Control of Breathing During Exercise

Hubert V. Forster,[*1] *Philippe Haouzi,*[2] *and Jerome A. Dempsey*[3]

ABSTRACT:

During exercise by healthy mammals, alveolar ventilation and alveolar-capillary diffusion increase in proportion to the increase in metabolic rate to prevent $PaCO_2$ from increasing and PaO_2 from decreasing. There is no known mechanism capable of directly sensing the rate of gas exchange in the muscles or the lungs; thus, for over a century there has been intense interest in elucidating how respiratory neurons adjust their output to variables which can not be directly monitored. Several hypotheses have been tested and supportive data were obtained, but for each hypothesis, there are contradictory data or reasons to question the validity of each hypothesis. Herein, we report a critique of the major hypotheses which has led to the following conclusions. First, a single stimulus or combination of stimuli that convincingly and entirely explains the hyperpnea has not been identified. Second, the coupling of the hyperpnea to metabolic rate is not causal but is due to of these variables each resulting from a common factor which link the circulatory and ventilatory responses to exercise. Third, stimuli postulated to act at pulmonary or cardiac receptors or carotid and intracranial chemoreceptors are not primary mediators of the hyperpnea. Fourth, stimuli originating in exercising limbs and conveyed to the brain by spinal afferents contribute to the exercise hyperpnea. Fifth, the hyperventilation during heavy exercise is not primarily due to lactacidosis stimulation of carotid chemoreceptors. Finally, since volitional exercise requires activation of the CNS, neural feed-forward (central command) mediation of the exercise hyperpnea seems intuitive and is supported by data from several studies. However, there is no compelling evidence to accept this concept as an indisputable fact. © 2012 American Physiological Society. *Compr Physiol* 2:743-777, 2012.

Introduction

The concept "d'homeostasie du milieu interieur" as developed by Claude Bernard, more than a century ago, assumes that living organisms tend to maintain constant the composition of their internal environment (40). This concept then requires that during exercise, the increase in O_2 extracted by the muscles from the blood must be replenished, and the CO_2 and H^+ produced by the muscles must be eliminated. These requirements will be met if alveolar ventilation ($\dot{V}_A$) and alveolar-capillary diffusion increase in proportion to the increase in metabolic rate. In many species, the respiratory system is also vital to eliminating at least a portion of the increased heat generated by exercise, which is achieved by increasing ventilation of the conducting airways (dead space ventilation). The increase in total or pulmonary ventilation ($\dot{V}_E$) required to meet these needs must be achieved efficiently with minimal oxygen consumed by the respiratory muscles. These requirements of the respiratory system during exercise depend on specific inputs to respiratory neurons in the brain that regulate breathing (Fig. 1).

For over a century, there has been intense interest among physiologists in the mechanism that regulates breathing during exercise. The long acknowledged and indisputable fact is that in healthy humans and most other mammals, the exercise hyperpnea is not associated with an increase in $PaCO_2$ or a decrease in Pa_{O_2} (Fig. 2). Mammals do not possess any known receptive mechanisms capable of directly sensing the rate at which CO_2 and O_2 are exchanged in the peripheral tissues or in the lungs; thus, one of the most puzzling challenges in integrative physiology is to resolve how respiratory neurons adjust their output to variables which can not be directly monitored. Particularly perplexing is that there is no known mechanism to account for over a twenty fold increase in $\dot{V}_E$, representing the largest nonvolitional drive to breathe (Fig. 3). This apparent paradox has lead to vigorous discussions and an incredible number of studies attempting to elucidate the mechanism. Several hypotheses have been extensively tested and impressive data were obtained supportive of different mechanisms that seemingly could mediate the hyperpnea. However, there seems to be contradictory data or reasons to question the validity of each hypothesized mechanism. As a result, there has never been a consensus among investigators that any of the proposed mechanisms mediates the hyperpnea.

