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SHORT- AND LONG-TERM MODULATION OF THE EXERCISE VENTILATORY RESPONSE

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Abstract

The importance of adaptive control strategies (modulation and plasticity) in the control of breathing during exercise has become recognized only in recent years. In this review we discuss new evidence for modulation of the exercise ventilatory response in humans, specifically, short- and long-term modulation. Short-term modulation is proposed to be an important regulatory mechanism that helps maintain blood gas homeostasis during exercise.

Keywords

Exercise hyperpnea; Respiratory control; Serotonin; Hypercapnia

1. Introduction

Although the ventilatory response to exercise is of fundamental importance to every-day activity, our understanding of ventilatory control during exercise remains poor and has advanced only incrementally in decades (21). The mechanism of exercise hyperpnea continues to pose a dilemma, and provokes controversy regarding the primary factors increasing breathing during exercise (16;22;51;59). In recent years, the potential importance of adaptive control strategies (modulation and plasticity) in the regulation of breathing during exercise has become apparent (38;43;51). We recently reviewed the concept that multiple, mechanistic “layers” contribute to exercise hyperpnea, including mechanisms of modulation and plasticity (40). In this symposium-based paper, we continue discussion of these factors and present recent evidence for modulation and plasticity of the exercise ventilatory response in humans.

In humans, moderate steady-state exercise is characterized by the maintenance of a constant partial pressure of CO₂ (P_{CO₂}) in the arterial blood (i.e., arterial isocapnia), an effect accomplished by increasing alveolar ventilation ($\dot{V}_A$) in direct proportion to increased metabolic CO₂ production ($\dot{V}_{CO_2}$). Since the partial pressure of O₂ (P_{O₂}) and [H⁺] in the arterial blood remain relatively constant, the ventilatory response to moderate exercise is not primarily driven by traditional chemoreceptor feedback (15;21).

Recent advances in neurobiology have raised new questions regarding neural mechanism(s) controlling ventilation ($\dot{V}_E$) during exercise (40). Over the past few decades, we have come to realize that the neural system controlling breathing exhibits considerable capacity for modulation and plasticity, including the exercise ventilatory response (43). Here, we will discuss two of these adaptive mechanisms: short-term (STM) and long-term modulation (LTM) of the exercise ventilatory response (4;36;38). We will limit our discussion to ventilatory responses during mild and moderate exercise since additional factors, such as increasing mechanofeedback and chemofeedback, complicate interpretations during high intensity exercise.

2. Modulation and Plasticity in Ventilatory Control

The concepts of modulation and plasticity as they apply to the neural system controlling breathing are closely linked, and are not mutually exclusive. Modulation and plasticity differ largely in the time domain of their effects. It is, in fact, possible for processes of modulation to initiate or trigger the longer-lasting plasticity. In essence, modulation is a neurochemically-induced alteration in cellular properties, or synaptic strength, that adjusts or even transforms neural network function, such as the neural circuits controlling breathing (43). Once the stimulus for modulation is removed, functional alterations in the neural system rapidly reverse, restoring ventilatory function to normal. In contrast, plasticity is an alteration in neural network function due to changes in cellular or synaptic properties that persist long after the initiating stimulus has ended (43). Initiating stimuli for respiratory plasticity include repetitive or prolonged hypoxia (intermittent or continuous), neural activity, exercise, injury, disease, and multiple other “experiences” (43).

In the context of these functional definitions, modulation of the exercise ventilatory response is an increased or decreased ventilatory response due to neural alterations that are rapidly (one trial) reversed in subsequent exercise trials if the inducing stimulus is removed. Plasticity, on the other hand, is manifest as an increased or decreased exercise ventilatory response that persists after the stimulus has ended, suggesting a form of “learning”. Once plasticity is established, it may be actively reversed, for example by repeated exercise trials at normal conditions. Much research has focused on plasticity in respiratory motor control in recent years, and these findings are extensively reviewed (5;6;12;17;^{19,31,34,35};40;42;43;47). Perhaps the most well-studied examples of modulation and plasticity in ventilatory control are initiated and orchestrated by the neurochemical serotonin (17;43). Examples of modulation and plasticity in the exercise ventilatory response discussed here are also serotonin-induced. In specific, we will discuss short- (STM) and long-term modulation (LTM) of the exercise ventilatory response. STM was first named as such in 1993 (4), based on previous studies of exercise with increased dead space in goats (38). Earlier studies describing an augmentation of the exercise ventilatory response with increased dead space in humans did not attach any specific name or definition to this phenomenon (29;50;60). LTM of the exercise ventilatory response was first described in 1993 based again on studies in goats (36); there were no previous reports in the literature prior to this time, although there has been subsequent study of its existence in humans (56;58;62).

