Mechanism and implications of hyperpnea exaggeration at the onset of exercise in mechanical hyperalgesia after eccentric exercise

Norio Hotta¹* and Koji Ishida²

¹ College of Life and Health Sciences, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan
² Research Center of Health, Physical Fitness and Sports, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8601, Japan

Received: December 5, 2017 / Accepted: March 27, 2018

Abstract The ventilatory response to moderate-intensity step load exercise has three temporal phases: an initial rapidly increasing phase I, followed by a slower exponential phase II, that leads to the steady state phase III. In muscles with mechanical hyperalgesia (delayed onset muscle soreness) and/or muscle damage a few days after eccentric exercise (ECC), an interesting phenomenon of increased ventilatory response at phases II and III during constant-load exercise and incremental exercise has been reported. However, the mechanisms behind this phenomenon have not been clarified. At least a neural mechanism is partly responsible for this phenomenon because the ventilatory response at neurally modulated phase I has been shown to be exaggerated 2 days after ECC (D2). In the present review, we focus on our previous work to identify the potential mechanism underlying the exaggerated modulation in phase I ventilatory response at D2, in which ECC-induced muscle pain is assumed to be at the peak. We also discuss the physiological and practical implications of this phenomenon.

Keywords: thin muscle afferents, pain receptor, peripheral neural reflex, phase I, ventilation, delayed onset muscle soreness

Introduction

The ventilatory response to moderate-intensity (below the lactate threshold) step load exercise has three temporal phases: an initial “phase I”, followed by a slower exponential “phase II”, that leads to the steady state “phase III” within 3-5 min1-3 (Fig. 1a). At phase I, there is a brief plateau until about 15-20 s, and ventilation reflexively, rapidly, and abruptly increases and reaches approximately 50% of steady state (Fig. 1a)⁴; thus, the mechanism subserving the control has been assumed to be neurally rather than humorally (e.g., chemoreflex) mediated⁵. Hence, phase I ventilatory response also has been referred to as initial exercise hyperpnea⁶, initial phase of exercise hyperpnoea⁷, initial component of the hyperpneic response⁸, fast exercise drive⁹, and fast neural drive to breathe¹⁰. The type of muscle contractions in which stimulated muscle fibers are forcibly stretched or extended by an external force is labeled eccentric contractions (ECC), lengthening contractions, or negative muscular work. At the same work rate, ventilatory response to ECC is lower than that to concentric contractions⁹. On the other hand, in comparable concentric contractions yielding a similar metabolic response, hyperventilation has been observed during ECC¹⁰, though the slope of the relationship between ventilation and arterial blood CO₂: partial pressure in concentric exercise and that in ECC are almost the same⁹.

Regarding the effect of a prior bout of ECC on ventilatory response to exercise, some investigators reported that the response at phases II and III during constant load or incremental exercise a few days after ECC was exaggerated¹¹-¹⁵. Gleeson et al.¹³ and Schneider et al.¹⁴ suggested that this phenomenon is due to ventilatory compensation for greater blood lactacidosis after ECC. Gleeson et al.¹³ and Schneider et al.¹⁴ also presumed that increased afferent discharges from pain receptors or metaboreceptors and sensation of muscle pain or soreness affected ventilatory response to exercise after ECC. Davis et al.¹²,¹⁵ proposed that the augmentation of ventilatory response and reduction in the gas exchange threshold, at least during incremental exercise after ECC, are most likely evoked by increased activation of thin muscle afferents (without using the terms “pain receptor” and “pain sensation”) stimulated via mechanical disruption of muscle fibers and local microvasculature, and are not the result of altered blood lactate. Furthermore, Gleeson et al.¹³ conjectured that central neural effects contributed to the increased ventilatory response.

Phase I ventilatory response has also been reported to be exaggerated 2 days after ECC (D2)¹⁶-¹⁸, suggesting that at least ECC-induced changes in neural adjustment are involved in the augmentation of ventilatory response. However, the neural mechanisms and implications of this
phenomenon have not been clarified.

In the present review, we discuss the potential mechanism underlying the exaggerated modulation in phase I ventilatory response at D2. We also discuss the physiological and practical implications of this phenomenon.

Effects of ECC on skeletal muscles

It is well known that ECC induces muscle damage and delayed onset muscle soreness (DOMS). The injury of muscle fibers results in neuromuscular dysfunction and in edema or muscle swelling. DOMS is classified as mechanical hyperalgesia, the symptoms of which are muscle tenderness and movement-induced pain; thus, no pain sensation is perceived at rest. The peak occurs around D2, and we therefore focus on the period around D2 in this paper. Although the exact mechanism responsible for this mechanical sensitization has not yet been clarified, at least nerve growth factor and glial cell line-derived neurotrophic factor produced by muscle fibers and/or satellite cells after ECC might be related to the mechanical hyperalgesia or DOMS.

Origin of the phase I ventilatory response

The neural mechanism of the phase I ventilatory response has been summarized in some reviews. Briefly, to begin with, activation of the respiratory center in the brain stem due to discharges of thin muscle afferents innervating the exercised skeletal muscles modulates ventilatory control. This is known as peripheral afferent feedback, peripheral neural reflex, peripheral neurogenesis, or muscle reflex. This mechanism has sometimes been called exercise pressor reflex in the same way as cardiovascular control even in the field of respiratory physiology. Thin muscle afferents are excited by mechanical stimuli such as muscle contraction and movement (muscle mechanoreflex) and metabolites (muscle metaboreflex). It has been assumed that the former contributes to phase I ventilatory response because an initial hyperpneic response arises before metabolites start to accumulate in the muscles.