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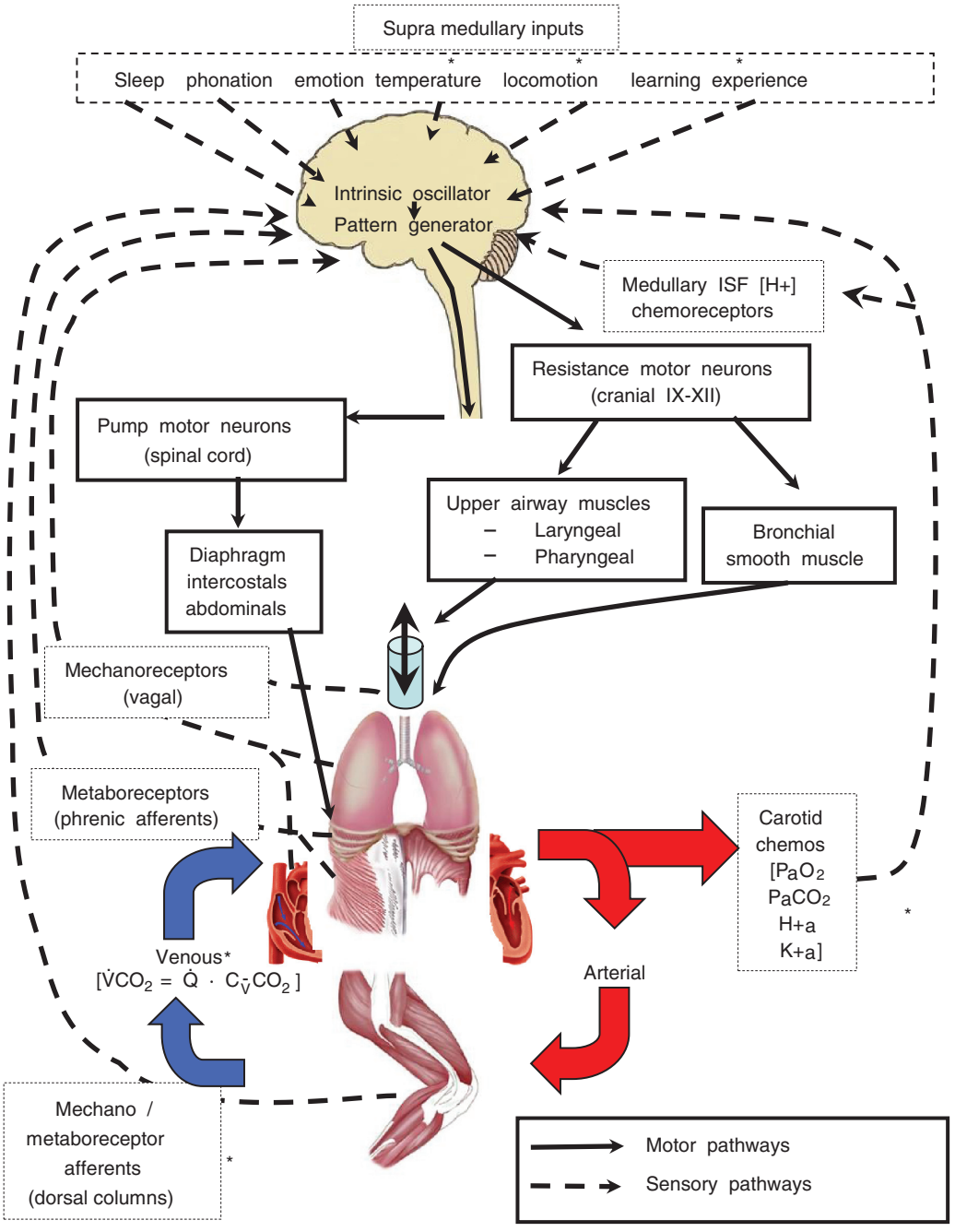

Figure 1 Schematic depicting multiple structures contributing to the control of breathing. It is hypothesized that respiratory rhythm originates within a brainstem oscillator which activates brainstem pattern generating neurons that provide for the proper sequential activation of respiratory pump (diaphragm, intercostal, and abdominal) and airway (laryngeal and pharyngeal) muscles. These brainstem neurons receive excitatory and inhibitory input from multiple sources including hypothesized supramedullary central command and mecho/metaboreceptor initiated spinal afferents from limb and respiratory skeletal muscles. In addition, the brainstem controller neurons receive carotid and intracranial chemoreceptor (retrotrapezoid nucleus, RTN) and vagal mechanoreceptor input critical to meet the proper ventilatory response to exercise. The figure is, with permission, from Dempsey et al. (86).