Although both STM and LTM were named “modulation” at the time they were first described (4;36), LTM is in fact an example of **plasticity** in respiratory motor control since it persists beyond the training-stimulus (40;43). Although increased respiratory dead space (or hypercapnia) triggers both STM and LTM in goats, STM is observed within a single exercise trial, and is gone during the next if the dead space is removed (4;38). In contrast, LTM results from repeated pairing of dead space and exercise, and is observed for many trials after dead space is no longer presented (36). These distinctions are outlined in our recent review (40).

3. Short-Term Modulation of the Exercise Ventilatory Response

STM has been studied extensively in conscious goats during exercise with added external dead space (38;44). Dead space increases resting ventilatory drive due to mild hypercapnia and traditional CO₂-chemoreceptor feedback caused by the dead space (38). In the goat model, exercise with added dead space augments the exercise ventilatory response sufficiently to maintain the same relative regulation of arterial P_{CO2} with respect to its new, elevated resting level; thus, the increased ventilatory response occurs by a mechanism independent from changes in chemoreceptor feedback between rest and exercise. This mechanism was named **short-term modulation** (STM) of the exercise ventilatory response since the exercise ventilatory response is reversibly augmented within a single exercise trial, and reverts to normal in the next trial if dead space is returned to normal. Subsequently, STM has been shown (in goats) to be serotonin-dependent (4), and to augment $\dot{V}_E$ by a mechanism that requires spinal serotonin receptor activation (45).

STM may reflect a more general property of the ventilatory control system whereby the exercise ventilatory response is linked to resting ventilatory drive (37;41;44) since both humans and goats exhibit constant relative PaCO₂ regulation from rest to exercise despite diverse treatments that increase or decrease resting ventilatory drive and/or PaCO₂ levels (21;44;48;53;54). For example, when resting $\dot{V}_E$ is diminished and PaCO₂ increased (e.g., carotid body denervation or metabolic alkalosis), or when resting $\dot{V}_E$ is increased and PaCO₂ decreased (e.g., metabolic acidosis, increased progesterone levels, serotonin depletion, increased dead space), PaCO₂ during exercise is regulated with the same precision relative to its new resting level. Such constant relative blood gas regulation requires active ventilatory control mechanisms that adapt the exercise ventilatory response to prevailing physiological conditions. Because these adjustments are found with a wide range of perturbations to resting $\dot{V}_E$, a common mechanism was originally proposed that links resting ventilatory drive (versus PaCO₂ *per se*) with the exercise ventilatory response (4;44;45;51).

Other investigators have described the effects of increased dead space (29;50;60) on the exercise ventilatory response in humans, although these studies did not explicitly or prospectively test the robustness of STM. In 1992, Poon (50) observed potentiation of the exercise ventilatory response with dead space, which was similar to that seen in earlier studies in goats (38). He explained this potentiation via his optimization model of respiratory regulation during exercise (2;50). While Poon also studied the effects of increased dead space in three middle-aged overweight men, the effect of age and gender on STM has not been thoroughly addressed, either in goats or humans. Although other models of serotonin-dependent respiratory plasticity display prominent age-dependent sexual dimorphisms (8;9), there seems to be less influence of age and/or sex on STM (see below).

