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Respiratory limitations to exercise in health: a brief review

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Although the lungs are traditionally considered to be overbuilt for exercise in healthy individuals, respiratory-related limitations to exercise have been identified. First, during exercise most humans develop an impairment in pulmonary gas-exchange, which can lead to a reduction in maximal oxygen uptake ($\dot{V}O_{2max}$). Second, ventilatory constraint, specifically expiratory flow limitation and dynamic hyperinflation, have been shown to impair exercise performance. Lastly, respiratory muscle fatigue and/or large increases in work of breathing can negatively affect exercise performance by triggering a sympathetic-mediated increase in vasoconstriction of the locomotor vasculature, which decreases locomotor muscle O_2 delivery. In this review, we provide a brief overview of these limitations to exercise, and examine recent advances in the field. In addition, relevant new work around sex-differences in these limitations to exercise will be examined.

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Introduction

Historically, the respiratory system was generally considered overbuilt for exercise in healthy individuals, with respect to its capacity to meet the maximal metabolic demands of exercise. However, it is now evident that respiratory limitations to exercise performance are present in young healthy individuals. This brief review will examine recent advances in three key respiratory-related limitations to exercise in health; 1) pulmonary gas-exchange impairment, 2) expiratory flow limitation and dynamic hyperinflation, and 3) respiratory muscle fatigue and sympathetic-mediated blood flow distribution. In addition, relevant new work around sex-differences in these limitations to exercise will be detailed.

Pulmonary gas-exchange

During incremental exercise, most humans develop an impairment in pulmonary gas-exchange, as determined by a widened alveolar-arterial difference (A-aDO_2). A-aDO_2 has been shown to be a primary contributor to exercise-induced arterial hypoxemia (EIAH), defined as a decrease in PaO_2 and/or the O_2 saturation of hemoglobin in arterial blood with exercise [1,2]. Substantial EIAH (i.e. >4–5% decrease in O_2 saturation from rest), can result in a reduction in maximal oxygen uptake ($\dot{V}O_{2max}$) [1,3,4] and therefore this represents an important potential limitation to exercise. The determinants of A-aDO_2 are ventilation-perfusion matching ($\dot{V}_A/\dot{Q}$), diffusion limitation, and shunt, and greater background is available in previous reviews [1,2].

During moderate to heavy exercise, $\dot{V}_A/\dot{Q}$ mismatch accounts for most of the increase in A-aDO_2 [5,6]. As exercise intensity approaches $\dot{V}O_{2max}$, diffusion limitation becomes the predominant contributor to the widened A-aDO_2, and is most common in highly fit individuals exercising near peak exercise (>~60 ml/kg/min) [6,7]. The mechanism of increased $\dot{V}_A/\dot{Q}$ mismatch during exercise is not certain, however, previous research has suggested interstitial pulmonary edema secondary to high pulmonary vascular pressures during exercise [5,8]. Interstitial edema would distort the surrounding architecture (i.e. alveoli and capillary network) and thus lead to a deterioration of $\dot{V}_A/\dot{Q}$ matching [5,9]. Altered diameter of the airways and blood vessels, secondary to the presence of edema-related cuffing, would negatively affect distribution of ventilation and perfusion, leading to areas of both low and high $\dot{V}_A/\dot{Q}$, respectively, within the lung [10]. Further, alveolar interstitial fluid may alter local lung compliance, which could lead to further impairments of airflow distribution, resulting in areas of low $\dot{V}_A/\dot{Q}$ and ultimately increased A-aDO_2 [10]. There is a large amount of evidence demonstrating that $\dot{V}_A/\dot{Q}$ mismatch is increased with exercise [5,6,8,9] and sustained in recovery [11], which is consistent with the development of edema during exercise. Additionally, previous work has suggested that $\dot{V}_A/\dot{Q}$ mismatch is potentiated during exercise with hypoxia [12], which may be secondary to the development of edema and/or hypoxic pulmonary vasoconstriction [12].

Previous work, using right heart catheterization, has shown that endurance-trained subjects demonstrate enhanced left ventricular compliance when compared to untrained individuals [13,14]. These data would suggest that the enhanced cardiac function in endurance-trained subjects may act to limit the rise in pulmonary vascular pressures with exercise and thus reduce the risk of edema [14–16]. While exercise-induced edema secondary to high pulmonary vascular pressure is a popular theory, to-date no study has directly linked anatomical evidence of edema with $\dot{V}_A/\dot{Q}$ mismatch quantified by the multiple inert gas elimination technique (MIGET). Techniques to increase accuracy of identifying edema during exercise (with simultaneous measurements of pulmonary gas exchange) are required to better support the hypothesis of edema as a cause of exercise-induced $\dot{V}_A/\dot{Q}$ mismatch.

