Respiratory System Limitations to Performance in the Healthy Athlete: Some Answers, More Questions!

The respiratory system contributes in three major ways to limitations in arterial O₂ content and/or blood flow during high-intensity exercise, namely: 1) exercise-induced arterial hypoxemia (EIAH) which occurs to a highly variable extent among highly trained male and female runners; 2) intrathoracic pressure effects on stroke volume; and 3) metaboreflex effects from respiratory muscle fatiguing contractions which activates sympathetic vasoconstrictor outflow and reduces locomotor muscle vascular conductance and blood flow. The consequences of these respiratory-linked limitations on limb fatigue were studied using supramaximal magnetic stimulation of the femoral nerve before and following endurance exercise. To determine the influence of these limitations on fatigue and performance, we prevented their occurrence by using supplemental FIO₂ (for hypoxemia) and mechanical ventilator support to reduce intrathoracic pressures. The effects of each respiratory limitation on O₂ transport negatively impacted VO₂max and increased the accumulation of muscle metabolites and the development of locomotor muscle fatigue, leading to feedback inhibition of central motor command and impacting endurance performance. We summarize the evidence which has examined the underlying causes as well as the consequences of these respiratory system limitations, with an emphasis on unresolved problems and contradictions.

Key Words: Hypoxemia, fatigue, respiratory muscles, metaboreflexes.

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tissue oxygenation was considered to be uncompromised. (41). However, we suggest that muscle tissue temperature changes better approximate muscle venous effluent than arterial blood temperatures and that a more appropriate means of testing the importance of any reduction in arterial PO$_2$ and SaO$_2$ is to prevent their reduction (via increased FIO$_2$) and to determine the effects on VO$_{2\text{MAX}}$, fatigue and/or performance (see above).

Although a true population prevalence of EIAH is not yet available from studies with appropriately measured arterial blood gases, it appears as though EIAH occurs in a minority of endurance trained athletes and is most common during treadmill running than cycling. Furthermore, two longitudinal studies also showed that training-induced increases in VO$_{2\text{MAX}}$ were accompanied by HbO$_2$ desaturation (31, 40). Finally, we also know that the major cause of the reduced PaO$_2$ is an excessively widened alveolar to arterial O$_2$ difference, with some of the more severe cases of EIAH showing a minimal or no hyperventilatory response during heavy exercise (11, 16, 23, 51) – see Figures 1 and 2.

Among athletic, non-human species with VO$_{2\text{MAX}}$ more than double that of the fittest humans, only the thoroughbred horse (mean VO$_{2\text{MAX}}$ > 160 ml/kg/min) consistently demonstrates substantial exercise-induced arterial hypoxemia with widened A-aDO$_2$, marked CO$_2$ retention and extreme pulmonary hypertension during treadmill running (9). Preventing EIAH in this species (via increased FIO$_2$) elicited an average 30 % increment in VO$_{2\text{MAX}}$ (49), i.e. about twice that observed in humans with the most severe EIAH (17). Clearly, the thoroughbred’s lung is truly under built to meet their huge demands for cardiac output, ventilation, O$_2$ and CO$_2$ transport during heavy intensity exercise. This consistent occurrence of EIAH among equine thoroughbreds contrasts sharply with its marked variability among highly trained humans (see below).

Thus far, this brief account has summarized what we know in regard to EIAH and its consequences. Now we deal with the many problems and unknowns.

**DEMAND VS. CAPACITY?**

The variability in EIAH among highly fit athletes – both men and women – is substantial, as many of these athletes show absolutely no change in PaO$_2$ from resting levels even at VO$_{2\text{MAX}}$ greater than 1.5 to 2 times those in the untrained, whereas others show reductions in SaO$_2$ in the 85-91 % range (see examples for progressive and sustained work loads during treadmill running in Figs. 1 and 2 and time trial cycling in Fig. 3). EIAH is highly reproducible between repeat trials. We and others (11,23,40) originally proposed that EIAH was likely the consequence of the net effects of a high demand for pulmonary O$_2$ transport because of the extraordinary capacities of the cardiovascular system and locomotor muscles in trained subjects to elicit a high VO$_{2\text{MAX}}$, combined with an alveolar; capillary diffusion surface, airways and pulmonary vasculature in the trained athlete which are not superior in capacity to those in the untrained. However, it is now clear – and should have been to us thirty years ago – that most subjects who experience EIAH during max exercise begin to develop hypoxemia in submaximal exercise. So while an alleged inferior “maximum (respiratory system) capacity” vs. “maximum demand” in the highly trained may still be relevant to explain why EIAH worsens near peak exercise, this theory does not account for the EIAH observed during submaximal exercise intensities and the very high inter-individual variability of its occurrence (11,16,33,36,51,52).