Secondly, parallel activation of the respiratory center caused by motor commands for contracting the target muscles from higher centers in the brain induces exercise hyperpnea. This is termed central command. In this paper, we do not address the difference in the origin of central command in the higher centers. Recently, except for the concept of parallel activation of locomotion and respiration, ventilatory response has been reported to be modulated by other neurogenic drives, e.g., imagined exercise and arousal response in the limbic system. We distinguish them from the conventional concept of central command in this paper.

Thirdly, some researchers have proposed a reflex mechanism from the cardiovascular system: cardiodynamic and vascular distension hypotheses. The former hypothesis is that an augmentation in ventilation depends on the degree of an increase in cardiac output (right ventricular distension). The latter hypothesis resembles that of muscle mechanoreflex; the discharge of thin muscle afferents that respond to distension of blood vessels in exercising muscles contributes to ventilatory control.
Mechanism underlying ECC-induced exaggeration in phase I ventilatory response (Fig. 2)

Neuromuscular dysfunction and central command (Fig. 2, 1). It is well known that ECC induces muscle damage and then neuromuscular dysfunction occurs partly due to the injury of muscle fibers (Fig. 2, 1-[1])\(^{20,21}\). As a result, effort sense during the same exercise increases after ECC compared with that before conducting ECC\(^{11-13,15,35}\). Since Williamson et al.\(^{36}\) suggested that effort sense is closely related to central command, central command might be augmented as a result of the loss of muscle strength after ECC (Fig. 2, 1-[2])\(^{35}\). However, passive movement (PAS), which was used to uncouple the muscle mechanoreflex from central command, exaggerated the phase I ventilatory response at D2\(^{18}\). Additionally, the degree of exaggeration in the phase I ventilatory response from before ECC (Pre) to D2 was not significantly different from PAS (the muscle mechanoreflex) to exercise (muscle mechanoreflex + central command)\(^{19}\). If central command is related to the exaggeration in phase I response at D2, the rate of increase from Pre to D2 during exercise should have been significantly higher than that of PAS\(^{19}\). Furthermore, the initial ventilatory response was still exaggerated at D2 even though the exercise load and effort sense were reduced in accordance with the degree of loss of muscle strength to lower the effect of putative increased central command\(^{35}\). Taken together, the results indicate that although central command could be reinforced at D2, the extent of reinforcement in central command does not reach significant exaggeration in phase I ventilatory response at D2 (Fig. 2, 1-[3]).

Cardiovascular response and cardiodynamic hypothesis (Fig. 2, 2). It is well accepted that input mechanisms (central command and afferent feedback) for cardiovascular and ventilatory responses to exercise are similar\(^{28}\). Nonetheless, heart rate (HR) and blood pressure responses at the onset of exercise were not exaggerated at D2 in previous studies (Fig. 2, 2-[1])\(^{11,16,17}\). If the cardiodynamic hypothesis has any influence on the phenomenon (Fig. 2, 2-[2]), changes in cardiovascular response would be indispensable. Therefore, it is difficult to account for the exaggeration in phase I ventilatory response at D2 by the cardiodynamic hypothesis (Fig. 2, 2-[3]).

Increase in intramuscular pressure (IMP), muscle mechanoreflex, and vascular distension hypothesis (Fig. 2, 3). Many investigators have revealed that edema or muscle swelling occurs after ECC\(^{19,22}\), and IMP in the

---

**Fig. 2** Schematic view of the pathways involving mechanisms for the exaggeration in phase I ventilatory response 2 days after eccentric exercise.

Black arrows indicate the input pathways to the respiratory center in the brain stem. The white arrow represents the output pathway from the respiratory center to respiratory muscles. Dotted lines show the causal relationships. HR and IMP indicate heart rate and intramuscular pressure, respectively. +positive effect; +/-no effect; ↓reduction; ↔no change.
resting state is known to increase subsequently (Fig. 2, 3-[1])\textsuperscript{37,38}. IMP also increases in line with muscle contraction even in a normal muscle condition\textsuperscript{37,38}. Hence, it is possible that thin muscle afferents were stimulated to a greater extent during exercise at D2 than at Pre, because the increase in IMP resulting from edema would add to the increase caused by muscle contraction (Fig. 2, 3-[2]). As a result, the muscle mechanoreflex at the onset of exercise might be enhanced. Furthermore, Yunoki et al.\textsuperscript{27} speculated in their article that the increase in IMP after ECC exaggerated the ventilatory response through activation of thin muscle afferents by blood vessel distension in active muscles.

Phase I ventilatory response was previously revealed to be unchanged even though IMP in the exercising or moving limb was increased by 25 mmHg of an inflated cuff, in a normal condition\textsuperscript{39}. Two studies have revealed that IMP in the resting state increased to approximately 6 mmHg at D2\textsuperscript{37,38}, and two other studies have revealed that pressure from the outside approximately reflects IMP in muscle\textsuperscript{40,41}. Therefore, it seems difficult to explain the augmentation in muscle mechanoreflex on the grounds of an ECC-induced increase in IMP and the vascular distension hypothesis (Fig. 2, 3-[3]).

**Effects of muscle pain (Fig. 2, 4).** It has been consistent that painful or nociceptive stimulation increases ventilation\textsuperscript{42-46}. This phenomenon has been reported to be mediated by a neural rather than a humoral mechanism\textsuperscript{45}. A pain pathway from thin muscle afferents to the central nervous system with bypass to the respiratory center certainly exists\textsuperscript{47}, though we do not explain this phenomenon in this paper because of its complexity\textsuperscript{46,48}. Many studies have demonstrated that ventilation at "rest" was changed by the degree of pain (mainly in the skin)\textsuperscript{13-46}, however; no study has been conducted to elucidate whether pain from exercised muscles affects "exercise" hyperpnea. If muscle pain is responsible for an exaggeration in phase I ventilatory response when mechanical hyperalgesia is present in the exercised muscles, the degree of exaggeration of ventilatory drive at the onset of exercise would be altered by the difference in the degree of muscle pain at D2.

