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Respiratory Determinants of Exercise Limitation: Focus on Phrenic Afferents and The Lung Vasculature

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Introduction

The maximal dimensions of the healthy respiratory system including airways, alveolar capillary diffusion surface, respiratory muscles and the pulmonary vasculature are generally viewed as adequate or even “overbuilt” to meet the requirements for ventilation and gas exchange demanded by maximum or sustained endurance exercise – at least in the untrained human. However, in the highly trained who undergo substantial adaptations in key determinants of maximal oxygen (O_2) transport such as red cell mass, stroke volume, as well as locomotor muscle mitochondrial volume, and capillary density, there is little evidence that the lung architecture adapts to training-induced increases in demands for O_2 and carbon dioxide (CO_2) transport. Accordingly, as determined previously in significant numbers of highly trained young and older athletes of both sexes, different components of the respiratory system present significant limitations to systemic O_2 transport and exercise performance¹. These limitations include inadequate oxygen exchange, expiratory flow limitation, high intrathoracic pressure effects on left ventricular stroke volume, and extra-thoracic airway narrowing. In this brief essay we focus on recent work highlighting respiratory muscle afferents and the pulmonary circulation as additional potential respiratory system limitations to exercise performance, with emphasis on the effects of endurance exercise and training.

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PULMONARY VASCULATURE ADAPTATION / MALADAPTATIONS TO EXERCISE

Characteristics / Responses of the Pulmonary Vasculature.

The pulmonary vasculature has unique structural and functional characteristics distinct from the systemic circulation, which appear to make it ideal for an efficient response to exercise, i.e. to accept the entirety of the increase in cardiac output (CO) without excessive increases in vascular pressures, which would overburden the right heart and interfere with adequate pulmonary gas exchange. Accordingly, the pulmonary vasculature is thin walled and highly compliant, thus as pulmonary blood flow rises during exercise vessel caliber is largely “passively” controlled and subject to the pressures imposed by the systemic circulation on the left heart²⁻⁴. Figures 1:A and B show the increases in pulmonary and capillary wedge pressures with increasing cardiac output in healthy young adults. Note that at rest the pulmonary arterial pressures are about 1/20th of those of the systemic circulation, as is pulmonary vascular resistance. With mild intensity exercise pulmonary vascular resistance drops abruptly, likely due to recruitment of previously unperfused vessels in the lung apex. Thereafter, pulmonary capillary blood volume increases exclusively by vessel distention. In turn, vessel distention primarily occurs secondary to increases in left atrial pressure that are transmitted downstream across the pulmonary vascular tree.

Estimates of pulmonary vascular distensibility *in vivo* during exercise are identical to those obtained *in vitro* in isolated vessels^{2,5}, demonstrating the almost purely passive, “mechanical” control of pulmonary vessel caliber during exercise. This highly compliant and recruitable vascular system bestows two major advantages on the exercise response. First, pulmonary capillary and arterial pressures increase at an average rate of about 1 mmHg per liter increase in cardiac output; thus at 15-20 l max cardiac output in an untrained subject pulmonary capillary pressures increase to about 15-20 mmHg. Given these relatively small increases in capillary pressure combined with a huge capacity of the thoracic lymphatic drainage system, alveolar edema is avoided during exercise, despite an increase of fluid flux from pulmonary capillaries into the lung’s interstitial fluid space. Secondly, this low resistance system also insures adequate alveolar to arterial O₂ exchange with two types of adaptations to exercise^{3,6}. First, as shown in Figure 2 the pulmonary capillary blood volume expands up to about 2 to 2 1/2 times resting levels at 20 l/min CO, thereby limiting the reduction in red cell transit time with a rising cardiac output and insuring equilibrium of end-pulmonary capillary blood with alveolar PO₂. Secondly, the passively induced distensibility of the pulmonary vasculature with increasing cardiac output appears to be independent of vessel diameter, thus distensibility would be similar across lung regions, ensuring a fairly homogeneous distribution of blood flow (Q) to match alveolar ventilation, (V). These adaptations minimize the exercise-induced increased heterogeneity in V/Q distribution and constrains the associated 2 to 2.5 fold increase (> rest) in the alveolar to arterial PO₂ difference. Finally, overall V_A increases out of proportion to Q during exercise, ensuring relatively high alveolar and end-capillary PO₂s throughout the lung.