*Figure 1: Mean changes in arterial blood gases during progressive exercise to VO$_{2\text{MAX}}$ in female subjects divided into three groups based on their fall in PaO2 at VO$_{2\text{MAX}}$ from resting values (age 18-42 years, VO$_{2\text{MAX}}$ 31 - 70 ml/kg/min, n=29). Group 1 (n=7), <-10mmHg ∆PaO$_2$ (●, continuous line); group 2 (n=7), 11-20mmHg (▲, dashed line); group 3 (n=15), >-20mmHg (▲, dotted line). Note that in the most hypoxemic group 3, SaO$_2$ fell from 96.7±0.1 % at rest to 90.4±0.2 % at maximal exercise; 42 % of the fall in SaO$_2$ was due to the fall in PaO$_2$, and 58 % of the desaturation was due to rightward shift of the HbO$_2$ dissociation curve because of increasing acidity and temperature. Values are means±s.e.m.; *denotes group 3 mean value significantly different from groups 1 and 2, P<0.05. Adapted from Harms et al. (16).*
MECHANISMS OF THE VARIABILITY IN THE EXCESSIVE A-aDO\textsubscript{2} AND/OR INADEQUATE HYPERVENTILATION?

A diffusion limitation (i.e. end capillary \textsubscript{O}2 disequilibrium) has been commonly cited as the cause of the excessively widened A-aDO\textsubscript{2} with exercise. In turn, this is believed to be secondary to an extraordinarily high cardiac output (and pulmonary blood flow) in combination with a normally expanded pulmonary capillary blood volume, thereby leading to critically shortened red cell transit times and alveolar to end-pulmonary capillary \textsubscript{O}2 disequilibrium (11, 40). Furthermore, it was argued that even very small inter-individual differences in one’s maximal achievable pulmonary capillary blood volume (at high cardiac output) could likely explain much of the inter-individual variability in A-aDO\textsubscript{2} (10, 11). However, with the occurring onset of EIAH in submaximal exercise in most subjects, a diffusion disequilibrium is highly unlikely; furthermore, use of an animal model (to allow manipulation of perfusion rates) has shown that even in the face of extremely high blood flows and shortened red cell transit times, \textsubscript{O}2 disequilibrium is unlikely – at least when V:Q distribution is uniform (7). Evidence obtained using broncho-alveolar lavage shows that pulmonary edema does exist during max exercise in some highly trained subjects (12, 21) but the findings that repeated max exercise bouts result in small, significant improvements - rather than decrements – in alveolar to arterial gas exchange in subjects with EIAH (45) speaks against this edema or disruption of the alveolar-capillary barrier as a cause of the impaired gas exchange.

Recent evidence supports an exercise-induced opening of intrapulmonary shunts (13,24) (via extra-numerary pathways) (48), but we do not yet know the magnitude of these shunts (in vivo) or how they might influence gas exchange. If the proposed shunts do indeed contain the markedly deoxygenated mixed venous blood present in heavy exercise (\textsubscript{P}\textsubscript{SV}O\textsubscript{2}~15 mmHg, \textsubscript{S}vO\textsubscript{2} 14% (19)), then even shunts in the range of 2-3% of cardiac output could account for much of the unexplained widening of A-a\textsubscript{DO\textsubscript{2}} – and maybe even the inter-subject variability in EIAH. Exercise-induced airway inflammation was also proposed as a cause of EIAH in older athletes (35) but Wetter et al. (52) observed no effect on gas exchange during heavy exercise of blocking airway inflammatory mediators in young female athletes with EIAH. Consistent with these negative findings, it was also observed that exercise-induced widening of A-a\textsubscript{DO\textsubscript{2}} occurred at the onset of prolonged heavy constant load exercise with no further changes as exercise continued to exhaustion (see Fig 2).

