Respiratory muscle fatigue modulates the circulatory response to exercise

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Abstract This is a brief review of recent evidence concerning the influences of respiratory muscle fatigue on the circulatory response to exercise, endurance exercise performance and associated peripheral locomotor muscle fatigue. Inspiratory muscle fatigue enhances muscle sympathetic vasomotor outflow and blood pressure during exercise. As a consequence, blood flow and oxygen transport to the working limbs are reduced, and this exacerbates the development of peripheral muscle fatigue and compromises endurance performance. These effects are relevant for healthy humans performing high intensity endurance, and, even at mild intensities, for patients with pulmonary disease and heart failure.

Keywords : respiratory muscle work, exercise, diaphragm, metaboreflex, blood flow

Introduction

A progressive increase in pulmonary ventilation occurs during incremental exercise, and this ventilatory response requires the recruitment of inspiratory and eventually expiratory muscles. Significant diaphragm and expiratory muscle fatigue occur when the exercise intensity exceeds 80% of maximum^{1,2}. In healthy humans, respiratory muscle fatigue does not limit the hyperventilatory response during exercise³⁻⁵. However, it is thought that the fatiguing diaphragm affects, via a classical reflex loop, the regulation of limb blood flow during exercise (Fig. 1). The purpose of this brief review is to consider the influences of respiratory muscle fatigue on sympathetic vasomotor outflow, arterial blood pressure (BP), blood flow to the working limb, and eventually the development of locomotor muscle fatigue. For a more in depth discussion of this topic, we refer the reader to previous, more detailed reviews³⁻⁸.

Characteristics of the respiratory muscles

Breathing consists of rhythmic changes in lung volume secondary to respiratory muscle activity triggered by medullary respiratory neurons. Several muscle groups are involved in pulmonary ventilation. First, muscles of the pharynx and larynx control upper airway resistance; second, the diaphragm, ribcage, spine, and neck muscles are related to inspiration; and finally, muscles of the abdominal wall, ribcage and spine are used when active expiration is required⁹. Many of these muscle groups have

common origins and attachments such that their activity is complex and dependent on each other⁹. Out of various inspiratory muscles, the diaphragm contributes most to inspiration, and is characterized by a very high aerobic enzymatic capacity, multiple sources of blood supply, and a unique resistance to vasoconstrictor influences on vascular diameter¹⁰⁻¹². In fact, the diaphragm is known as the most fatigue-resistant skeletal muscle.

The unique structural characteristics of inspiratory and expiratory muscles combined with the precise neural regulation of breathing assure that the capacity of these muscles for pressure generation usually exceeds the demands placed on them. Thus, in most untrained healthy subjects, the pressures produced by the expiratory muscles during maximal exercise are well within the constraints for effective pressure generation (<40% of their maximal capacity), and the pressures produced by the inspiratory muscles are only 40-60% of maximum dynamic capacity¹³.

Exercise-induced respiratory muscle fatigue

During sustained high-intensity exercise, progressive time- and intensity-dependent hyperventilation occurs³ (Fig. 2). This ventilatory response requires the progressive recruitment of inspiratory and expiratory muscles, and significant diaphragm and expiratory muscle fatigue develops during exercise¹⁻³.

Fatigue is reflected in a reduction in the force generating capacity from pre- to post-exercise. To evaluate force output, two methods are commonly used: 1) force measurements during a maximal voluntary muscle contraction, and 2) twitch force measurements evoked by

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Fig. 1 Influences of respiratory muscle fatigue on sympathetic outflow, blood flow to the locomotor muscle, and exercise performance. Fatigue-related metabolite accumulation in respiratory muscles raises the discharge frequency of group IV phrenic afferents, which causes increased sympathetic efferent discharge and limb vasoconstriction. This sequence exacerbates the development of limb fatigue and compromises endurance performance.

Fig. 2 Changes in power output, minute ventilation ($\dot{V}E$), and arterial partial pressure of CO_2 ($PaCO_2$) during a 5-km time trial conducted on a cycle ergometer. Data adapted from Amann et al.²⁴) and Dempsey et al.³.

electric or magnetic stimulation of the peripheral motor nerve. Respiratory muscle strength has been assessed by measuring maximal inspiratory pressure (MIP or PI_{max}) and the maximal expiratory pressure (MEP or PE_{max}). The pressure measured during these maneuvers reflects the pressure developed by the respiratory muscles, plus the passive elastic recoil pressure of the respiratory system including the lungs and chest wall¹⁴). Reductions in MIP or PI_{max} following maximal exercise to exhaustion have previously been reported¹⁵⁻²¹) and are thought to reflect the occurrence of exercise-induced diaphragm fatigue. Although MIP maneuvers can potentially reveal pre- to post-exercise changes in the diaphragm's ability to generate force, this method is effort-dependent, and there are situations in which subjects are unable or unwilling to perform valid MIP^{22,23}).