The max dimensions, high compliance and passively-controlled distensibility of the healthy pulmonary vasculature ensure that exercise-induced increases in pulmonary

artery and capillary pressures and decreases in red cell transit time throughout the lung are minimized, even up to about a four-fold increase in cardiac output at max exercise in the untrained healthy adult.

An Underbuilt / Overloaded Pulmonary Vasculature in the Highly Trained?

The endurance trained athlete with high peak work capacities and correspondingly high cardiac outputs which can reach 35 – 40 l/min at $\dot{V}O_2$ max and be sustained at 80-90% of these maximum values for prolonged periods, presents specific challenges to the pulmonary circulation. A key difference in the pulmonary vs. systemic circulation during exercise is that the latter has a huge reserve for vasodilation within the contracting limb muscles which receive the major share of the increasing cardiac output in exercise. On the other hand, the pulmonary circulation's reserve for vasodilation is markedly restricted. Accordingly, in heavy exercise pulmonary vascular resistance is reduced only a small amount below that achieved in moderate intensity exercise (see Fig 1:A) and as CO exceeds 30-40 l/min pulmonary capillary pressures exceed 40 mmHg reflecting the effect of the linear increase in blood flow on left atrial pressure which in turn is transmitted across the pulmonary vasculature (see Fig 1 :B). This presents a highly disproportionate load and wall stress on the right ventricle, eliciting marked increases in myocardial O_2 extraction and $\dot{V}O_2$. So this load on the right ventricle at max exercise approximates that imposed on the left ventricle; however the load is a "disproportionate one" imposed on the relatively thin walled right heart. La Gerche et al.⁷⁻⁹ make the point that the human has a pulmonary vasculature that seems to be "adapted" for resting and mild to moderate intensity exercises as noted by the low (relative to systemic) pulmonary vascular resistance and capillary pressures under these conditions, but has not been adapted to handle the very high cardiac outputs demanded by the high work rates of the endurance trained athlete. Given the similar slope of increases in pulmonary artery and wedge pressures per liter increase in cardiac output in the trained and untrained it appears as though the athlete's pulmonary vascular distensibility during exercise has also undergone only limited, if any, positive adaptation to chronic physical training (also see below).

Three types of potential short and long-term maladaptations may result from the effects of high and sustained pulmonary blood flow on the right heart as a result of endurance training. First, while it is widely recognize that limitations of left heart stroke volume present a primary limitation to O_2 transport and $\dot{V}O_2$ max, it is worth recalling that right and left heart stroke volumes must be equalized during exercise and that "...the maximum obtainable stroke volume could only be as high as its weakest ventricle"⁹. Given the disproportionately high load and wall stress placed on the right ventricle it has been reasoned –but not yet verified – that a major source of stroke volume and therefore cardiac output limitation may well reside in the high work rates and fatigability of the right heart.

Secondly, pulmonary gas exchange and arterial hypoxemia during exercise occur in a significant number of male and female endurance trained athletes^{1,6}, owing primarily to an excessively widened alveolar to arterial O_2 difference. Given the limited expansion of the pulmonary capillary blood volume during exercise, it is conceivable – but not proven – that

pulmonary blood flows in excess of 30 – 35 l/min would result in red cell transit times through at least some portions of the lung that are too short to ensure complete alveolar – end capillary O₂ equilibrium (see Figure 2)¹⁰ Higher capillary pressures and blood flows will also increase lung interstitial fluid turnover and pressure, thereby contributing to V / Q inhomogeneity and in some rare cases promote red cell movement into the alveolar space¹¹.

Thirdly, the long term effect of repeated bouts of intense endurance exercise results in slightly greater enlargement of the right-sided heart chamber verses the left side^{9,12}. A minority of athletes with extremely high endurance training loads develop arrhythmias and the origin of this arrhythmia is frequently associated with more pronounced remodeling and dysfunction of the right ventricle⁷. An interaction between excessive genetic abnormalities and cardiac structure has been proposed to be manifested in arrhythmogenic cardiomyopathy.