The mechanism for the development of diffusion limitation during exercise is not well known; however, it has been hypothesized that diffusion limitation may be due to the development of edema, and/or inadequate pulmonary transit time [1,6,17]. With the increased oxygen consumption during exercise, the pulmonary diffusing capacity must increase in order to maintain gas exchange and limit the increase in A-aDO_2. While endurance-trained athletes show enhanced cardiovascular function compared to untrained individuals, it is generally accepted that exercise training has no effect on lung function or structure [18–20], and therefore a diffusion limitation may develop at high work rates because of an inability to increase diffusing capacity sufficiently to meet metabolic demand.

Two important determinants of diffusing capacity are pulmonary capillary blood volume (Vc) and diffusing membrane capacity (Dm). As pulmonary arterial pressure increases with exercise, Vc increases secondary to capillary recruitment and distension. With greater capillary recruitment, Dm is increased as more capillaries are perfused [2,21]. The recruitment and distension of pulmonary capillaries also aid to reduce pulmonary vascular resistance and mitigate the increases in pulmonary artery pressure typically observed during high-intensity exercise [14,22]. Lalande *et al.* recently demonstrated that a high $\dot{V}O_{2max}$ is associated with a greater resting Vc [23]. Similarly, Zavorsky and Smoliga found a positive correlation between resting diffusing capacity for carbon monoxide (DLCO) and $\dot{V}O_{2max}$ in young healthy individuals [24•]. Tedjasaputra *et al.* examined the pulmonary diffusing capacity, Vc and Dm responses to exercise in endurance-trained males athletes, and untrained individuals with normal lung function [25••]. They found that athletes had a greater Vc at rest and a higher DLCO during high intensity exercise (90% $\dot{V}O_{2max}$) [25••]. Interestingly, the larger diffusing capacity was primarily the result of enhanced Dm, independent of pulmonary blood flow or alveolar volume [25••]. Similarly, Coffman *et al.* found that, during exercise at 90% $\dot{V}O_{2max}$, DLCO, Vc and Dm were greater in highly fit older adults (mean age = 65 ± 5 yrs, $\dot{V}O_{2max}$ = 162 ± 18% of predicted) as compared to older adults of average fitness (mean age = 69 ± 5 yrs, $\dot{V}O_{2max}$ = 116 ± 13% of predicted), suggesting that any fitness or training-induced difference is maintained regardless of age [26]. When combined, these recent studies suggest that endurance-trained athletes appear to have differences within the alveolar-capillary membrane that facilitate the increased O_2 diffusion required during high-intensity exercise [23,24•,25••]. Further, the higher Vc in endurance-trained athletes despite similar (or lower) perfusion pressures observed in these individuals [13,14], would suggest greater pulmonary compliance and/or a lower threshold for capillary recruitment as compared to less trained subjects. These vascular adaptations would help to 1) facilitate efficient pulmonary gas-exchange and minimize the A-aDO_2 typically observed during heavy exercise, and, 2) limit the rise in pulmonary perfusion pressure during exercise. The latter would help decrease the likelihood for pulmonary edema, while also diminishing the increase in right ventricle stroke work, which would facilitate a greater stroke volume and ultimately, cardiac output.

Blood that passes through the pulmonary circulation without taking part in gas-exchange is defined as an intra-pulmonary (I-P) shunt. Previous work has shown evidence that exercise recruits intrapulmonary arteriovenous anastomoses (IPAVA) [27,28]. IPAVA recruitment has been associated with an increased A-aDO_2 during exercise [27], and it has been hypothesized that IPAVA may be involved in reducing pulmonary vascular pressures during exercise [27,28]. While IPAVA has been consistently documented using a variety of techniques in humans [27–30] and animals [31], the physiological significance of these vessels as they pertain to gas exchange is controversial, as gas-exchange techniques such as MIGET have never documented significant right-to-left shunt during exercise in healthy subjects [1,6,32]. The reader is referred to two key review articles [33,34] and a point-counterpoint discussion [32,35] for a more thorough review of shunt and pulmonary gas exchange.

In summary, pulmonary gas exchange impairment during heavy exercise is complex and multifactorial. Despite considerable research, the mechanism(s) for the increased A-aDO_2 with exercise still remain to be fully explained.

