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

Das Atemsystem schränkt die Leistung eines gesunden Athleten ein: Einige Antworten, noch mehr Fragen!

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ZUSAMMENFASSUNG

Das respiratorische System begrenzt den arteriellen Sauerstoffgehalt und/oder den Blutfluss während hochintensiven Belastungen auf drei unterschiedliche Weisen: 1.) belastungsinduzierte arterielle Hypoxämie (EIAH), die bei hochtrainierten männlichen und weiblichen Läufern verbreitet ist; 2.) Effekte von intrathorakalen Druckänderungen auf das Schlagvolumen; und 3.) metabolisch-reflektorisch bedingte Effekte von Atemmuskulatur-ermüdenden Kontraktionen welche konsekutiv zu einer vegetativ bedingten Vasokonstriktion führt und die Gefäßleitfähigkeit und den Blutfluss in der Bewegunsgmuskulatur reduziert. Die Folgen dieser atemabhängigen Limitationen auf die Ermüdung der Extremitäten wurden durch eine supramaximale Magnetstimulation des Femoralnervs vor und nach Ausdauerbelastung untersucht. Um den Einfluss dieser Limitationen auf Erschöpfung und Leistung zu bestimmen, wurde das Auftreten durch Steigerung des O_2-Anteils (um die arterielle Hypoxämie zu reduzieren) und eine mechanische Atemunterstützung verhindert (um den intra-thorakalen Druck zu reduzieren). Der Effekt jeder einzelnen respiratorischen Limitation am Sauerstofftransport wirkte sich negativ auf die $\dot{V}O_{2max}$ aus und führte zu einer Anhäufung von Muskelmetaboliten sowie zu einer Ermüdung der Bewegungsmuskulatur. Dies führte über eine Rückkopplung zu einer Blockade der zentral motorischen Steuerung und beeinflusste dadurch die Ausdauerleistungsfähigkeit. Weiterhin werden die Gründe für die Ursachen sowie die Folgen von den atemabhängigen Limitationen zusammen gefasst, zudem werden die ungelösten Probleme und Widersprüche herausgestellt.

Schlüsselwörter: Hypoxämia, Ermüdung, Atemmuskulatur, Metaboreflexe.

SUMMARY

The respiratory system contributes in three major ways to limitations in arterial O_2 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 FIO_2 (for hypoxemia) and mechanical ventilator support (to reduce intra-thoracic pressures). The effects of each respiratory limitation on O_2 transport negatively impacted $\dot{V}O_{2MAX}$ 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.

EXERCISE-INDUCED ARTERIAL HYPOXEMIA

Reductions in arterial O_2 desaturation in excess of 3-4% below resting levels are usually due to a combination of a > 10-15 mmHg reduction in PaO_2 plus an acidity / temperature induced rightward shift in the HbO_2 disassociation curve. Preventing these reductions in SaO_2 (via small increments in FIO_2) will increase peak work rate and $\dot{V}O_2$ by ~ 3-15% i.e. in proportion to the degree of O_2 desaturation incurred breathing room air (17), reduce limb fatigue and enhance exercise performance (2,5). Even in the face of O_2 desaturation the CaO_2 during exercise might approximate that at rest because of the concomitant increase in Hb content due to exercise-induced hemoconcentration; thus EIAH prevents what would otherwise be

an increase in CaO_2 (11,40). A recent study confirmed that PaO_2 was reduced during exercise in many athletes when blood gas measurements were corrected to the measured esophageal temperature but were unchanged from rest when corrected to intramuscular temperature changes. These findings were interpreted to mean that EIAH was of no consequence to O_2 transport, apparently because muscle

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 $\dot{V}O_{2MAX}$, 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 $\dot{V}O_{2MAX}$ 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 (11,16,18,23,51) – see Figures 1 and 2.