These effects of high pulmonary blood flows on vascular pressures are especially evident during exercise in elderly subjects and in sojourners to high altitude. With aging, starting as early as the third decade, pulmonary vascular compliance begins to decrease, combined with a similar age dependent fall in lung elastic recoil i.e. a stiffer pulmonary vasculature resides within a floppier lung. Accordingly Reeves analysis of *in vivo* distensibility shows significantly lower values in 70-year-olds versus young adult subjects during exercise^{2,4}. Similarly, decreased distensibility was also reported for young adults exercising after a few weeks sojourn to high-altitude, presumably due to reduced compliance secondary to hypoxic-induced pulmonary vasoconstriction. Thus, in highly trained athletes at advanced age or during high altitude sojourn it might be expected that even greater pulmonary vascular pressures and right ventricular wall stress will occur at even lower absolute work loads and cardiac outputs as previously reported in younger athletes exercising at sea level (see above). In turn, it might also be expected – but not yet tested – that excessive right ventricular remodeling will occur over time with high intensity training in both the elderly endurance athlete or those who habitually train at high altitudes.

An increased slope of the pulmonary artery pressure (PAP):Q relationship during exercise will also occur with upstream transmission of high left atrial pressure (LAP) and in the presence of increased intra-thoracic pressure. Accordingly patients with left heart conditions and raised LAP or COPD patients who develop expiratory flow limitation, dynamic hyperinflation and excessive intra-thoracic pressures during exercise will experience elevated PAP:Q slopes^{13,14}. In turn, in these patients the right heart will be subjected to excessive, disproportionate loads even during submaximal intensity exercise.

The endurance-trained athlete is capable of achieving and maintaining cardiac outputs in heavy intensity exercise in excess of 30+ l/min but pulmonary vasculature recruitment and reductions in vascular resistance are limited. Accordingly, excessive increases occur in pulmonary artery and capillary pressures, thereby placing a disproportionate load on the right heart and – over time – maladaptive ventricular hypertrophy commonly develops. Similar acute and long-term maladaptations may be present during submaximal

intensity exercise in older subjects and those sojourning at high altitudes, as well as in patients with COPD and left heart failure conditions.

Finally, the thoroughbred horse epitomizes the ultimate “underbuilt” pulmonary vasculature as this cursorial animal’s lung must accommodate a 400 l/min plus cardiac output during max exercise requiring 160 ml/kg/min plus $\dot{V}O_2$. (see Figure 3)¹⁵. Thus, pulmonary arterial pressure exceeds 100 mmHg during heavy intensity exercise and excessive pulmonary capillary pressures cause alveolar capillary rupture and pulmonary hemorrhage. Over time, the thickness of the right ventricle approaches that of the left ventricle in the thoroughbred⁹. When these responses in the pulmonary vasculature are combined with evidence of severe arterial hypoxemia and CO₂ retention beginning with even moderate intensity exercise (see Figure 3) it is apparent that the lung and pulmonary vasculature are truly the primary limiting factors to O₂ transport and exercise performance in the thoroughbred horse. Furthermore, while exercise-induced arterial hypoxemia occurs in a minority of highly trained human athletes (at sea level)⁶ it appears to be universal among thoroughbred horses. Indeed, preventing the exercise-induced hypoxemia in the thoroughbred (via supplemental O₂) raises $\dot{V}O_{2\max}$ ~30% above normoxic room air breathing values⁶.