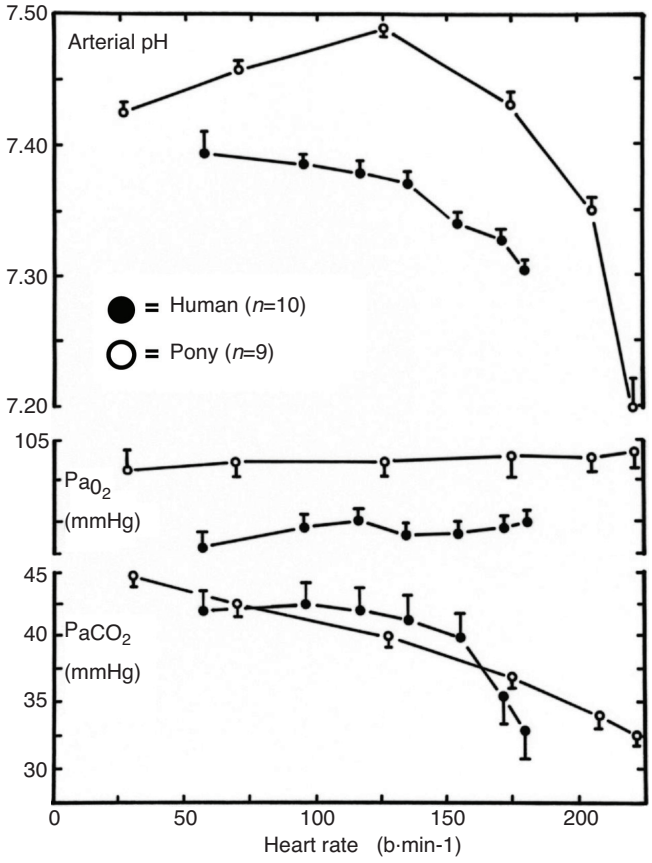

Figure 2 Steady-state arterial blood gas and pH status during spontaneous exercise in humans and ponies. Exercise intensity is depicted by heart rate rather than metabolic rate to avoid use of a mask or breathing valve which that can affect the ventilatory response. Note in humans arterial homeostasis is maintained from rest to a heart rate of about 150 and thereafter pH and $PaCO_2$ decrease. In ponies, $PaCO_2$ is inversely related to exercise intensity from rest to maximum irrespective of initially an alkaline but then an acid pH. In both species, PaO_2 homeostasis is maintained throughout exercise. Data are, with permission, from Forster et al. (119, 124, 126).

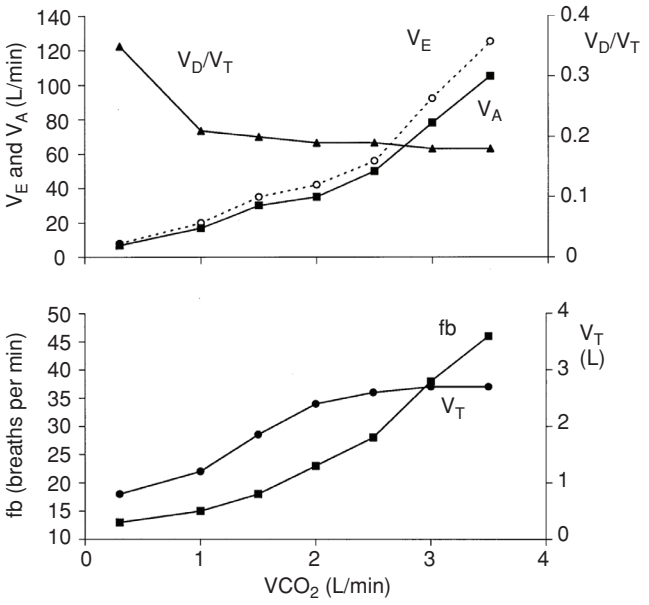

Figure 3 Effect of steady-state exercise intensity (expressed as CO_2 excretion, $\dot{V}_{CO_2}$) in humans on pulmonary ($\dot{V}_E$) and alveolar ($\dot{V}_A$) ventilation, breathing frequency (fb), tidal volume (V_T), and dead space (V_D) to V_T ratio. Note $\dot{V}_E$ and $\dot{V}_A$ increase linearly as $\dot{V}_{CO_2}$ increases to about 2.5 l/min but thereafter $\dot{V}_E$ and $\dot{V}_A$ increase relatively more than $\dot{V}_{CO_2}$. Adapted, with permission, from Dempsey et al. (86).