To elucidate this hypothesis, we performed the following unpublished new experiment for the current review (Fig. 3). Participants performed ECCs with their left and right arms separately, and we measured ventilatory responses to 20-s single-arm extension-flexion voluntary exercise at Pre and D2. We defined the 20-s single-arm exercise for data collection, in which the arm with greater pain was used, as the "stronger pain trial" and the other as the "weaker pain trial". We found that ventilatory response was significantly exaggerated in the stronger pain trial compared to that in the weaker pain trial, suggesting that at least the degree of muscle pain during exercise is related to the degree of exaggeration in phase I ventilatory response at D2.

**Muscle pain (DOMS sensation) and neurogenic drive (Fig. 2, 4-1).** Bell et al.\textsuperscript{49} revealed that arousal response in the limbic system had an influence on exercise hyperpnea; thus, it is possible that the pain sensation (Fig. 2, 4-1-[1])-induced increase in arousal level (Fig. 2, 4-1-[2]) results in the exaggeration in phase I ventilatory response. However, noxious stimulation of skeletal muscles is known to augment ventilation even in anesthetized or decerebrate animals\textsuperscript{42,43}. In fact, Ward and Karan\textsuperscript{47} stated in their review that the pain-induced increase in ventilation does not occur solely through arousal of higher centers, because pain might stimulate ventilation without cortical structures. Therefore, we do not contradict the participation of neurogenic drive since the subjects in the current study (Fig. 3) and our previous studies were awake humans\textsuperscript{16-18}, but it is likely that the neurogenic drive induced by DOMS sensation and/or discomfort from DOMS is not the primary cause of exaggeration in phase I ventilatory response after ECC (Fig. 2, 4-1-[3]).

**Muscle pain (mechanical hyperalgesia) and muscle mechanoreflex (Fig. 2, 4-2).** Previous animal experiments have revealed that the threshold of response of thin muscle afferents to mechanical stimuli was reduced in muscle with DOMS after ECC\textsuperscript{49}. The exact mechanism responsible for the sensitization of thin muscle afferents to mechanical stimuli in muscles with DOMS has not yet been clarified. However, at least nerve growth factor and glial cell line-derived neurotrophic factor, produced by muscle fibers and/or satellite cells after ECC, might be responsible for the mechanical hyperalgesia (DOMS)\textsuperscript{25}.

Thin muscle afferents are assumed to play a role in pain receptors. ECC could lower the threshold of the response of thin muscle afferents to mechanical stimuli at D2 (mechanical hyperalgesia) (Fig. 2, 4-2-[1])\textsuperscript{49}, and consequently their discharge during exercise might stimulate not only the sensorial pathway related to the perception of DOMS, but also the respiratory center (Fig. 2, 4-2-[2]), so that the muscle mechanoreflex in ventilation could be emphasized (Fig. 2, 4-2-[3]). In fact, ventilation started to become exaggerated as soon as a given subject began performing the exercise and decreased immediately after stopping the exercise at D2 (Fig. 3a), and it was assumed that subjects perceived DOMS sensation only during exercise because of the characteristics of mechanical hyperalgesia.

**Physiological implications**

The mechanism underlying an exaggeration in phase I ventilatory response in muscle with mechanical hyperalgesia after ECC could possibly be at least due to augmentation in the muscle mechanoreflex caused by sensitization in thin muscle afferents. This would have the following implications.
Subjects (n = 12) performed ECC in the same way as in our previous study\(^\text{18}\) for the right and left arms, consecutively. At D2, related behavior in mice. Mizumura and Kumazawa\(^\text{42}\) exercise, but also significantly reduced alterations in pain-

The degree of increase in ventilation from Rest to EX was higher at D2 than at Pre. These results were confirmed by a signifi-

- **Role of thin muscle afferents.** Thin muscle afferents are known to respond to both painful and painless stimuli. These fibers are classified as pain receptors (nociceptors) and ergoreceptors, which contribute to the reflex modulation of ventilatory and cardiovascular responses to muscular exercise. Since primary afferent nociceptive neurons have polymodal characteristics\(^\text{50}\), it has not been fully clarified whether or not thin muscle afferents contribute to both peripheral afferent feedback in ventilatory drive during exercise and the perception of pain\(^\text{51,52}\).

- Smith et al.\(^\text{52}\) revealed that the abolition of capsaicin-sensitive fibers, which play a role in nociceptors, caused a significant abnormality in the cardiovascular response to both muscle contraction and stretching in rats. Queme et al.\(^\text{53}\) demonstrated that inhibition of ADP-responsive P2Y1 receptors, which are related to ischemic pain, not only prevented the increase in mean blood pressure after exercise, but also significantly reduced alterations in pain-related behavior in mice. Mizumura and Kumazawa\(^\text{42}\) also showed that nociceptive chemical stimulations to thin muscle afferents, that are assumed to be polymodal receptors in dogs, induced a significant increase in ventilation. These results support the physiological concept\(^\text{11,52}\) that at least some pain receptors (nociceptors) contribute to peripheral afferent feedback in cardiovascular and respiratory responses to exercise in animals. The present findings in human studies also support the idea that at least some thin muscle afferents are relevant to dual modulation of pain sensation as pain receptors and respiratory reflex during exercise as ergoreceptors.