RESPIRATORY VS. LOCOMOTOR MUSCLE AFFERENTS, BLOOD FLOW DISTRIBUTION AND FATIGUE: A TWO-WAY STREET

Exercise-Induced Blood Flow Distribution and Muscle Fatigue

During exercise a rising cardiac output is redistributed primarily to contracting skeletal muscle with the amount of blood flow determined by the net effect of two opposing mechanisms, namely vasodilation primarily via release of local metabolites vs. sympathetically mediated vasoconstriction. The vasodilation serves O₂ transport needs while the opposing vasoconstriction serves to preserve perfusion pressures in the face of the skeletal muscles’ prodigious capabilities for vasodilation if left unopposed¹⁶. Below we present evidence to support the concept that activation of metaboreceptor afferents from *both* limb locomotor and respiratory muscles are important sources of this exercise-induced sympathetic vasoconstrictor activity and that they have reciprocal modulatory influences on blood flow distribution to each set of muscles, thereby contributing to each other’s exercise-induced fatigue¹⁷.

Exercise-induced muscle fatigue is quantified objectively by determining the influence of exercise on force output of the muscle in response to supramaximal 1-20 Hz stimulation of the motor nerves – phrenic nerves for the diaphragm and femoral nerves for the quadriceps. For both muscle sets, max force output is reduced significantly immediately following exhaustive endurance exercise at intensities in excess of 80% of max $\dot{V}O_2$ in both trained and untrained subjects^{18,19}. Diaphragm fatigue is first noted about halfway through the high intensity exercise, is further exacerbated over time and usually it takes an hour or more for complete recovery. Blood flow and O₂ transport are well known to be important determinants of both diaphragm and locomotor muscle fatigue^{19,20}.

Muscle metabolite accumulation and fatigue limits performance in two ways: 1) by reducing the capability for maximum force output by the muscle, thereby forcing the athlete to work at higher relative intensities of exercise; and 2) by increasing sensory input from the fatiguing muscle supraspinally which in turn will inhibit central locomotor output and “effort”, i.e. so called central fatigue¹⁹. This dual effect of peripheral muscle fatigue of both central and peripheral components of exercise limitation are based on the demonstrated effects of partial blockade of locomotor muscle feedback using an intrathoracically administered opiate agonist. This blockade of muscle afferents promoted a greater central motor drive and force output during a cycling time trial and prevented the normal feedback inhibition of central motor drive. Thus, excessive levels of limb fatigue were achieved at end exercise with blockade than in the presence of muscle feedback and performance time was improved.¹⁹

Measurements of quadriceps blood flow in humans using thermal dilution techniques showed vascular conductance and flow rising linearly with cardiac output and plateauing at about 90 to 100% of $\dot{V}O_2\text{max}$ ^{16,21}. In ponies exercising at maximum, microsphere measurements of blood flow to all the respiratory muscles averaged 15-20% of cardiac output²² with similar values estimated in fit humans for respiratory muscle blood flow and the oxygen cost of breathing^{21,23}.

Influence of Respiratory Muscle Work and Respiratory Muscle Afferents

Does the high work of breathing (WOB) incurred during exercise influence blood flow to and fatigue of limb locomotor muscles? This question was addressed by a series of studies, all using a unique proportional assist mechanical ventilator in healthy fit young adults to unload the inspiratory muscles during exercise at 80-90% of $\dot{V}O_2\text{max}$ which prevented 50-70% of the normal exercise-induced increase in respiratory muscle work. The effects of preventing this normally occurring increase in the work of breathing are summarized below and in Fig 4.

- Diaphragm fatigue was prevented, demonstrating the critical importance of the work of the diaphragm during exercise to its own fatigue²⁴. Based on these findings we assume that reducing the inspiratory muscle work and preventing their fatigue means that exercise-induced metaboreceptor activation in inspiratory muscle was also significantly reduced (see below).
- Blood flow and vascular conductance were increased in the working quadriceps muscle and decreased in the accessory respiratory muscle, the sternocleidomastoid (see Fig 5²⁵). These changes in blood flow and vascular conductance with respiratory muscle unloading (and loading) were accompanied by reciprocal changes in norepinephrine spillover across the quadriceps muscle during exercise – indicating changes in sympathetic efferent activity in the quadriceps vasculature.
- Quadriceps muscle fatigue at end exercise – compared with control conditions at equal times and work rates – was reduced, exercise time to exhaustion was

prolonged and exercise-induced perception of dyspnea and limb discomfort reduced.