Among athletic, non-human species with $\dot{V}O_{2MAX}$ more than double that of the fittest humans, only the thoroughbred horse (mean $\dot{V}O_{2MAX} > 160$ 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 $\dot{V}O_{2MAX}$ (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 $\dot{V}O_{2MAX}$s gre-
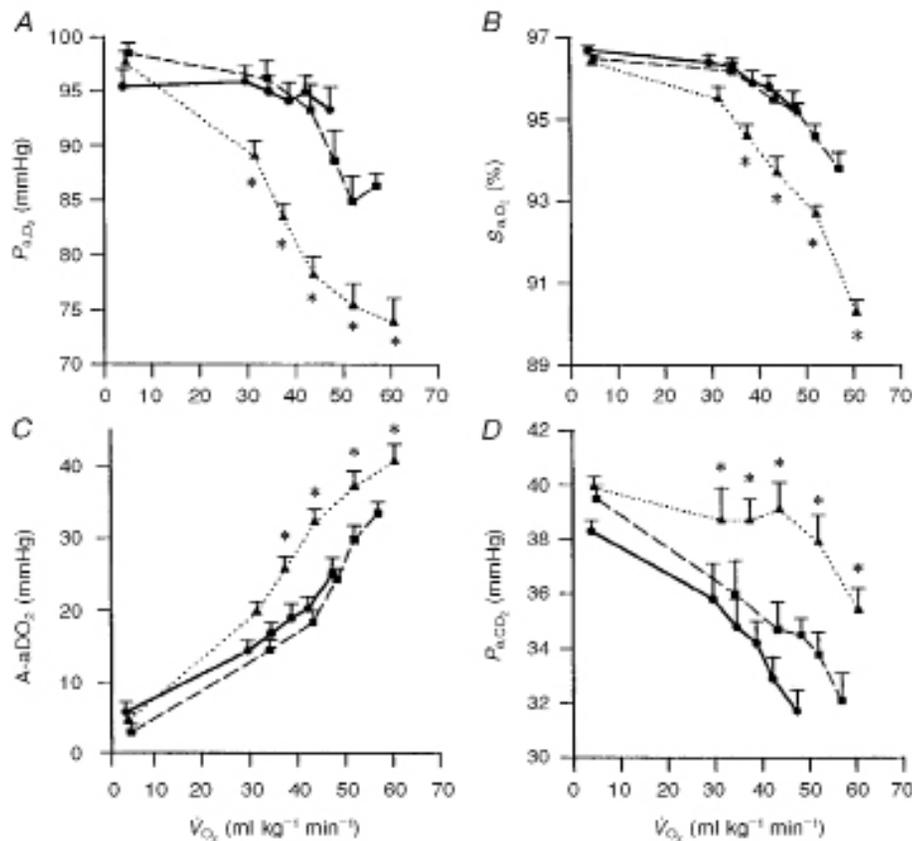
Figure 1: Mean changes in arterial blood gases during progressive exercise to $\dot{V}O_{2MAX}$ in female subjects divided into three groups based on their fall in PaO2 at $\dot{V}O_{2MAX}$ from resting values (age 18-42 years, $\dot{V}O_{2MAX}$ 31-70 ml/kg/min, n=29). Group 1 (n=7), <-10 mmHg ΔPaO_2 (●, continuous line); group 2 (n=7), 11-20 mmHg (■, dashed line); group 3 (n=15), >-20 mmHg (▲, 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).

ater 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 $\dot{V}O_{2MAX}$, 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 (11,16,33,36,37,51,52).

MECHANISMS OF THE VARIABILITY IN THE EXCESSIVE A-aDO₂ AND/OR INADEQUATE HYPERVENTILATION?

A diffusion limitation (i.e. end capillary O_2 disequilibrium) has been commonly cited as the cause of the excessively widened A-aDO₂ with exercise. In turn, this is believed to be secondary to a 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 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-aDO₂ (10,11). However, with the occuring 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, 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 fin-dings 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 (PⱴO₂~ 15 mmHg, SⱴO₂ 14 % (19)), then even shunts in the range of 2-3% of cardiac output could account for much of the unexplained widening of A-aDO₂ – 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-aDO₂ 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 PO_2 sufficiently to compensate for widening of the A-aDO₂, 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).