STM is robust during mild to moderate exercise with increased dead space in healthy younger men (aged 25–35 years) (50;63). The exercise ventilatory response (defined as the slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ from rest to exercise) is augmented with increased dead space in a manner similar to goats (38;63). Indeed, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ increased progressively as the volume of added dead space increased (Fig. 1, Top Panel). Further, as the exercise intensity increased, the effect of the added dead space on $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ was reduced. Thus, as in goats, there is a limited capacity for STM to augment the exercise ventilatory response (38). We confirmed that the augmented ventilatory response was due to STM, and not to changes in chemoreflex stimulation, by demonstrating that the relative regulation of end-tidal P_{CO2} (P_{ETCO2}) from rest to exercise was preserved with increased dead space. Although P_{ETCO2}, unlike PaCO₂, increases from rest to exercise, there were no

differences in the P_{ETCO_2} change (ΔP_{ETCO_2}) from rest to exercise. Thus, there was no additional chemoreceptor stimulus during exercise with added dead space as compared with control conditions (Fig. 1, Bottom Panel). In fact, the apparent increase in ΔP_{ETCO_2} with added dead space was lower than without dead space, confirming that $\dot{V}_E$ was augmented via mechanisms independent from changes in chemoreceptor feedback (i.e., STM).

We concluded that STM is observed in younger men, and that the magnitude of STM is less robust at higher levels of dead space volume or exercise intensity. Thus, STM may be limited in its range.

At the onset of exercise without added dead space, $\dot{V}_E$ increased via increases in both tidal volume and breathing frequency. As exercise intensity increased, further increases in $\dot{V}_E$ were accomplished via changes in tidal volume only. Increased tidal volume was accomplished at the expense of both inspiratory reserve volume (i.e., increase in end-inspiratory lung volume, EILV) and expiratory reserve volume (i.e., decrease in end-expiratory lung volume, EELV). In contrast, during exercise with added dead space, there was very little change in the breathing frequency, and $\dot{V}_E$ was augmented via increased tidal volume (63), an effect accomplished exclusively via changes in EILV (Figure 2) (64). Differences in the patterns of lung volume recruitment between exercise without and with added dead space indicate differential recruitment of respiratory muscles, and hence, suggest fundamental differences in the control of breathing. Respiratory muscle recruitment during STM appears to result from additional recruitment of the same (inspiratory) muscles activated by exercise and dead space (i.e., hypercapnia). This finding is consistent with the hypothesis that STM in humans results from modulation of inspiratory motor neurons at the level of the spinal cord, as previously proposed in goats (45), and indirectly supports the proposed neural mechanism of STM (40;45) (see section 4).

A plausible hypothesis is that STM of the exercise ventilatory response would be absent or diminished in older men, due to changes in respiratory function associated with normal aging (3;14;50) and/or potential age-related changes in the capacity for serotonin-dependent respiratory plasticity (7;9). Hence, we investigated STM of the exercise ventilatory response in older men aged 65–75 yr. Aging is associated with a progressive decline in lung function mainly because of a loss of elastic recoil, decreased chest wall compliance, decreased respiratory muscle strength, and increased ventilation-perfusion mismatch (due to increased shunt and physiological dead space) (1;33). In addition, a number of studies suggest that the ventilatory chemoreflexes, in particular the ventilatory response to hypercapnia (HCVR), are reduced in older as compared with younger people (10;11;32;49). In contrast, the exercise ventilatory response is increased with aging (52), as a result of increased dead space ventilation in older people relative to younger adults (25). We used the same volumes of added dead space and the same exercise levels as in our study of younger men. These results are preliminary and have been published in abstract form only, but suggest remarkably

similar findings to those observed in the younger men; $\Delta \dot{V}_E / \Delta \dot{V}_{CO_2}$ was augmented with added dead space by a diminishing amount with increased work rate (Fig. 3). As in younger men, ΔP_{ETCO_2} from rest to exercise was lower with added dead space than without, confirming that the ventilatory response was augmented via STM versus changes in chemoreceptor feedback from rest to exercise (data not shown). However, more research is required to address this issue.