- **Muscle afferents for transmission of DOMS.** According to the traditional scientific knowledge, pain is perceived via thin fiber afferents. However, there has been disagreement as to which groups of muscle afferents, large fibers such as groups I and II\(^\text{24,55}\) or thin fibers such as groups III and IV\(^\text{23,49}\), contribute to the perception of DOMS. Large afferent fibers are known to be unrelated to peripheral
afferent feedback in exercise hyperpnea\(^5\). Accordingly, if large afferent fibers contribute to the perception of DOMS, it may be the case that the muscle mechanoreflex in ventilation in DOMS is not exaggerated. Therefore, the fact that the muscle mechanoreflex in ventilation during phase I is exaggerated in DOMS might suggest that at least thin muscle afferents contribute to the perception of DOMS.

**Practical implications**

In this review, we have proposed that at least a peripheral neural response for perceiving DOMS sensation is related to the augmentation in phase I ventilatory response after ECC. Then, are there any practical implications of this phenomenon for performing sports or exercise? In this section, we will specifically discuss the relationships of the augmentation in initial ventilatory response with the effect of muscle pain on exercise performance and with the impact of ECC-induced alteration in muscle condition on oxygen uptake (\(\text{VO}_2\)) kinetics at the onset of exercise.

**Impact of exaggerated initial ventilatory response on muscle pain-induced reduction of exercise performance.**

It is evident that strong muscle pain limits exercise performance\(^5\). For instance, in intermittent claudication, which is the primary symptom of peripheral arterial disease, an affected individual is forced to stop ambulating, owing to ischemic leg muscle pain\(^5\). Fibromyalgia is characterized by widespread muscle pain\(^5\). Anaerobic threshold (AT) and peak \(\text{VO}_2\) were reported to be lower in patients with fibromyalgia\(^5\), presumably indicating that they could not exert maximal effort due to muscle pain. In addition, stimulation of nociceptive afferents has been reported to attenuate the initial discharge rate of motor units during muscle contraction\(^5\). Conversely, when muscle pain is reduced, not only endurance but also resistance exercise performance is likely to be improved\(^5\).

It is well known that long-duration exercise attenuates muscle pain in response to exercise, i.e., exercise-induced hypoalgesia (EIH)\(^5\) or exercise-induced analgesia\(^5\). DOMS sensation is also known to be reduced by exercise or muscle contractions\(^5\). Indeed, EIH might work to attenuate the DOMS pain-induced decline in exercise performance, though EIH is less likely to be evoked at the onset of exercise. Instead, increases in inspiratory flow and volume have been demonstrated to be responses to acute pain and might help to reduce muscle pain\(^5\). Hence, the exaggeration in phase I ventilatory response might have an analgesic effect on DOMS sensation, helping the exercise performance not to be attenuated by muscle pain at the onset of exercise.

As mentioned above, ECC-induced muscle damage lowers muscle function\(^5\). As a result of a loss of muscle strength, range of motion, and flexibility\(^5\), the best athletic performance is presumably difficult to be achieved regardless of DOMS pain. Thus, this review is only able to disclose the effect of DOMS pain on exercise performance after ECC. Further study is needed to obtain information regarding how much DOMS pain affects exercise performance after ECC.

**Effects of the exaggerated phase I ventilatory response on \(\text{VO}_2\) kinetics.**

In the same way as ventilation, \(\text{VO}_2\) response to step-load exercise, measured at the pulmonary level, shows three phases (Fig. 1b). \(\text{VO}_2\) kinetics at the onset of exercise, evaluated at the pulmonary level, might serve as an index of overall efficiency and conditioning of the integrated systems, providing information on the mechanisms regulating \(\text{O}_2\) delivery and \(\text{O}_2\) utilization in active skeletal muscles\(^5\). Pulmonary \(\text{VO}_2\) at phase I is assumed to reflect circulatory transit time from active muscles to lungs\(^5\). The results of most previous studies indicate that muscle condition with DOMS does not impact the duration of phase I\(^5\). Phase III corresponds to the \(\text{VO}_2\) steady state when moderate exercise is performed at a given work rate that is below the anaerobic threshold (AT). As of yet, there has been no study showing that prior ECC had an impact on the \(\text{VO}_2\) steady state in moderate intensity exercise\(^5\). In exercise in which the intensity is above AT, phase III would correspond to the slow component of \(\text{VO}_2\) kinetics. For detailed information on the slow component, see Jones et al.\(^5\). Previous experimental results regarding the effects of the DOMS condition on amplitude of the slow component have not been consistent\(^5\). Further studies are warranted because there have been few studies making reference to this topic.

The time constant (\(\tau\)) of phase II \(\text{VO}_2\) response is assumed to reflect the speed at which \(\text{O}_2\) consumption increases at the active muscle level\(^5\). Results regarding effects of the muscle state after ECC on phase II \(\tau\) have not been consistent. Molina et al.\(^5\) showed that ECC induced slowing of \(\text{VO}_2\) kinetics during moderate intensity exercise at a high pedal cadence. On the other hand, Nederveen et al.\(^5\) reported that in subjects whose phase II \(\tau\) was slower in the control condition before ECC, \(\tau\) accelerated after ECC in moderate intensity exercise. Schneider et al.\(^5\) and Davis et al.\(^5\) did not observe any significant change in phase II \(\tau\) in either heavy or severe intensity exercise. However, Baranauskienë et al.\(^5\) revealed that prior ECC accelerated phase II \(\tau\) during heavy intensity cycling in men only, and that the ECC-induced acceleration of faster \(\text{VO}_2\) kinetics had a negative impact on cycling economy.