We proposed that the reductions in limb fatigue with respiratory muscle unloading were due to the coincident 5-10% increase in limb blood flow and O₂ transport. In turn, we propose that peripheral muscle fatigue and accumulation of locomotor muscle metabolites impact endurance exercise performance by enhancing both peripheral and central fatigue¹⁹.

These effects of reducing inspiratory muscle work during exercise and preventing respiratory muscle fatigue on reducing sympathetic vasoconstrictor outflow and increasing locomotor muscle vascular conductance and blood flow are likely mediated by the reduced activity of inspiratory muscle type III-IV metaboreceptors. The evidence supporting this postulate includes the following:

- Most fibers in the phrenic nerve are sensory in function and with supraspinal projections to medullary neurons involved in cardiorespiratory control²⁶.
- Group IV metaboreceptors in the diaphragm are activated by fatiguing the diaphragm in the rodent²⁶.
- Infusion of lactic acid into the phrenic nerve in the exercising dog causes vasoconstriction in the exercising limb and increased mean arterial pressure – effects that were prevented via sympathetic blockade²⁷.

We propose that sympathetically-mediated vasoconstriction invoked via the respiratory muscle metaboreflex during the course of fatiguing exercise is sufficiently robust to overcome a significant portion of the powerful local vasodilatory influence operative in near maximally contracting locomotor muscle, thereby contributing to limb fatigue and limiting exercise performance.

Influence of Locomotor Muscle Work and Locomotor Muscle Afferents

On the other hand, we need to emphasize that the work of the locomotor muscles also contributes significantly to sympathetically mediated vasoconstriction, blood flow limitation and fatigue in the respiratory muscles during whole body exercise. This “two-way street” of sympathetically mediated vasomotor influences between respiratory and limb locomotor muscle is illustrated in Figure 6. The sympathetically mediated vasoconstrictor activity activated via locomotor muscle contraction occurs via group III-IV afferents which enter the spinal cord through the dorsal roots and make their synapse in the dorsal horn of the grey matter. Babcock et al.²⁸ demonstrated the effect of locomotor muscle exercise on diaphragm fatigue by comparing the effects of high intensity treadmill running vs. a voluntarily produced work of breathing while at rest which mimicked that during exercise in both magnitude and duration (see Fig 6). In the resting subject, diaphragm fatigue was less consistent across subjects, substantially less in magnitude and recovered much more quickly than that experienced as a result of whole body exercise, i.e. when both the limbs and the respiratory muscles were simultaneously active. These data likely reflect the critical influence of limited blood flow distribution to the diaphragm during coincidental limb

locomotor muscle exercise, secondary to high levels of sympathetic vasoconstrictor activity emanating from locomotor muscle afferents, thereby contributing to diaphragmatic fatigue.

Just as sympathetically mediated vasoconstriction in the exercising limbs is in part modulated via afferents from the working respiratory muscles, so is vasoconstriction in the diaphragm in part mediated via metaboreceptor afferent, influences from the working limbs.

Prioritization of blood flow distribution during exercise / clinical implications.

Is sympatholysis in the face of sympathetically driven vasoconstriction during exercise greater in the diaphragm (and other respiratory muscles) than in limb locomotor muscles? ... thereby providing a preferential distribution of the available cardiac output to the diaphragm and respiratory muscles vs. locomotor muscles? This complex question does not yet have a definitive answer, but there are some hints supporting the hypothesis, including some limited data from clinical investigations.