4. Postulated Neural Mechanism of Short-Term Modulation

The neural mechanism giving rise to STM has been reviewed elsewhere (40;41;43;57). Briefly, based on studies in goats, a neural mechanism has been proposed to explain STM as

shown in Figure 4 (40). With exercise, brainstem premotor neurons activate spinal respiratory motor neurons, subsequently driving respiratory muscles to increase ventilation (i.e., the exercise ventilatory response). When a dead space is added at rest, breathing is stimulated by traditional chemoreceptor feedback (38). Furthermore, brainstem serotonergic raphe neurons are stimulated, elevating 5-HT release in the vicinity of respiratory motor neurons, thereby increasing motor neuron excitability (i.e., serotonergic modulation from descending brainstem-spinal cord projections of raphe neurons) (4;24;37;41). With exercise onset, the same feedforward exercise stimulus is amplified at the level of the respiratory motor neurons, resulting in a greater drive to the respiratory muscles and an augmented exercise ventilatory response (i.e., STM). In goats, STM with added dead space is abolished after: 1) 5-HT depletion (via blocking tryptophan hydroxylase with p-chlorophenylalanine (4)), 2) blocking systemic 5-HT receptors with a broad spectrum serotonin receptor antagonist (4), and 3) selectively blocking **spinal** 5-HT receptors (45). Thus, spinal serotonin receptor activation is necessary for STM of the exercise ventilatory response with increased dead space in goats; the most likely serotonin receptor is of the 5-HT₂-receptor subtype (45). It is not yet known if STM in humans is also serotonin dependent, or if STM is diminished or enhanced in patient populations.

4. Long-Term Modulation of the Exercise Ventilatory Response

If exercise and hypercapnia (dead space or raised inspired P_{CO_2}) are repeatedly and explicitly paired over multiple exercise trials in goats (36) and humans (62), the ventilatory response to future exercise trials is enhanced, many exercise trials after the hypercapnic stimulus has been removed. This persistent augmentation of the exercise ventilatory response is a form of serotonin-dependent respiratory plasticity termed **long-term modulation** (LTM) of the exercise ventilatory response (27;28;36;40). Although the name long-term modulation suggests rapid reversibility, the persistent nature of LTM is sufficient to categorize this mechanism as a form of plasticity (43). However, we suspect that repeated activation of the STM mechanism is a causal factor in establishing LTM since both are serotonin-dependent mechanisms (26). Since repeated activation of STM may trigger LTM, these mechanisms appear to be mechanistically linked (40;43). To date, these concepts have been developed largely in a female goat model (26;36;38;43;44;57).

Evidence supporting the existence of LTM in humans has been more controversial; however, the controversy may be related to the modest training protocols used in some of these studies. Only one study has reported a robust LTM of the exercise ventilatory response during steady-state cycling. This was after a large number of exercise trials paired with raised inspired P_{CO_2} (62); thus, LTM may require many repetitions of hypercapnic exercise to be observed in humans. Other studies of LTM in humans have reported increases in the dynamic, but not steady state, ventilatory response at exercise onset (23;58), but these studies used more modest training protocols. Still other studies reported little effect of repeated hypercapnic exercise on the exercise ventilatory response (13;46), but these studies utilized far fewer exercise trials and may have been insufficient to elicit LTM.

LTM of the exercise ventilatory response at the onset of exercise has also been evoked by repeated exercise paired with inspiratory resistive loading (without hypercapnia) (56). Therefore, LTM may be initiated by increased tidal volume, ventilatory drive or proprioceptor feedback versus hypercapnia *per se* (56). This finding is significant because it extends the concept of LTM to multiple physiological conditions associated with altered respiratory system mechanics, but with minimal disruption of blood gas homeostasis. Thus, LTM may be important in enabling individuals to accommodate mechanical challenges, ensuring adequate ventilatory responses during exercise in diverse conditions such as

SCUBA diving, wearing occupational breathing apparatus, aging, weight gain, or the onset of lung disease (40).