What has an influence on \(\text{O}_2\) delivery and \(\text{O}_2\) utilization, which are factors having an influence on phase II \(\tau\), in a DOMS condition? At least local superficial femoral arterial function in the muscles forced to perform ECC was observed to be impaired\(^5\), though systemic circulatory response, e.g., HR\(^5\) and arterial vascular function in nonlocal regions that are not affected by ECC\(^5\), is not likely to change after ECC. A few studies have suggested
JPFSM: Initial exercise hyperpnea and delayed onset muscle soreness

The subjects (n = 8) performed a series of 5-min square-wave transitions from rest to 60 or 90-W cycling exercises using a bicycle ergometer. The pedaling rate was kept constant at 60 rpm. To examine the effect of an excessively forced increase in phase I ventilatory response, the subjects voluntarily increased ventilation only for 10 s just after the start of exercise in the voluntary hyperventilation trial. The experimenter directed each subject to breathe faster and more strongly. The voluntary hyperventilation trial and control trial were performed randomly and repeated at least four times for each subject. The breath-by-breath VO₂ data were aligned with the onset of exercise and then linearly interpolated between each breath to yield a data point at 1-s intervals, and ensemble averaging was carried out. The resultant VO₂ response was modeled with nonlinear least-squares fitting procedures to an exponential response beginning after the end of phase I and continuing to a steady state. The results of a paired t-test showed that the response magnitude of phase I VO₂ was significantly (P = 0.01) higher in the voluntary hyperventilation trial [20.8 ± 4.3 mL/min (mean ± SE)] than in the control trial (8.6 ± 0.9 mL/min), evoking a significant (P < 0.001) temporal increase and decrease in PETO₂ and PETCO₂ responses for the initial 20 s after the start of exercise in the voluntary hyperventilation trial compared with those in control trial. No significant difference between trials was detected in HR response during phase I (P = 0.39). A previous study showed that lower PETCO₂ and hypocapnic alkalosis, induced by voluntary hyperventilation through the entire exercise session including 20-min rest before exercise onset, blunted VO₂ response. Temporal change in PETCO₂ evoked by the hyperventilation for the initial 10 s of exercise in this experiment is, however, unlikely to induce alkalosis that affects VO₂ kinetics.

The time constant (τ) of phase II was not significantly (P = 0.67) different in the voluntary hyperventilation trial (26.1 ± 1.7 s) and control trial (27.5 ± 2.3 s). These results suggest that the speed in metabolic response at the onset of exercise does not change even if phase I ventilatory response is exaggerated in the control condition; but in a DOMS condition, this exaggerated response may assist O₂ delivery to compensate for the ECC-induced delay in metabolic response at the onset of exercise.

Subjects provided written consent after they were informed of the experimental protocol and the possible risks involved in this study. The study was approved by the Ethics Committee of the Institutional Review Board of Aichi Shukutoku University (No. 2010-1). We performed this experiment only for the current review article. The data have not been previously published and will not be submitted elsewhere well into the future.

Fig. 4  Averaged expiratory minute ventilation (VE), oxygen uptake (VO₂), end-tidal PO₂ (PETO₂), PETCO₂, and heart rate (HR) in a control trial (black solid line) and a voluntary hyperventilation trial (dotted line).
that ECC-induced mitochondrial disturbances decrease muscle O2 utilization. On the other hand, by evaluating muscle deoxygenation kinetics assessed with near-infrared spectroscopy (NIRS) (For detailed information on the relationship between NIRS and VO2 kinetics, see DeLorey et al.80), previous studies have suggested that: 1) prior ECC improves microvascular O2 delivery and/or distribution of O2 resulting in a faster VO2 response80, 2) augmentation in O2 delivery as a result of prior ECC preserves VO2 kinetics by substituting an elevation of the microvascular driving pressure for blood-myocyte O2 flux11,12, and 3) enhancement of O2 supply tries to compensate for the slowed VO2 kinetics, but is insufficient73. Hence, the balance between O2 delivery and O2 utilization altered by ECC might have an influence on phase II τ in DOMS conditions. Therefore, DOMS-induced exaggeration in phase I ventilatory response might help O2 delivery to compensate for the dulled metabolic response at the onset of exercise after ECC.

One may wonder if augmentation in phase I ventilatory response has an impact on VO2 kinetics when DOMS is absent. We therefore performed an unpublished new experiment for this review, and the results showed that excess voluntary hyperventilation at phase I did not significantly impact the VO2 response at phase II in the control condition (Fig. 4). This result agrees with the premise that VO2 τ in phase II is independent of O2 delivery in upright moderate intensity cycle exercise in at least young healthy subjects. However, Davies et al.11 suggested that the muscle condition following ECC, even in healthy individuals, shifts the so-called “tipping point”, proposed by Poole et al. (see Fig. 1 of Poole et al.80), beyond which VO2 τ in phase II becomes limited by O2 delivery, so that VO2 τ in phase II is affected by the O2 delivery component in the DOMS condition. Nederveen et al.80 suggested the possibility that VO2 response at phase II is affected by ECC-induced alteration of O2 delivery to the active muscles because an O2-dependent zone even exists in young healthy adults whose VO2 τ is slower than about 20 s77.

Again, the exaggeration in phase I ventilatory response after ECC might at least help prevent an external respiratory function from limiting O2 supply response, presumably providing a rapid matching of alveolar ventilation to the subsequent tissue metabolism as much as possible at the onset of exercise in any muscle condition after ECC.