- A substantially blunted norepinephrine induced vasoconstrictor response was reported in isolated vessels from the diaphragm vs. those from the limb muscle vasculature²⁹. This difference was not explained by differences in either oxidative capacity or muscle fiber type. Presumably then if this observation held for in vivo conditions a heightened sympathetic nerve activity during exercise would be expected to preferentially affect vasoconstriction more in the limbs than in the diaphragm vasculature¹.
- Congestive heart failure (CHF) is accompanied by high levels of sympathetic nerve activity and also an elevated work of breathing during exercise, achieved via excessive hyperventilation and a reduced lung compliance. In rodent models of CHF blood flow throughout exercise was shown to be preferentially distributed to the diaphragm vs. limb locomotor muscles³⁰ and in humans with CHF, unloading the respiratory muscles even during very low intensity submaximal exercise elicited substantial increases in limb vascular conductance and blood flow³¹ – similar to the effects previously seen in healthy subjects near maximum exercise³². Similarly, reducing the work of breathing with mechanical ventilation in COPD patients during mild intensity exercise at 50% of max prevented 25-30% of their exercise-induced limb fatigue³³. That these patients still showed substantial limb fatigue at this mild exercise intensity despite a complete normalization of their work of breathing revealed the markedly compromised aerobic capacity of their locomotor musculature^{33,34}.
- Specific training of the respiratory muscles in health and in CHF patients increased vasculature conductance and blood flow and reduced fatigue in exercising limbs^{35,36}.

¹Although sympatholysis may be greater in the diaphragm vs. locomotor muscle vasculature, endurance exercise at high intensity does induce diaphragm fatigue suggesting that blood flow and O₂ transport to the diaphragm does not precisely match metabolic demand. To this point, while the sympathetically mediated vasoconstrictor response may be less in the diaphragm vasculature it still must occur to a significant extent.

- In the maximum exercising equine, microsphere measures of blood flow distribution showed that maximum vasodilation was achieved in the diaphragm but not in the limb muscle vasculature²².

The clinical implications of this “two-way street” of muscle metaboreflex effects in such chronic diseases as CHF and COPD pertain to both exercise limitation and strategies for rehabilitation. Excessive metaboreflex activity affecting sympathetically mediated vasoconstriction from both the diaphragm and limb afferents during exercise may be expected in these patients because of the excessive work of breathing during exercise and because of the greatly limited aerobic capacity of locomotor muscles. Secondly, these excessive fatigue-producing influences from respiratory and limb muscle may be substantially modified by specific training of the respiratory musculature through resistive breathing treatment procedures, as well as through the use of single leg extension exercise which will enhance the aerobic capacity and reduce the fatigability of locomotor muscles – without requiring the dyspneic producing ventilatory response of two-legged exercise.

Patients with COPD and CHF are especially susceptible to the influence of elevated levels of respiratory muscle work and the accompanying metaboreceptor-induced sympathetic activation. Thus, even during low intensity exercise in these patients blood flow is redistributed preferentially to the respiratory muscles at the expense of locomotor muscle blood flow and fatigue.

SUMMARY: THE OVERBUILT AND UNDERBUILT RESPIRATORY SYSTEM DURING EXERCISE

The capacity of the lung diffusion surface area, airways, pulmonary vasculature, and respiratory muscle and the precision achieved by the neurochemical ventilatory control system are generally considered to be near-ideal to meet the ventilatory and gas exchange demands of exercise at sea-level. Well-documented evidence in support of this generalization is to be found primarily in healthy untrained subjects, as follows:

- The precise control of alveolar ventilation with respect to CO₂ output ($\dot{V}CO_2$) and the excess capacity to meet ventilation requirements within the maximum flow: volume envelope
- The protection from diaphragm fatigue during short-term incremental exercise achieved through the high perfusion and high aerobic capacity of the diaphragm
- The high compliance and low vascular resistance of the pulmonary vasculature minimize increases in pulmonary artery and capillary pressures during exercise.
- The increase in alveolar ventilation in excess of cardiac output insures a high alveolar PO₂ throughout the lung and an expanded pulmonary capillary blood volume minimizes reductions in red cell transit time pulmonary as cardiac output rises. These adaptations ensure that arterial PO₂ is maintained in the face of an exercise-induced increase in V/Q inhomogeneity and a progressively widened alveolar to arterial PO₂ difference.

In our current essay we have focused on two scenarios wherein the respiratory system is *not* optimally built to meet the demands of exercise. First, we considered the scenario of respiratory system limitations in endurance trained athletes whose extraordinary work capacity and accompanying high cardiac outputs are not matched by proportional adaptations in their pulmonary vasculature. Accordingly, during heavy intensity exercise at high cardiac outputs, reductions in pulmonary vascular resistance are limited, excessive increases in pulmonary artery and capillary pressures are common, as are marked reductions in red cell transit time – both potentially contributing to reduced stroke volume, and impaired O₂ exchange. With high intensity endurance training over time the occurrence of right ventricular remodeling is maladaptive.