Expiratory flow limitation and dynamic hyperinflation

Expiratory flow limitation (EFL) is defined as an increase in transpulmonary pressure with no increase in expiratory flow [36], and when exercising at near-maximal intensities, it is common for individuals with normal lung function to develop EFL. In the presence of EFL, end-expiratory lung volume (EELV) may increase above resting values, resulting in dynamic hyperinflation. Dynamic hyperinflation is initially an effective strategy

to facilitate greater airflow; however, the change in operating lung volume places tidal volume on the flat non-compliant portion of the sigmoidal pressure–volume curve, substantially increasing the elastic work of breathing, which can intensify the sensation of dyspnea [37,38]. Dynamic hyperinflation can also reduce the ability of tidal volume to expand appropriately with exercise, leading to ventilatory constraint and alveolar hypoventilation, which can contribute to EIAH [37]. Although EFL and dynamic hyperinflation are more common and severe in patients with chronic lung disease (i.e. COPD and asthma), they can occur in young individuals with normal lung function, leading to respiratory muscle fatigue and/or ventilatory constraint, which can negatively affect exercise performance [39–42].

The presence of increased EFL and/or dynamic hyperinflation has been shown to have adverse effects on cardiac output, as increased expiratory pressure, secondary to EFL, can raise right atrial pressure and central venous pressure, which reduces the gradient for venous return and cardiac filling [36,43,44•]. Recently, Cheyne *et al.* experimentally induced various levels of dynamic hyperinflation during spontaneous breathing at rest in young healthy individuals and observed a progressive reduction in left ventricular end-diastolic volume and stroke volume [44•]. Although these data were acquired in a resting state, it is plausible that the observed impairment in left ventricular function could be exacerbated during exercise, especially in individuals who are prone to severe dynamic hyperinflation [44•]. Additional experiments are required to better understand the complex relationship between ventilatory mechanics and cardiac function during exercise in young healthy individuals.

Although the mechanism of dynamic hyperinflation is not fully understood, it has been hypothesized that dynamic hyperinflation (increased EELV above resting levels) with the occurrence of EFL is the result of a reflex inhibition of respiratory motor output and early termination of expiration, secondary to dynamic compression of airways [45,46]. A more recent hypothesis suggests that a reflex mechanism may be triggered to increase EELV and avoid both EFL and dynamic compression [47••,48]. The former hypothesis has been supported by numerous studies, which have demonstrated an increase in EELV in the presence of EFL, during moderate to very heavy exercise [45,46,49,50]. However, recent findings have provided evidence that the increase in EELV, typically observed during very heavy exercise, is coincident with EFL [42,47••,51]. Both Dominelli *et al.* and Taylor *et al.* demonstrated that EELV was increased throughout incremental exercise in young healthy individuals without EFL, indicating that EFL is not a requirement for dynamic hyperinflation [47••,51]. Similar results were observed during incremental exercise in young healthy mild asthmatics [42]. These findings support older work that previously demonstrated dynamic hyperinflation in the absence of EFL during exercise [52]. When combined, these data suggest that factors other than the development of 'frank' EFL contribute to dynamic hyperinflation during heavy exercise.

Respiratory muscle fatigue and sympathetic-mediated blood flow distribution

Accumulating evidence suggests that respiratory muscle fatigue can occur during heavy intensity (>80% $\dot{V}O_{2max}$), sustained whole-body exercise in healthy individuals and negatively affect exercise performance by triggering a metaboreflex, which decreases locomotor muscle O_2 delivery. Briefly, fatigue of the respiratory muscles and increased metabolite accumulation increases phrenic afferent feedback, which in turn increases sympathetic-mediated vasoconstriction of the locomotor vasculature, via a supra-spinal reflex, and decreases O_2 delivery to these muscles, secondary to reduced limb blood flow [38,53–56]. Importantly, recent work has shown that the respiratory-related increases in vasoconstriction can be triggered with short bouts of exercise, without the development of respiratory muscle fatigue [57••,58]. Dominelli *et al.* demonstrated that when work of breathing was experimentally increased, locomotor blood flow decreased during exercise, and conversely, when work of breathing was reduced, locomotor blood flow was improved [57••]. Interestingly, the opposing changes in blood flow distribution occurred simultaneously with changes in work of breathing [57••]. Further, these data suggest that changes in sympathetic vasoconstrictor outflow and blood flow distribution may be sensitive to large increases in work of breathing, even without the development of respiratory muscle fatigue [57••,58,59]. Regardless of the presence of respiratory muscle fatigue, these data provide further evidence that the respiratory-mediated changes in limb blood flow suggest competition between respiratory and limb blood flow in the face of limited cardiac output [53,57••,60]. Readers are referred to a recent review by Sheel *et al.* that provides an excellent summary of the competition for blood flow distribution between respiratory and locomotor muscle [61•].