In contrast, force output is objectively determined by electrically or magnetically stimulating the motor nerves innervating a particular skeletal muscle (or muscle group) before and again immediately after exercise²⁴⁻³⁰). Due to difficulties associated with the accessibility of the diaphragm, fatigue in this muscle, compared to limb muscles, is rather difficult to assess. Therefore, force development across the diaphragm is estimated by evaluating the difference between gastric (P_{ga}) and esophageal (P_{es}) pressures (i.e., transdiaphragmatic pressure [P_{di}]) ($P_{di} = P_{ga} - P_{es}$) evoked by stimulation of both phrenic nerves^{1,31,32}). Short term incremental exercise to exhaustion does not cause diaphragm fatigue³³⁻³⁵). However, reductions of 15-30% in the transdiaphragmatic pressure

(Pdi) response to supramaximal stimulation of the phrenic nerves have been reported following high-intensity [$>80\%$ of maximal oxygen uptake ($\dot{V}O_{2\max}$)] constant-load whole-body endurance exercise^{1,32,36-40}. These studies suggest that, when the exercise intensity is high, the diaphragm starts to show fatigue relatively early during exercise. Furthermore, gastric pressures in response to magnetic thoracic nerve stimulation declined following exercise at $>90\% \dot{V}O_{2\max}$ ^{2,41}, suggesting that whole-body exercise can also induce abdominal (expiratory) muscle fatigue.

Effect of respiratory muscle fatigue on ventilation and dyspnea during exercise

Respiratory muscle fatigue could potentially limit exercise tolerance through inadequate ventilation (i.e., relative alveolar hypoventilation), an alteration in breathing mechanics, an increase in unpleasant or uncomfortable respiratory effort sensations (dyspnea), or a combination of these factors⁵. Recent work has shown that, despite significant respiratory muscle fatigue, the ventilatory response to exercise remains adequate. This is based on the fact that arterial partial pressure of CO_2 ($PaCO_2$) during exercise with fatigued respiratory muscles remains at – or even falls below – resting values of ~ 40 mmHg, and arterial oxygen saturation (SaO_2) remains similar to resting levels^{3,5,24} (Fig. 2). These findings suggest that exercise-induced diaphragm fatigue might not limit the hyperventilatory response to exercise in healthy humans^{3,6}.

During fatiguing inspiratory tasks, several researchers observed a progressive increase in the sense of effort related to breathing⁴²⁻⁴⁴, i.e., dyspnea. Mador et al.⁴⁴ observed respiratory effort during heavy exercise after loaded breathing; and respiratory effort during exercise, compared to a control trial, was larger when the identical bout was performed with pre-existing respiratory muscle fatigue. These authors also found that minute ventilation and tidal volume/inspiratory time increased after induction of fatigue, indicating an increase in central motor

drive. In contrast, it is thought that the sensation of inspiratory effort during resistive loading is independent of the presence of fatiguing diaphragmatic motor patterns. During prolonged high-intensity exercise, exercise-induced diaphragmatic fatigue is accompanied by the recruitment of accessory inspiratory and expiratory muscles⁴⁵. This progressive recruitment of accessory respiratory muscles would be expected to increase sensory input to the central nervous system and, therefore, increase the intensity of dyspnea. This effect might be specific to the accessory respiratory muscles⁴⁵, because diaphragm fatigue does not increase neural respiratory drive⁴⁶. Therefore, it is possible that fatigue of the inspiratory accessory muscles contributes independently to inspiratory effort sensation⁴⁷.

Effect of respiratory muscle fatigue on sympathetic vasomotor outflow, blood pressure, and blood flow distribution during exercise

High-intensity voluntary contraction of the inspiratory muscle against resistive loads causes a time-dependent increase in muscle sympathetic nerve activity (MSNA) with a corresponding increase in arterial blood pressure (BP)^{48,49} (Fig. 3). The diaphragm has an abundance of type IV metaboreceptors; and diaphragm fatigue, evoked via electric phrenic nerve stimulation, causes an increase in type IV afferent discharge in anesthetized rats⁵⁰. Furthermore, when metaboreceptors in the diaphragm of animals are stimulated electrically, pharmacologically, or with local lactic acid infusions, efferent sympathetic nerve activity increases and vascular conductance decreases in selected vascular beds⁵¹⁻⁵³. This is similar in humans where the respiratory muscle fatigue-induced gradual increase in MSNA has been shown to be accompanied by a significant increase in limb vascular resistance^{48,54} (Fig. 4). Based on these results, it is thought that the sympathoexcitation limiting limb blood flow during intense exercise is associated with a diaphragm fatigue-induced metaboreflex^{3,5,6,55,56}. However, in these studies,