Secondly, we considered the dual positive and negative influences of both locomotor and respiratory muscle metaboreflexes on blood flow distribution and muscle fatigue. Activation of locomotor muscle metaboreflexes during moderate and heavy intensity exercise contributes significantly to increased systemic O₂ transport via increased ventilation and cardiac output and also to sympathetic vasoconstriction to maintain perfusion pressure. On the other hand these metaboreflex effects also appear to constrain blood flow to the respiratory muscles and hasten diaphragm fatigue. Similarly, excessive sympathetic activation of metaboreflexes from the respiratory muscles during heavy intensity exercise in normal trained and untrained subjects and even during mild exercise in CHF and COPD patients or in healthy subjects exercising in hypoxia, appears to deprive locomotor muscles of optimal blood flow and promotes limb fatigue. Enhanced sympatholysis of respiratory muscle over locomotor muscle vasculature may prevail during exercise, allowing prioritization of blood flow distribution to respiratory muscles. This scenario of a two way street metaboreflex effect between locomotor and respiratory muscles occurs during heavy intensity endurance exercise in both trained and untrained healthy subjects and during submaximal exercise in patients with chronic heart and lung disease and in healthy subjects in hypoxia.

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Abbreviations

CHF	congestive heart failure
CO	cardiac output
COPD	chronic obstructive pulmonary disease
LAP	left atrial pressure
PAP	pulmonary artery pressure
Q	perfusion

V	ventilation
VCO₂	carbon dioxide output
VO₂	oxygen uptake
WOB	work of breathing

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KEY POINTS

- In untrained, healthy subjects, the respiratory system is highly precise and efficient in its response to exercise
- Intense endurance exercise activates metaboreceptor afferents from both the respiratory and locomotor muscles, which mediate increased sympathetic vasoconstriction
- The increased sympathetic vasoconstriction limits blood flow to both respiratory and locomotor muscles thereby contributing to their fatigue.
- In the endurance trained subject capable of working at high VO_2 and cardiac outputs, pulmonary vascular pressures are markedly elevated, leading to exercise limitation and to maladaptive remodeling of the right heart over time.

SYNOPSIS

We examine two means by which the healthy respiratory system contributes to exercise limitation. These include the activation of respiratory and locomotor muscle afferent reflexes which constrain blood flow and hasten fatigue in both sets of muscles and the excessive increases in pulmonary vascular pressures at high cardiac outputs which constrain O₂ transport and precipitate maladaptive right ventricular remodeling in endurance trained subjects.

Figure 1A.

Pulmonary artery and capillary pressures and pulmonary vascular resistance during steady-state exercise in untrained (up to 15-20 l/min cardiac output) and trained (>20 l/min CO) young adults

Data from Reeves J, Grover RF, Dempsey JA. "Pulmonary circulation during exercise". In: Weis E, Reeves J, eds. *Pulmonary Vascular Physiology and Pathology*. New York: Dekker; 1989:107-133

Figure 1B.

Pulmonary artery pressures during upright exercise in 24 healthy untrained and endurance trained subjects measured via right heart catheterization

From Naeije R, Vanderpool R, Dhakal BP, Saggar R, Vachiery JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med.* 2013;187(6):576-583.

↑ VO₂max, Cardiac Output in Highly Trained: Effects on Pulmonary Transit Time

Rest

VO₂max 50-80 ml/kg/min

$$\text{Red cell Transit time} = \frac{\text{Capillary Blood Volume}}{\text{Blood Flow}}$$

$$0.8 \text{ secs} = \frac{70 \text{ ml}}{5\text{L/min (83 ml/sec)}}$$

$$0.6 \text{ secs} = \frac{210 \text{ ml}}{20\text{L/min}}$$

$$0.4 \text{ secs} = \frac{210 \text{ ml}}{30\text{L/min}}$$

$$0.3 \text{ secs} = \frac{210 \text{ ml}}{40\text{L/min}}$$

Figure 2.

