 57 for review). This critical dependence of $\dot{V}O_{2\max}$ on O₂ transport may only apply to normal or highly trained subjects, whereas the $\dot{V}O_{2\max}$ in the extremely sedentary subject or animal may not be O₂ supply dependent (4, 23).

EIAH becomes an especially important determinant of $\dot{V}O_{2\max}$ in hypoxic environments, particularly in the highly trained athlete, who usually suffers the greatest decrement in $\dot{V}O_{2\max}$ at high altitudes (10, 28). Thus even relatively small decrements in inspired PO₂ (for example to 120–130 Torr or ~1,000 m altitude), which would not be expected to influence Sa_{O₂} or $\dot{V}O_{2\max}$ 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 $\dot{V}O_{2\max}$ 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 PO₂ (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 $\dot{V}O_{2\max}$

The effect of EIAH on $\dot{V}O_{2\max}$ is fairly predictable based solely on the reduction in Sa_{O₂} and Ca_{O₂} 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 Ca_{O₂} has not been documented directly with studies that have prevented EIAH but has been shown when Ca_{O₂} 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 PO₂ difference between red blood cells and mitochondria. EIAH will lower microvascular PO₂ 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 $\dot{V}O_{2\max}$ directly to an impairment of O₂ delivery to the working locomotor muscles because of reduced Ca_{O₂}; 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 relief of this hypoxemia may increase myocardial O₂ supply, force of ventricular contraction, and \dot{Q} (36). A companion concept requiring further testing is that changes in Ca_{O₂} affect limb blood flow inversely with the change in Pa_{O₂}, thereby resulting in no net change in O₂ transport to the working limb (58). Any resulting change in $\dot{V}O_{2\max}$ is attributable, then, to differences in the $\dot{V}O_2$ of nonexercising tissue, such as hypoperfused splanchnic tissue. Finally, an important related question concerns the effect of EIAH on exercise performance per se, rather than on $\dot{V}O_{2\max}$, two outcome measurements that are sometimes (but not always) closely related (35, 36). Hyperoxic O₂ supplementation studies usually show a concomitant effect on exercise performance, but these effects may be substantially less than on $\dot{V}O_{2\max}$ (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 \dot{V}_A/\dot{Q} 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 O_2 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 \dot{V}_A/\dot{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 $\dot{V}O_{2\max}$. 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 arterial hypoxemia limits $\dot{V}O_{2\max}$ or exercise performance. Is the elusive concept of a "critical PO_2 " in the muscle capillary or mitochondria for ATP generation valid or worthwhile?... and, specifically, what organ system involved directly or indirectly with O_2 transport is most vulnerable and, therefore, primarily responsible for the limitation of $\dot{V}O_{2\max}$ in the presence of EIAH?

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