Opinions as to why some athletic subjects inadequately hyperventilate i.e. fail to raise alveolar \textsubscript{P}O\textsubscript{2} sufficiently to compensate for widening of the A-a\textsubscript{DO\textsubscript{2}}, are divided between a mechanical constraint on the ventilatory response because of expiratory flow limitation and a suppressed sensitivity to the locomotor drives to breathe and/or chemoreceptor stimuli. Certainly both mechanisms might operate simultaneously (23). Evidence is also accumulating that young adult female athletes are more susceptible to expiratory flow limitation at high ventilatory demand, primarily because of their reduced airway diameters at any given lung volume i.e. so called airway dysanapsis (25,27,44).

Figure 2: Individual and mean arterial blood-gas data at rest and during constant load treadmill running exercise at ~90% \textsubscript{VO\textsubscript{2MAX}} exercise to exhaustion in trained female runners (age 19-44 years, \textsubscript{VO\textsubscript{2MAX}} 44-60 ml/kg/min, n=17). Data for Lo-\textsubscript{PO\textsubscript{2}} group (n=8); ○, data for Hi-\textsubscript{PO\textsubscript{2}} group (n=9); For individual data, thin solid lines represent subjects in Lo-\textsubscript{PO\textsubscript{2}}, gp and dotted lines represent subjects in Hi-\textsubscript{PO\textsubscript{2}} gp. Thick lines join gp mean values. Values are means±SD. *Significant difference between groups (P<0.05). Time effect was significant (P<0.001) for all variables except A-a\textsubscript{DO\textsubscript{2}} (P=0.015). Adapted from Wetter et al. (51).

Reducing respiratory muscle work via mechanical ventilation during heavy sustained exercise prevents fatigue of the diaphragm (8), increases limb vascular conductance and limb blood flow (15,19) and reduces the rate of development of limb fatigue (39), and improves endurance performance (3,17). Evidence in
animals (20,38) points to a (heavy) exercise-induced respiratory muscle metaboreflex transmitted via phrenic afferents which activates sympathetically mediated vasoconstrictor activity. The beneficial effects of reducing the work of breathing (WOB) in health at sea level occurred only during heavy intensity exercise (> 80% max); but these cardiovascular effects of reducing the WOB have also been observed at much lower workloads in patients with COPD (4) and CHF (34) and in acute hypoxia in healthy subjects (3). Unlike EIAH, these effects of WOB seem to occur consistently among healthy, fit subjects. However several key questions remain.

- What mechanisms activate the type III – IV respiratory muscle afferents? Is an imbalance between O$_2$ supply and demand to the respiratory muscles required?...or is simply rhythmic contractions with increased blood flow and vascular distension a sufficient "signal" for activation (14)? Outright "fatigue" of the diaphragm and/or respiratory muscles might be required for sympathetic activation (42,43,46). In this regard it is of interest to note the recent use of novel phrenic nerve stimulation techniques in humans to show that significant diaphragm fatigue begins to develop relatively early and well in advance of exercise termination during trials of heavy intensity sustained exercise (50). Finally, does the activation of group III – IV muscle afferents always coincide with increased sympathetic vasoconstrictor activity?

- We presume, with only limited evidence (reported in the exercising rat with heart failure (32)), that increased respiratory muscle work causing reduced limb blood flow in the human means that diaphragm blood flow must have increased. Recent attempts have used dye infusion combined with near infrared spectroscopy to assess intercostal muscle blood flow in the exercising human but it remains unknown whether this technique is sensitive and specific enough – especially during the hyperpnea of exercise – to detect small shifts in flow (6).

- How might the diaphragm be spared from sympathetic induced vasoconstriction in the face of respiratory muscle metaboreflex activation? Studies in isolated phrenic (vs. gastrocnemius muscle) arterioles suggests that the former are much less sensitive to norepinephrine induced vasoconstriction (1). We do not yet know if these functional changes might be explained by differences in the relative densities of adrenergic receptors on the various muscle vascularatures.

