Respiratory muscle fatigue modulates the circulatory response to exercise

Keisho Katayama1* and Markus Amann2

1 Research Center of Health, Physical Fitness and Sports, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8601, Japan
2 VA Medical Center, Department of Medicine, University of Utah, Salt Lake City, UT 84148, USA

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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 maximum1-2). 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 required7). 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 vascula

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 exercise4,5).

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
Respiratory muscle fatigue
Group IV phrenic afferent discharge
(Metaboreflex)

Enhancement of metaboreflex-induced sympathetic outflow
Increase in arterial blood pressure

Locomotor muscle vasoconstriction
Reduction of limb blood flow
and oxygen transport

Afferent feedback

Respiratory muscle

Central nervous system

Sympathetic outflow
Efferent discharge

Locomotor muscle
(working limb)

Afferent feedback

Effort perception
Central fatigue

Development of peripheral muscle fatigue
Group III/IV afferent discharge

Decrease in endurance performance

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.

electric or magnetic stimulation of the peripheral motor nerve. Respiratory muscle strength has been assessed by measuring maximal inspiratory pressure (MIP or PI\text{max}) and the maximal expiratory pressure (MEP or PE\text{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 wall\textsuperscript{14}. Reductions in MIP or PI\text{max} following maximal exercise to exhaustion have previously been reported\textsuperscript{15-21} 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\textsuperscript{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 exercise\textsuperscript{24-30}. 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 (Pga) and esophageal (Pes) pressures (i.e., transdiaphragmatic pressure [Pdi]) (Pdi = Pga – Pes) evoked by stimulation of both phrenic nerves\textsuperscript{1,31,32}. Short term incremental exercise to exhaustion does not cause diaphragm fatigue\textsuperscript{33-35}. However, reductions of 15-30% in the transdiaphragmatic pressure

Fig. 2  Changes in power output, minute ventilation (\(\dot{V}E\)), and arterial partial pressure of CO\textsubscript{2} (PaCO\textsubscript{2}) during a 5-km time trial conducted on a cycle ergometer. Data adapted from Amann et al.\textsuperscript{24} and Dempsey et al.\textsuperscript{3}.
(Pdi) response to supramaximal stimulation of the phrenic nerves have been reported following high-intensity (>80% of maximal oxygen uptake (VO₂max)) constant-load whole-body endurance exercise. 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% VO₂max(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 factors. 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 CO₂ (PaCO₂) during exercise with fatigued respiratory muscles remains at – or even falls below – resting values of ~40 mmHg, and arterial oxygen saturation (SaO₂) remains similar to resting levels(3,24,26) (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 breathing, i.e., dyspnea. Mador et al. 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 muscles. 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 muscles, because diaphragm fatigue does not increase neural respiratory drive. Therefore, it is possible that fatigue of the inspiratory accessory muscles contributes independently to inspiratory effort sensation.

**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 rats. 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 beds. 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(51,54) (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. However, in these studies,
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 vasoconstrictors\(^5\). 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%\(\dot{V}O_{2\text{max}}\)) with inspiratory resistive breathing 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
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. reported that the exercise-induced reduction in quadriceps twitch force was, compared to healthy control subjects, substantially relieved when inspiratory muscle work was, 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 subjects and patients with COPD. 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. 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 conditions. 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. Indeed, Amann et al. 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
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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