Exercise-induced changes in pulmonary capillary blood volume, cardiac output and mean red cell transit time in the lung in healthy young men – untrained (15-20 l/min maxCO) and trained (> 20 l/min maxCO). The max pulmonary capillary blood volumes at max exercise were assumed to be 3x resting values and similar in trained and untrained. The micrographs show the expanded pulmonary capillary blood volume from rest to max exercise.

Adapted from Dempsey JA, Miller JD, Romer LM. The respiratory system. In: Tipton C, ed. ACSM "Advanced Exercise Physiology". Philadelphia: Lippincott; 2006:246-299.

Figure 3.

Effects of incremental exercise (treadmill running) in the thoroughbred horse on alveolar, arterial and mixed venous PO₂. Note the minimal increase in alveolar PO₂, the substantial, progressive widening of the alveolar to arterial PO₂ difference and arterial hypoxemia throughout exercise and the near maximal extraction of O₂ by the locomotor muscles. Other max exercise values include PaCO₂ 50-55 mmHg, arterial pH 7.15, Ppa 120 mmHg, mixed venous PCO₂ 135 mmHg.

From Bayly WM, Hodgson DR, Schulz DA, Dempsey JA, Gollnick PD. Exercise-induced hypercapnia in the horse. *J Appl Physiol* (1985). 1989;67(5):1958-1966.

Unloading the Inspiratory Muscles at 85% $\dot{V}O_{2\max}$

Reducing Diaphragmatic Work via Proportional Assist Mechanical Ventilation (PAV):

- Prevents exercise-induced diaphragm fatigue
- ↓ sympathetic tone, ↑ limb vascular conductance, and ↑ blood flow to limb locomotor muscles
- ↓ blood flow to accessory inspiratory muscles
- ↓ locomotor muscle fatigue
- ↓ perceived sensation of dyspnea and limb discomfort
- ↑ exercise duration to exhaustion

Figure 4.

Summary of effects of reducing the work of breathing during high intensity exercise in healthy fit subjects (see text for details). The figure shows a typical effect of the proportional assist ventilator on reducing esophageal and transdiaphragmatic pressures during high intensity exercise (see text for details).

Adapted from Sheel AW, Boushel RC, Dempsey JA. Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *J Appl Physiol* (1985). 2018.

Figure 5.

Summary of the effects of respiratory muscle loading and unloading on esophageal pressures, work of breathing (WOB) and blood flow to the locomotor muscles (V. Medialis and V. Lateralis) and sternocleidomastoid accessory inspiratory muscle (SCM). Relative changes in muscle blood flows were measured using the combination of iodicyanate dye infusion with near-infrared spectroscopy.

Adapted from Dominelli PB, Archiza B, Ramsook AH, et al. Effects of respiratory muscle work on respiratory and locomotor blood flow during exercise. *Exp Physiol.* 2017; 102(11): 1535-1547.

Figure 6.

Schematic illustrating the “two-way street” of muscle afferent reflexes between respiratory and locomotor muscles which during exercise elicit sympathetically mediated vasoconstriction of the vasculature supplying both sets of muscles, thereby constraining their blood flow and hastening fatigue

From Sheel AW, Boushel RC, Dempsey JA. Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *J Appl Physiol* (1985). 2018.

Figure 7.

Diaphragm fatigue (% control Pdi) was determined by supramaximal bilateral electrical stimulation of the phrenic nerves before and in recovery from exhaustive exercise vs. before and in recovery from voluntary mimic of the exercise $\int Pdi \cdot fb$ while at rest. The difference in diaphragm fatigue following whole body exercise vs. mimic of the exercise-induced $\int Pdi \cdot fb$ while at rest reflects the effects of coincidental locomotor muscle exercise, per se. Data from Babcock MA, Pegelow DF, McClaran SR, Suman OE, Dempsey JA. Contribution of diaphragmatic power output to exercise-induced diaphragm fatigue. *J Appl Physiol* (1985). 1995;78(5):1710-1719.