Fig. 3 Changes in arterial blood pressure (BP), mouth pressure, and muscle sympathetic nerve activity (MSNA) associated with fatiguing inspiratory muscle work (via resistive loading) at rest. Data adapted from St Croix et al.⁴⁹ and Dempsey et al.⁶.

inspiratory resistive breathing was performed during resting condition^{48,49,54}.

During whole body exercise, the situation is more complicated, because an increase in limb muscle blood flow depends on the cardiac output limitation and the opposing effects of local vasodilators and vasoconstrictors⁵. Therefore, it is necessary to confirm whether diaphragm fatigue, and thus the respiratory muscle metaboreflex, leads to alternations in sympathetic nerve activity and cardiovascular variables during dynamic leg exercise at submaximal intensity. Recently, Katayama et al.⁵⁷ assessed MSNA and BP during dynamic leg cycling at mild intensity ($40\% \dot{V}O_{2\max}$) with inspiratory resistive breath-

ing in sedentary subjects; the time-dependent increase in MSNA appeared during submaximal exercise with inspiratory resistance and was also accompanied by increases in diastolic BP (DBP) (Fig. 5). The series of experiments described above suggests that respiratory muscle fatigue – and associated metaboreflex – leads to enhanced sympathetic vasomotor outflow and BP during exercise.

How do these reflexes affect the distribution of blood flow during exercise? Harms et al.⁵⁵ investigated the regulation of working limb blood flow, with or without inspiratory resistive breathing, during high intensity endurance exercise. They revealed that, when the work of breathing, during leg cycling, is artificially increased via resistive loading, a reduction of blood flow and an increase in vascular resistance occurs in the femoral artery (Fig. 6). Conversely, when the work of breathing is reduced, an increase in blood flow and a reduction in vascular resistance in the leg occurs (Fig. 6).

Although the evidence appears to implicate a significant role of inspiratory muscle fatigue in the sympathetically mediated vasoconstriction of exercising limb-muscle vasculature, it is necessary to consider whether the respiratory muscle metaboreflex is solely responsible for this vasoconstrictor effect. In addition, we do not know how activation of the limb muscle metaboreflex affects vasoconstriction and blood flow to the respiratory muscle^{4,5}. In studies of isolated arterioles, it was shown that alpha-adrenergic receptors in the diaphragm are less responsive to vasoconstrictor influences^{11,12}. Therefore, it is assumed that a global increase in muscle sympathetic activity would result in greater vasoconstriction in the limb muscle than in the respiratory muscle, and this would contribute to maintaining blood flow and oxygen transport to the diaphragm during high-level exercise.

Effect of respiratory muscle metaboreflex on locomotor muscle fatigue and exercise performance

Reductions in blood flow and oxygen transport to the working limb exacerbate limb fatigue and compromise exercise performance^{3,8,23,44,58,59}. Romer et al.⁶⁰ measured

Fig. 4 Changes in heart rate (HR), mean arterial blood pressure (BP), muscle sympathetic nerve activity (MSNA), leg vascular resistance (LVR), and leg blood flow during fatiguing diaphragm work. Data adapted from Sheel et al.⁴⁸.

Fig. 5 Changes in arterial blood pressure (BP) and muscle sympathetic nerve activity (MSNA) during mild intensity leg cycling with resistive breathing. Data adapted from Katayama et al.⁵⁷.

Fig. 6 Relative effects of alternations in the work of breathing on leg blood flow and leg vascular resistance in femoral artery during leg cycling. Data adapted from Harms et al.⁵⁵.

quadriceps twitch force by using magnetic stimuli of the femoral nerve before and after leg cycling, with increased or reduced inspiratory muscle work, in trained cyclists. Loading the respiratory muscles using inspiratory resistors exacerbated the development of quadriceps fatigue during exercise; while unloading the respiratory muscle using a mechanical ventilator alleviated end-exercise locomotor muscle fatigue. Mador et al.⁴⁴ compared exercise performance following fatiguing inspiratory muscle work with the performance achieved under control conditions, i.e., without pre-existing respiratory muscle fatigue. Time to exhaustion, compared to control conditions, was significantly reduced when the endurance task was started with fatigued respiratory muscles. Combined, these results suggest that respiratory muscle fatigue accelerates the development of locomotor muscle fatigue and limits endurance exercise performance.