In this review, we will first describe key characteristics of the exercise hyperpnea which have provided direction for many past studies. We will then critically review major theories on mechanisms regulating the hyperpnea and provide our conclusions regarding these theories.

Characteristics of the Exercise Hyperpnea

Ventilatory response to a step change to a constant work load

The temporal profile of $\dot{V}_E$ during a constant work rate has been characterized by time constants and a time delay (84,212, 213,345,348). Indeed, the $\dot{V}_E$ response to a constant work load can be divided into a fast component (phase I) with a time constant of a few seconds, followed by a slow exponential-like rise in $\dot{V}_E$ (phase II) with a ~60 s time constant and a time delay leading to a steady state (phase III) (Fig. 4A), (37, 63, 66,343,347). The steady state is achieved within 3 min during light or moderate levels of exercise. During heavy exercise, $\dot{V}_E$ continues to rise until exhaustion (63). This temporal pattern describes the response in humans. In other mammals, the phase II time constants are shorter.

A similar approach has been used to determine the dynamics of pulmonary gas exchange, namely, oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide excretion ($\dot{V}_{CO_2}$). The $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ responses to a constant moderate work load follow a pattern similar to that of $\dot{V}_E$ but with faster phase II kinetics of 30 to 35 s for $\dot{V}_{O_2}$ and 40 to 50 s for $\dot{V}_{CO_2}$ (37, 63, 66, 343). Like $\dot{V}_E$, the $\dot{V}_{O_2}$ and $\dot{V}_{O_2}$ time constants lengthen during heavy exercise and a steady state is never achieved.

At the cessation of moderate exercise intensity, $\dot{V}_E$ (Fig. 4), $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ decrease over about 3 min to resting values following an exponential pattern which have temporal characteristics similar to the on-transients. Specifically, an initial and short lasting drop in these parameters is followed by phase II decreases with time constants similar to the phase II on-transients. The magnitude of the rapid drop of $\dot{V}_E$ at the cessation of exercise has been found to be higher (84) or lower (180) than during the on-transient, but there is no apparent relationship between their amplitudes. Finally the rapid $\dot{V}_E$ off-transient following exercise performed above the lactate threshold appears to be dramatically depressed, regardless of the level of blood acidosis (182).

Except for heavy exercise, a hallmark of the exercise hyperpnea is that in the steady state, the $\dot{V}_E$ response is