**Summary**

After ECC, ventilatory response during exercise is exaggerated. It is evident that at least a neural mechanism is involved in this phenomenon because the neurally modulated phase I ventilatory response is exaggerated. Enhancement in central command, cardiodynamic and vascular distension hypotheses, and the edema/swelling-induced increase in mechanical stimuli are difficult to account for as mechanisms of this phenomenon. DOMS sensation-induced neurogenic drive in the brain could be related to the increase in ventilation; however, it is more likely that augmentation in the muscle mechanoreflex caused by sensitization in thin muscle afferents contributes to the exaggeration in phase I ventilatory response. The assumption that thin muscle afferents stimulate not only pain pathways, but also the respiratory center simultaneously after ECC, supports the physiological concept that some thin muscle afferents play a role as both pain receptors and ergoreceptors, and that not large but thin muscle afferents are related to DOMS sensation. The present review proposes practical implications in that the exaggerated phase I ventilatory response might reduce pain sensation, thus attenuating pain-induced reduction of exercise performance, and might contribute to the absence of delay in VO2 response at the onset of exercise even when the active muscles are being damaged by ECC.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

**Acknowledgement**

This work was supported in part by JSPS KAKENHI Grant Number JP 21800074.

**References**

1) Ward SA. 2007. Ventilatory control in humans: constraints and limitations. *Exp Physiol* 92: 357-366.

2) Whipp BJ, Ward SA, Lamarn A, Davis JA and Wasserman K. 1982. Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 52: 1506-1513.

3) Ward SA. 2000. Control of the exercise hyperpnoea in humans: a modeling perspective. *Respir Physiol* 122: 149-166.

4) Ishida K and Miyamura M. 2012. Neural regulation of respiration during exercise -Beyond the conventional central command and afferent feedback mechanisms-. *J Phys Fitness Sports Med* 1: 235-245.

5) Wasserman K, Whipp BJ and Castagna J. 1974. Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. *J Appl Physiol* 36: 457-464.

6) Bell HJ, Feenstra W and Duffin J. 2005. The initial phase of exercise hyperpnoea in humans is depressed during a cognitive task. *Exp Physiol* 90: 357-365.

7) Bell HJ. 2006. Respiratory control at exercise onset: an integrated systems perspective. *Respir Physiol Neurobiol* 152: 1-15.

8) Duffin J. 2012. The fast exercise drive to breathe. *J Physiol* 592: 445-451.

9) Miyamura M, Folyerging HT, Binkhorst RA and Smolders FD. 1976. Ventilatory response to CO2 at rest and during positive and negative work in normoxia and hyperoxia. *Pflugers Arch* 364: 7-15.

10) Rorke S. 1995. Positive (Concentric) and negative (Eccentric) muscular activity: a review. *Sports Med Training and Rehab*
11) Davies RC, Eston RG, Poole DC, Rowlands AV, DiMenna F, Wilkerson DP, Twist C and Jones AM. 2008. Effect of eccentric exercise-induced muscle damage on the dynamics of muscle oxygenation and pulmonary oxygen uptake. *J Appl Physiol* 105: 1413-1421.

12) Davies RC, Rowlands AV and Eston RG. 2009. Effect of exercise-induced muscle damage on ventilatory and perceived exertion responses to moderate and severe intensity cycle exercise. *Eur J Appl Physiol* 107: 11-19.

13) Gleeson M, Blannin AK, Zhu B, Brooks S and Cave R. 1995. Cardiorespiratory, hormonal and haematological responses to submaximal cycling performed 2 days after eccentric or concentric exercise bouts. *J Sports Sci* 13: 471-479.

14) Schneider DA, Berwick JP, Sabapathy S and Minahan CL. 2007. Delayed onset muscle soreness does not alter O\textsubscript{2} uptake kinetics during heavy-intensity cycling in humans. *Int J Sports Med* 28: 550-556.

15) Davies RC, Rowlands AV, Poole DC, Jones AM and Eston RG. 2011. Eccentric exercise-induced muscle damage dissociates the lactate and gas exchange thresholds. *J Sports Sci* 29: 181-189.

16) Hotta N, Sato K, Sun Z, Katayama K, Akima H, Kondo T and Ishida K. 2006. Ventilatory and circulatory responses at the onset of exercise after eccentric exercise. *Eur J Appl Physiol* 97: 598-606.

17) Hotta N, Yamamoto K, Katayama K, Fukuoka Y and Ishida K. 2007. The effect of the amount of eccentric exercise on ventilatory response at the onset of exercise. *J Physiol Sci* 57: 193-197.

18) Hotta N, Yamamoto K, Katayama K and Ishida K. 2009. The respiratory response to passive and active arm movements is enhanced in delayed onset muscle soreness. *Eur J Appl Physiol* 105: 483-491.

19) Smith LL. 1991. Acute inflammation: the underlying mechanism in delayed onset muscle soreness? *Med Sci Sports Exerc* 23: 542-551.

20) Armstrong RB. 1984. Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. *Med Sci Sports Exerc* 16: 529-538.

21) Clarkson PM and Hubal MJ. 2002. Exercise-induced muscle damage in humans. *Am J Phys Med Rehabil* 81: S52-S69.

22) Nosaka K and Clarkson PM. 1996. Changes in indicators of inflammation after eccentric exercise of the elbow flexors. *Med Sci Sports Exerc* 28: 953-961.

23) Taguchi T, Matsuda T, Tamura R, Sato J and Mizumura K. 2005. Muscular mechanical hyperalgesia revealed by behavioural pain test and e-Fos expression in the spinal dorsal horn after eccentric contraction in rats. *J Physiol* 564: 259-268.

24) Graven-Nielsen T and Arendt-Nielsen L. 2003. Induction and assessment of muscle pain, referred pain, and muscular hyperalgesia. *Curr Pain Headache Rep* 7: 443-451.