The exercise-induced reduction of locomotor force output assessed via direct motor nerve stimulation, before and again after exercise, indicates “peripheral fatigue”⁶¹. Peripheral fatigue will impact, via group III/IV afferent feedback, central motor output to the limbs, i.e., influence the development of “central fatigue”^{62,63}. Furthermore, during whole-body endurance exercise, it has been shown that the exercise-induced alteration of the metabolic milieu (and associated peripheral fatigue) of locomotor muscles affects the firing rate - and thus the central projection - of muscle afferents which provide inhibitory feedback to the determination of central motor drive^{3,24,63,64}.

There are several situations/conditions in healthy subjects which are characterized by an increased work of breathing during submaximal exercise, e.g., aging. Moreover, clinically, respiratory muscle work plays a particularly important role in determining oxygen transport and limb muscle fatigue, and, hence, exercise tolerance in obstructive sleep apnea (OSA)^{65,66}, chronic heart failure (CHF)^{67,68}, and chronic obstructive pulmonary disease (COPD)^{69,70}. Simon et al.⁷¹ investigated leg blood flow during exercise in COPD patients. They found that blood flow to the exercising legs appeared to plateau during sub-

maximal exercise in some patients with COPD, despite the fact that total oxygen uptake, i.e., cardiac output, continued to increase. The authors contributed this observation to redistribution of cardiac output and oxygen transport in favor of the respiratory muscle, but at the cost of the exercising leg muscles. Furthermore, Amann et al.⁶⁹ reported that the exercise-induced reduction in quadriceps twitch force was, compared to healthy control subjects, substantially relieved when inspiratory muscle work during low intensity exercise was reduced in COPD patients (Fig. 7). Thus, it is assumed that the vasoconstriction associated with the respiratory muscle metaboreflex affects locomotor muscle oxygen transport and, consequently, the development of locomotor muscle fatigue and exercise tolerance in patients.

Some investigators have demonstrated that inspiratory muscle training increases respiratory muscle endurance and/or whole body endurance exercise performance in healthy subjects⁷² and patients with COPD⁷³. It is thought that the development of respiratory muscle fatigue during exercise is alleviated following a period of inspiratory muscle training; and that this improvement might attenuate the respiratory muscle metaboreflex and, therefore, increase blood flow and oxygen transport to the working limbs.

Finally, there are circumstances in which people perform exercise under hypoxic conditions, e.g., at altitude or under pathophysiological conditions. Respiratory muscle fatigue is exaggerated during exercise in hypoxia^{74,75}. In a recent animal study, the electromyographic activity of the diaphragm was bigger in hypoxia than in normoxia. In other words, motor unit recruitment for the rat diaphragm was larger under hypoxic vs. normoxic conditions⁷⁶. Based on these findings, it is thought that large inspiratory muscle fatigue during exercise under a hypoxic condition induces sympathetically mediated vasoconstrictor activity, thereby compromising blood flow to the active limb^{8,57,77}. Indeed, Amann et al.⁷⁷ assessed quadriceps force output by means of magnetic stimulation before and following hypoxic exercise with or without proportional assist ventilation. They found that inspiratory muscle work has

Fig. 7 A: Inspiratory muscle work (expressed as the pressure-time product) during constant-load cycling in patients with COPD, exercising either with or without proportional assist ventilation (PAV). Pes: esophageal pressure, f: breathing frequency. B: Pre- to 10-min post-exercise changes in potentiated quadriceps twitch force (expressed as a percent change from pre-exercise baseline). * $P < 0.05$. Data adapted from Amann et al.⁶⁹.

a much greater effect on peripheral locomotor muscle fatigue in hypoxia as compared to normoxia.

Summary

Numerous studies over the last years suggest that respiratory muscle fatigue influences the circulatory response to exercise via a metaboreflex, i.e., increases in sympathetic vasomotor outflow secondary to an increase in the discharge frequency of group IV muscle afferents innervating respiratory muscle. As a consequence, blood flow and oxygen transport to the working limbs are reduced, which exacerbates the development of peripheral muscle fatigue and compromises exercise performance. These effects have an important clinical relevance to various disease populations, i.e., OSA, CHF, and COPD patients. Also, it seems likely that respiratory muscle work under a hypoxic condition has a larger impact on the circulatory response to exercise, and eventually on the development of locomotor muscle fatigue. These detrimental effects might be alleviated by respiratory muscle training.

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