- There are limited data to support the reasoning that specific respiratory muscle training might delay diaphragm fatigue, thereby preventing (or delaying) metaboreceptor activation and associated vasoconstriction of the limb musculature (22,26). However, this hypothesis needs further testing to determine whether training-induced alterations in respiratory muscle fatigability will change blood flow distribution during whole body exercise.

**INTRATHORACIC PRESSURES AND CARDIAC OUTPUT**

This is the respiratory limitation that has been the most difficult to evaluate during exercise. To date, in exercising humans and dogs, reducing the negativity of inspiratory intrapleural pressure reduces right ventricular preload and stroke volume in health (19). On the other hand, increasing expiratory threshold pressure reduces stroke volume – presumably because left ventricular afterload is increased thereby reducing transventricular pressure differences which would slow the rate of ventricular filling during diastole (28,47). Further, increasing abdominal vs. intrathoracic pressures with predominantly diaphragm vs. ribcage inspirations, respectively, has marked cyclical effects on femoral venous return from the limbs at rest and even during mild intensity leg exercise (29). Understanding how the cardiovascular effects of isolated alterations in pressures during various phases of the respiratory cycle translate into the complex effects of breathing during whole body exercise will be a formidable task – especially in the elite athlete ventilating in excess of 150 l/min who experiences expiratory flow limitation, positive expiratory pressures which often exceed the critical closing pressure of the airways and hyperinflation with inspiratory pressures that are approaching the limits of the dynamic capacity of the inspiratory muscles (23). Equally intriguing and clinically relevant is

![Figure 3: Power output and arterial blood gases group and mean esophageal temperature and arterial pH during a 5k cycling time trial (time=8.1±0.1 mins) in eight trained young adult male cyclists (VO$_{2\text{MAX}}$=63±1 ml/min/kg). Note that four of the eight trained cyclists developed significant EIAH (SaO$_2~87-90\%$) due primarily to the developing metabolic acidosis (lactate = 10 to 15 mmol • l$^{-1}$) and secondarily to the reduction in PaO2. When this O2 desaturation was prevented and maintained at resting levels (via FFIO2), mean power output (+6%) and time trial performance (+3%) were improved and the rate of development of quadriceps fatigue during the trial was reduced. Adapted from Amann et al. (2).](image-url)
the need to explain why reducing the magnitude of negative italics pressure on inspiration increases stroke volume and cardiac output in a dose dependent manner in heart failure animals (30) and hu-
mans (34) during exercise – effects which are in the opposite direc-
tion to those in the healthy subject.

CONCLUSIONS

We have discussed the role of pulmonary gas exchange and cardio-
respiratory interactions in exercise limitation in the highly trained.
Although some progress has been made in understanding the im-
pact and mechanisms underlying each of these limitations, several
fundamental, difficult to study questions remain. For example, the
mechanisms underlying even the normal exercise-induced wide-
ning of A-a\textsubscript{DO\textsubscript{2}} remain controversial; hence the causes of an ex-
cessive and highly variable A-a\textsubscript{DO\textsubscript{2}} leading to significant EIAH in
a minority of highly trained athletes have not been forthcoming.
High levels of respiratory muscle work, as incurred in high intensi-
sity sustained exercise, appear to influence locomotor muscle blood
flow– but the factors that trigger the responsible metaboreflex and
resultant selective sympathetic vasoconstriction are unclear. Fur-
thermore, we have just barely begun to describe the influence of
respiratory-induced intrathoracic and intra abdominal pressures
on cardiac output in the intact exercising human. Quantitatively,
cardiovascular limitations to VO\textsubscript{2\text{MAX}} and endurance performance
dominate those attributable to a healthy respiratory system. How-
ever, we also note the growing evidence that respiratory system limi-
tations to gas exchange and/or blood flow will likely play a more
significant and consistent role in certain highly fit groups, such as
females, the aged and asthmatics and especially when heavy-inten-
sity exercise is attempted in even mildly hypoxic environments at
high altitudes.

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LITERATURE

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