6. Potential Relevance of STM to Ventilatory Control during Exercise

Although the neural system subserving respiratory control during exercise has traditionally been regarded as fixed and immutable, compelling evidence has accumulated in recent years, demonstrating that the respiratory control system exhibits considerable capacity for modulation and/or plasticity of the exercise ventilatory response (40;43;51). This capacity may allow humans to augment ventilatory output and/or respiratory muscle drive in order to accommodate changes in prevailing physiological conditions (i.e., altered respiratory mechanics, impaired pulmonary gas exchange) and environmental situations (i.e., imposed breathing apparatus, altitude). A unique aspect of this capacity for modulation and plasticity is that it imparts a degree of flexibility, enabling adjustments of the primary feedforward stimulus or stimuli that increase breathing during exercise (Fig. 5, label 1). This capacity has been regarded by some as evidence that the exercise ventilatory response results from an optimization paradigm, minimizing the opposing costs represented as the work of breathing versus inadequate regulation of arterial blood gas composition (51). For example, the primary stimulus for ventilation is carefully linked to the central drive to the exercising

muscles so that ventilation and metabolic production of carbon dioxide ($\dot{V}_{\text{CO}_2}$) during exercise are appropriately matched, thereby maintaining isocapnia during submaximal exercise (Fig. 5). The strength of this link becomes apparent when attempting to change exercise perception while maintaining a given work rate (18;20;30;55;61).

The existence of STM and LTM may allow augmentation of respiratory muscle drive to preserve ventilation when pulmonary mechanics are compromised, for example in lung disease or obesity (Fig. 5, label 2). Available evidence suggests that the critical neural mechanisms arise in the spinal cord near respiratory motor neurons, although this evidence does not rule out a role for other sites in the central nervous system (43). Thus, STM and LTM represent a capacity to preserve an appropriate exercise ventilatory response despite challenges encountered during life.

The existence, potential, relevance, and operational robustness of these neural mechanisms in human health and disease must be further explored, but their identification offers remarkable potential to understand the layers of complexity in ventilatory control during exercise. Furthermore, a detailed understanding of cellular mechanisms giving rise to such plasticity may inspire novel therapeutic approaches to clinical conditions with compromised ventilatory capacity such as spinal injury, motor neuron disease, obstructive sleep apnea, obesity and lung disease (39).

7. Summary

While STM and LTM occur in humans, further prospective studies are needed to investigate mechanisms of human modulation (e.g. is it serotonin-dependent) and whether aged and/or diseased populations utilize this strategy to preserve the capacity for submaximal exercise. We propose that STM is an important homeostatic mechanism by which the exercise ventilatory response can be augmented to maintain a normal ventilatory response, preventing loss of blood gas homeostasis during exercise.

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Figure 1.

Short-term modulation of the exercise ventilatory response in younger men. *Top Panel:* slope of the exercise ventilatory response ($\Delta \dot{V}_E / \Delta \dot{V}_{CO_2}$) from rest to each work rate. *Bottom Panel:* change in end-tidal PCO_2 (PET_{CO_2}) from rest to each work rate. DS, dead space.

Figure 2.

Typical flow-volume loops in younger men. Left Panel: at rest and each work rate with no added dead space, indicating main effect of exercise on lung volumes; Right Panel: without (Control) and with each added dead space volume during exercise at 50 W, indicating main effect of dead space on lung volumes. Max loop, maximal flow-volume loop at rest; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume. Adapted from Wood et al. 2009.

Figure 3. Short-term modulation of the exercise ventilatory response in older men. Slope of the exercise ventilatory response ($\Delta \dot{V}E / \Delta \dot{V}CO_2$) from rest to each work rate.

Figure 4.

Proposed neural mechanism of STM. Exercise increases ventilation via activation of premotor neurons in the brain stem, driving spinal respiratory motor neurons to activate respiratory muscle contraction. The addition of external dead space activates brain stem raphe serotonergic neurons that project to the ventral spinal cord, increasing serotonin release in the vicinity of respiratory motor neurons. This amplifies the descending respiratory drive resulting in greater ventilation at a given exercise intensity (see text for full details). 5-HT, serotonin.

Figure 5.

Hypothetical mechanisms modulating the exercise ventilatory response when dead space is increased (STM) with the central command for locomotion and feedback. Model assumes that the primary feedforward stimulus for ventilation [1] does not necessarily need to be altered for ventilation to be augmented during STM. However, during STM respiratory muscle drive is increased via increased excitability of spinal motor neurons [2] to synaptic inputs from descending feedforward stimulus for ventilation.