25) Mizumura K and Taguchi T. 2016. Delayed onset muscle soreness: involvement of neurotrophic factors. *J Physiol Sci* 66: 43-52.

26) Miyamura M. 1994. Control of ventilation during exercise in man with special reference to the feature at the onset. *Jpn J Physiol* 44: 123-139.

27) Yunoki T, Arimitsu T, Yamanaka R, Lian CS, Afromdee R, Matsura R and Yano T. 2011. Ventilatory response to moderate incremental exercise performed 24 h after resistance exercise with concentric and eccentric contractions. *Eur J Appl Physiol* 111: 1769-1775.

28) Ishida K, Sato Y, Katayama K and Miyamura M. 2000. Initial ventilatory and circulatory responses to dynamic exercise are slowed in the elderly. *J Appl Physiol* 89: 1771-1777.

29) Kaufman MP. 2010. Control of breathing during dynamic exercise by thin fiber muscle afferents. *J Appl Physiol* 109: 947-948.

30) Momen A, Bower D, Boehmer J, Kunselman AR, Leuenberger UA and Sinoway LI. 2004. Renal blood flow in heart failure patients during exercise. *Am J Physiol Heart Circ Physiol* 287: H2834-H2839.

31) Krogh A and Lindhard J. 1913. The regulation of respiration and circulation during the initial stages of muscular work. *J Physiol* 47: 112-136.

32) Thornton JM, Guz A, Murphy K, Griffith AR, Pedersen DL, Kardos A, Leff A, Adams L, Casadei B and Paterson DJ. 2001. Identification of higher brain centres that may encode the cardiorespiratory response to exercise in humans. *J Physiol* 15: 823-836.

33) Williamson JW, McColl R, Mathews D, Mitchell JH, Raven PB and Morgan WP. 2002. Brain activation by central command during actual and imagined handgrip under hypnosis. *J Appl Physiol* 92: 1317-1324.

34) Haouzi P, Chenuel B and Hussezczuk A. 2004. Sensing vascular distension in skeletal muscle by slow conductingafferent fibers: neurophysiological basis and implication for respiratory control. *J Appl Physiol* 96: 407-418.

35) Hotta N, Yamamoto K, Ogata H, Maher P, Okumura N and Ishida K. 2016. Does degree of alteration in effort sense caused by eccentric exercise significantly affect initial exercise hyperpnea in humans? *J Physiol Anthropol* 35: 18. doi: 10.1186/s40101-016-0107-5.

36) Williamson JW, Fadel PJ and Mitchell JH. 2006. New insights into central cardiovascular control during exercise in humans: a central command update. *Exp Physiol* 91: 51-58.

37) Fridén J, Sfäkianos PN and Hargens AR. 1986. Muscle soreness and intramuscular fluid pressure: comparison between eccentric and concentric load. *J Appl Physiol* 61: 2175-2179.

38) Crenshaw AG, Thornell LE and Fridén J. 1994. Intramuscular pressure, torque and swelling for the exercise-induced sore vastus lateralis muscle. *Acta Physiol Scand* 152: 265-277.

39) Hotta N, Yamamoto K and Ishida K. 2009. The effect of external cuff pressure on initial exercise hyperpnea. *J Physiol Anthropol* 28: 91-95.

40) Crenshaw AG, Wiger P and Styf J. 1998. Evaluation of techniques for measuring negative intramuscular pressures in humans. *Eur J Appl Physiol Occup Physiol* 77: 44-49.

41) Säggaard K, Orizio C and Sjøgaard G. 2006. Surface mechanomyogram amplitude is not attenuated by intramuscular pressure. *Eur J Appl Physiol* 96: 178-184.

42) Mizumura K and Kumazawa T. 1976. Reflex respiratory response induced by chemical stimulation of muscle afferents. *Brain Res* 109: 402-406.

43) Waldrop TG, Millhorn DE, Eldridge FL and Klingler LE. 1984. Respiratory responses to noxious and nonnoxious heating of skin in cats. *J Appl Physiol* 57: 1738-1741.

44) Duranti R, Pantaleo T, Bellini F, Bongianni F and Scano G. 1991. Respiratory responses induced by the activation of somatic nociceptive afferents in humans. *J Appl Physiol* 71: 2440-2448.
45) Sarton E, Dahan A, Teppema L, Berkenbosch A, van den Elen M and van Kleeck J. 1997. Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. Anesthesiology 87: 289-296.

46) Jafari H, Courtois I, Van den Bergh O, Vlaeyen JWS and Van Diest I. 2017. Pain and respiration: a systematic review. Pain 158: 995-1006.

47) Ward DS and Karan S. 2002. Effects of pain and arousal on the control of breathing. J Anesth 16: 216-221.

48) Millan MJ. 1999. The induction of pain: an integrative review. Prog Neurobiol 57: 1-164.

49) Taguchi T, Sato J and Mizumura K. 2005. Augmented mechanical response of muscle thin-fiber sensory receptors recorded from rat muscle-nerve preparations in vitro after eccentric contraction. J Neurophysiol 94: 2822-2831.

50) Kumazawa T and Mizumura K. 1977. Thin-fibre receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. J Physiol 273: 179-194.

51) Wenk HN and McCleskey EW. 2007. A novel mouse skeletal muscle-nerve preparation and in vitro model of ischemia. J Neurosci Methods 159: 244-251.

52) Smith SA, Williams MA, Mitchell JH, Mammen PP and Garry MG. 2005. The capsaicin-sensitive afferent neuron in skeletal muscle is abnormal in heart failure. Circulation 111: 2056-2065.