BREATHING MECHANICS AND BLOOD FLOW DISTRIBUTION

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
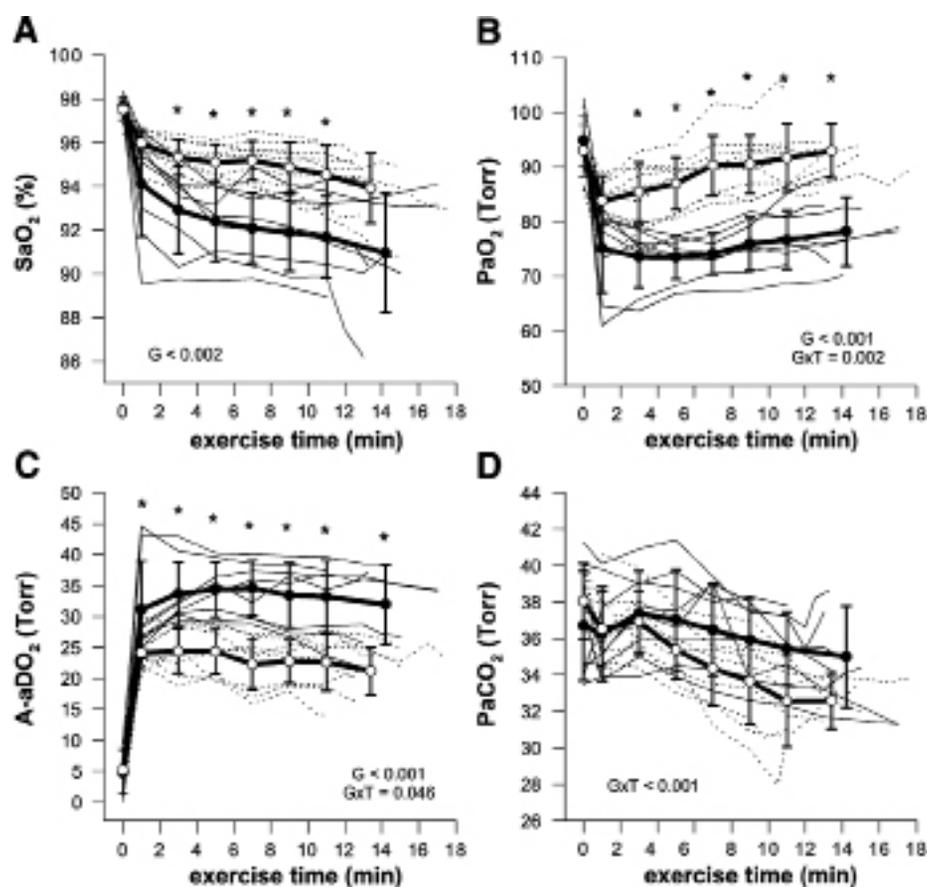
Figure 2: Individual and mean arterial blood-gas data at rest and during constant load treadmill running exercise at ~ 90 % V̇O₂MAX exercise to exhaustion in trained female runners (age 19-44 years, V̇O₂MAX 44-60 ml/kg/min, n=17). ●, Data for Lo-PO₂ group (n=8); ○, data for Hi-PO₂ group (n=9); For individual data, thin solid lines represent subjects in Lo-PO₂ gp and dotted lines represent subjects in Hi-PO₂ 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-aDO₂ (P=0.015). Adapted from Wetter et al. (51).

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 expiratory 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 vasculatures.

- 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,
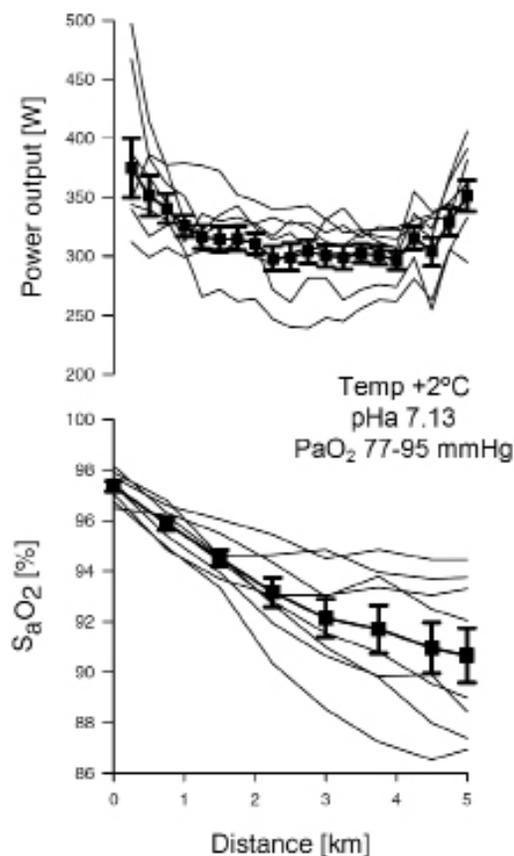
Figure 3: Power output and arterial blood gases group and mean esophageal temperature and arterial pH during a 5k cycling time trial (time=8.1±0.1 mins) in eight trained young adult male cyclists ($\dot{V}O_{2MAX}$=63±1 ml/min/kg). Note that four of the eight trained cyclists developed significant EIAH (SaO_2 ~87-90%) due primarily to the developing metabolic acidosis (lactate = 10 to 15 mmol • l) and secondarily to the reduction in PaO2. When this O2 desaturation was prevented and maintained at resting levels (via ↑FIO2), 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).

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

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 humans (34) during exercise – effects which are in the opposite direction 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 impact and mechanisms underlying each of these limitations, several fundamental, difficult to study questions remain. For example, the mechanisms underlying even the normal exercise-induced widening of A-aDO$_2$ remain controversial; hence the causes of an excessive and highly variable A-aDO$_2$ 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 intensity sustained exercise, appear to influence locomotor muscle blood flow– but the factors that trigger the responsible metaboreflex and resultant selective sympathetic vasoconstriction are unclear. Furthermore, 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 $\dot{V}O_{2MAX}$ and endurance performance dominate those attributable to a healthy respiratory system. However, we also note the growing evidence that respiratory system limitations 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-intensity exercise is attempted in even mildly hypoxic environments at high altitudes.

ACKNOWLEDGEMENTS

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