The previously discussed evidence (Dominelli *et al.*) would suggest that during heavy exercise, the distribution of cardiac output may be prioritized to the respiratory muscles over limb muscles [57••]. Conversely, Vogiatzis *et al.* showed that respiratory conductance (measured using near-infrared spectroscopy on the 7th intercostal) in trained cyclists was significantly lower during maximal exercise as compared to resting isocapnic hyperpnea trials at ventilation rates matched to those observed during exercise (i.e. ~150 l/min) [62]. These data provide evidence of the substantial influence of locomotor muscle activity on respiratory muscle blood flow and suggests that blood flow may not always be prioritized to the respiratory

muscles at near-maximal ventilation rates [62]. Despite the work by Vogiatzis and the recent findings of Dominelli, it remains to be determined whether there is specific prioritization of blood flow between respiratory and locomotor muscles during heavy exercise in humans.

Sex-differences in ventilatory mechanics and pulmonary gas exchange

Women have smaller lungs and airways, and fewer alveoli than men of the same height [63]. Recently, multiple studies have investigated sex differences in pulmonary gas exchange, ventilatory mechanics, perceptual responses to exercise, and the respiratory-related influences on cardiovascular regulation during exercise [64,65,66•,67–69,70•,71,72••,73,74]. To briefly summarize, at the same minute ventilation, women have a higher work of breathing and oxygen cost of breathing as compared to men, with the difference becoming greater with increased ventilation (i.e. at ventilation rates greater than 60 l/min) [64,69,70•]. Further, women tend to breathe at a higher proportional operating lung volume, compared to men, and expiratory flow limitation is more common in highly trained women as compared to highly trained men [64]. Not surprisingly, at comparable exercise ventilation rates, women tend to report a greater sensation of dyspnea [65,66•,67]. Interestingly, sex differences were consistently abolished when dyspnea was compared to relative ventilation rates (i.e. percentage of peak ventilation and/or maximal voluntary ventilation), which suggests that perceived dyspnea rises proportionally to ventilatory capacity in young healthy men and women [66•]. Despite having a greater work of breathing during exercise, the respiratory metaboreflex has been shown to be attenuated in young women [73]. Further, diaphragm fatigability is lower in women, than men, which may explain the lower prevalence of respiratory metaboreflex activation [74].

One recent publication showed compelling evidence that women with average fitness ($\dot{V}O_{2max}$ ~40 ml/kg/min) are prone to developing EIAH [71], which is in contrast to men, where there is no published work demonstrating EIAH in untrained men. In the study by Dominelli *et al.*, women with a wide range of aerobic fitness ($\dot{V}O_{2max}$ = 28–62 ml/kg/min) completed maximal exercise tests with and without heliox gas. Although the development of EIAH was more common in the aerobically trained woman, some untrained women ($\sim\dot{V}O_{2max}$ = 38 ml/kg/min) also developed EIAH. Experimentally reversing mechanical constraint (with heliox gas) partially reversed EIAH, in the women who had developed expiratory flow limitation, leading the authors to conclude that EIAH in women was in part, but not exclusively, due to mechanical ventilatory constraint during heavy exercise [71].

In addition to examining breathing mechanics, recent work by Bouwsema *et al.* examined potential sex differences in pulmonary diffusing capacity, Vc and Dm responses to exercise [72••]. When compared to height-matched men, women have lower DLCO, Vc and Dm at rest and during exercise, up to 90% of $\dot{V}O_{2max}$ [72••]. However, these sex differences were eliminated when accounting for differences in alveolar volume (i.e. lung size). The methods used in this study also allowed for calculation of red blood cell pulmonary transit time, and found no sex differences even at peak exercise in the most fit women and men. The results from Bouwsema *et al.* suggest that there are no intrinsic differences in DLCO, Vc, Dm and pulmonary transit time between men and woman, and that the greater susceptibility to EIAH in women is unlikely to be related to determinants of pulmonary diffusion [72••].

Conclusion

In this brief review, we highlighted several areas of emerging research examining pulmonary system limitations to exercise performance in healthy individuals. Pulmonary gas-exchange impairment, ventilatory constraint and respiratory muscle fatigue are all key respiratory-related limitations to exercise in health; however, there are unanswered questions in each area that require future investigation. First, additional work examining the mechanisms for the increased A-aDO_2 during exercise ($\dot{V}_A/\dot{Q}$ matching, diffusion limitation, and shunt) is required. Second, further experiments are needed to better understand the mechanism(s) for dynamic hyperinflation and expiratory flow limitation, and their relationship (or lack thereof) to one another. Third, additional experiments are required to better understand the complex relationship between respiratory and locomotor afferent feedback, and the distribution of blood flow at near-maximal exercise intensities. Lastly, future experiments, investigating sex-differences in pulmonary gas exchange during exercise, are required to better understand why EIAH is more prevalent in women than men.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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