53) Queme LF, Ross JL, Lu P, Hudgins RC and Jankowski MP. 1999. Effects of pain and arousal on cardiovascular rates during sustained submaximal contractions. J Physiol 528: 331-338.

54) Weerakody NS, Percival P, Hickey MW, Morgan DL, Gregory JE, Cann BJ and Proske U. 2003. Effects of local pressure and vibration on muscle pain from eccentric exercise and hypertonic saline. Pain 105: 425-435.

55) Weerakody NS, Whitehead NP, Cann BJ, Gregory JE and Proske U. 2001. Large-fiber mechanoreceptors contribute to muscle soreness after eccentric exercise. J Pain 2: 209-219.

56) McCloskey DJ and Mitchell JH. 1972. Reflex cardiovascular and respiratory responses originating in exercising muscle. J Physiol 224: 173-186.

57) Cote JN and Hoeger Bement MK. 2010. Update on the relation between pain and movement: consequences for clinical practice. Clin J Pain 26: 754-762.

58) Meru AV, Mittra S, Thyagarajan B and Chugh A. 2006. Intermittent claudication: an overview. Atherosclerosis 187: 221-237.

59) Ericsson A and Mannerkorpi K. 2016. How to manage fatigue in fibromyalgia: nonpharmacological options. Pain Manag 6: 331-338.

60) Valim V, Oliveira LM, Suda AL, Silva LE, Faro M, Neto TL, Feldman D and Natour J. 2002. Peak oxygen uptake and ventilatory anaerobic threshold in fibromyalgia. J Rheumatol 29: 353-357.

61) Farina D, Arendt-Nielsen L and Graven-Nielsen T. 2005. Experimental muscle pain reduces initial motor unit discharge rates during sustained submaximal contractions. J Appl Physiol 98: 999-1005.

62) Duncan MJ and Oxford SW. 2012. Acute caffeine ingestion enhances performance and damps muscle pain following resistance exercise to failure. J Sports Med Phys Fitness 52: 280-285.

63) Astokorki AH and Mauger AR. 2017. Transcutaneous electrical nerve stimulation reduces exercise-induced perceived pain and improves endurance exercise performance. Eur J Appl Physiol 117: 483-492.

64) Kami K, Tajima F and Senba E. 2017. Exercise-induced hypoalgesia: potential mechanisms in animal models of neuropathic pain. Anat Sci Int 92: 79-90.

65) O’Connor PJ and Cook DB. 1999. Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. Exerc Sport Sci Rev 27: 119-166.

66) Zaimuddin Z, Sacco P, Newton M and Nosaka K. 2006. Light concentric exercise has a temporarily analgesic effect on delayed-onset muscle soreness, but no effect on recovery from eccentric exercise. Appl Physiol Nutr Metab 31: 126-134.

67) Cheung K, Hume P and Maxwell L. 2003. Delayed onset muscle soreness: treatment strategies and performance factors. Sports Med 33: 145-164.

68) Poole DC, Barstow TJ, McDonough P and Jones AM. 2008. Control of oxygen uptake during exercise. Med Sci Sports Exerc 40: 462-474.

69) Spencer MD, Gravelle BM, Murias JM, Zerbini L, Pogliaghi S and Paterson DH. 2013. Duration of “Phase I” VO2: a comparison of methods used in its estimation and the effects of varying moderate-intensity work rate. Am J Physiol Regul Integr Comp Physiol 304: R238-R247.

70) Nederveen JP, Major B, Paterson DH and Murias JM. 2014. Faster VO2 kinetics after eccentric contractions is explained by better matching of O2 delivery to O2 utilization. Eur J Appl Physiol 114: 2169-2181.

71) Molina R and Denadai BS. 2011. Muscle damage slows oxygen uptake kinetics during moderate-intensity exercise performed at high pedal rate. Appl Physiol Nutr Metab 36: 848-855.

72) Jones AM, Grassi B, Christensen PM, Krustup P, Bangsbo J and Poole DC. 2011. Slow component of VO2 kinetics: mechanistic bases and practical applications. Med Sci Sports Exerc 43: 2046-2062.

73) Baranauskiene N, Nikilaitiene N, Tasiule J, Civinskiene G and Stasiulis A. 2017. Gender differences in residual effect of prior drop jumps on oxygen uptake during heavy cycling exercise. Medicina 53: 331-338.

74) Caldwell JT, Wardlow GC, Branch PA, Ramos M, Black CD and Ade CJ. 2016. Effect of exercise-induced muscle damage on vascular function and skeletal muscle microvascular deoxygenation. Physiol Rep 4: e13032.

75) Ahmadi S, Sinclair PJ, Foroughi N and Davis GM. 2008. Monitoring muscle oxygenation after eccentric exercise-induced muscle damage using near-infrared spectroscopy. Appl Physiol Nutr Metab 33: 743-752.

76) DeLorey DS, Paterson DH and Kowalchuk JM. 2007. Effects of ageing on muscle O2 utilization and muscle oxygenation during the transition to moderate-intensity exercise. Appl Physiol Nutr Metab 32: 1251-1262.

77) Murias JM, Spencer MD and Paterson DH. 2014. The critical role of O2 provision in the dynamic adjustment of oxidative phosphorylation. Exerc Sport Sci Rev 42: 4-11.

78) Chin LM, Leigh RJ, Heigenhauser GJ, Rossiter HB, Paterson DH and Kowalchuk JM. 2007. Hyperventilation-induced hypocapnic alkalosis slows the adaptation of pulmonary O2 uptake during the transition to moderate-intensity exercise. J Physiol 583: 351-364.