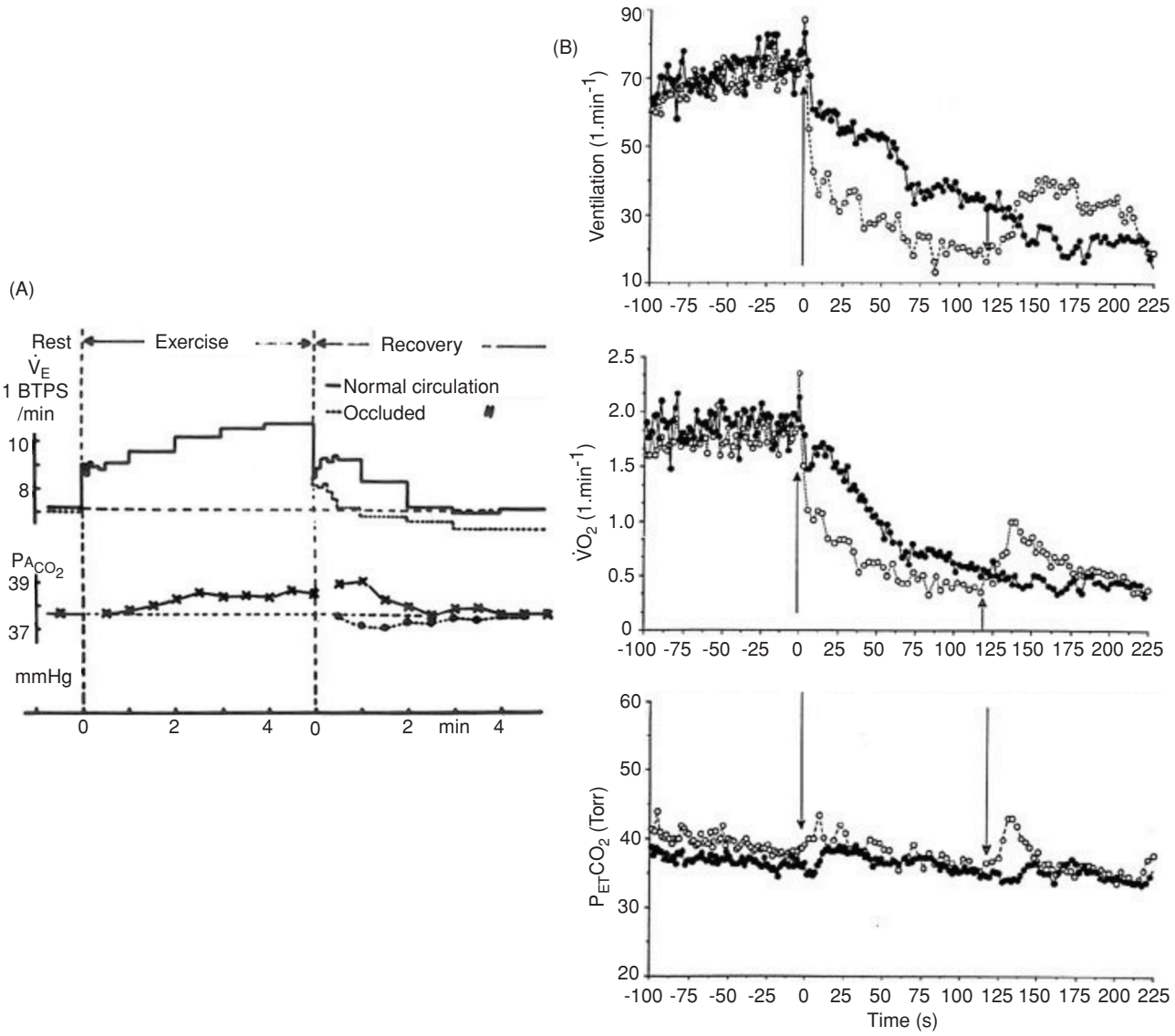

Figure 4 Temporal pattern of ventilatory responses during and after exercise by healthy humans. Panel A shows the normal fast (phase I) and slow (phase II) responses to mild exercise and also shows that occlusion of blood flow to the muscles during the recovery hastens the return of ventilation to control levels [data, with permission, from Dejours (84)]. In panel B are data during and after heavy constant work rate cycloergometer exercise. Between the two arrows, cuffs around the legs were inflated to occlude blood flow (open symbols) and these data are compared to unoccluded flow (closed symbols). Note again that the ventilatory decline during recovery was increased during cuff occlusion despite expected accumulation of metabolites in the muscle circulation [data, with permission, from Haouzi et al. (158)].

proportional to $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ (Fig. 3). For heavy exercise leading to production of lactic acid, $\dot{V}_E$ increases proportionately more than $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. The slope of the $\dot{V}_E$-$\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ relationships are influenced by such conditions as exercise type (88, 193, 232, 319), posture (88), muscle mass (16), acid-base status (121, 259), levels of oxygenation (84, 89, 125), and levels of certain hormones or neurotransmitters (197, 242, 272, 293). These relationships are less well established for non-human mammals, but based on changes in $PaCO_2$ (presented below), it appears that in most non-human species, $\dot{V}_E$ increases during exercise proportionately more than $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

Arterial blood gases during constant load exercise

In humans, $PaCO_2$ and Pa_{O_2} change minimally from rest during exercise up to approximately 60% to 70% of maximal $\dot{V}_{O_2}$ (Fig. 2). In most subjects there is a transient 1 to 3 mmHg hypocapnia at the onset of exercise (27, 126, 255, 367). There is also a transient 1 to 3 mmHg hypocapnia in the mild to moderate exercise transition (Fig. 5). Similarly during steady state submaximal exercise, $PaCO_2$ differs from rest by at most 1 to 3 mmHg (14, 27, 84, 90, 126, 367). However, during heavy exercise coincident with the lactacidosis, $PaCO_2$ decreases from rest by as much as 10 mmHg in most humans (14, 84,

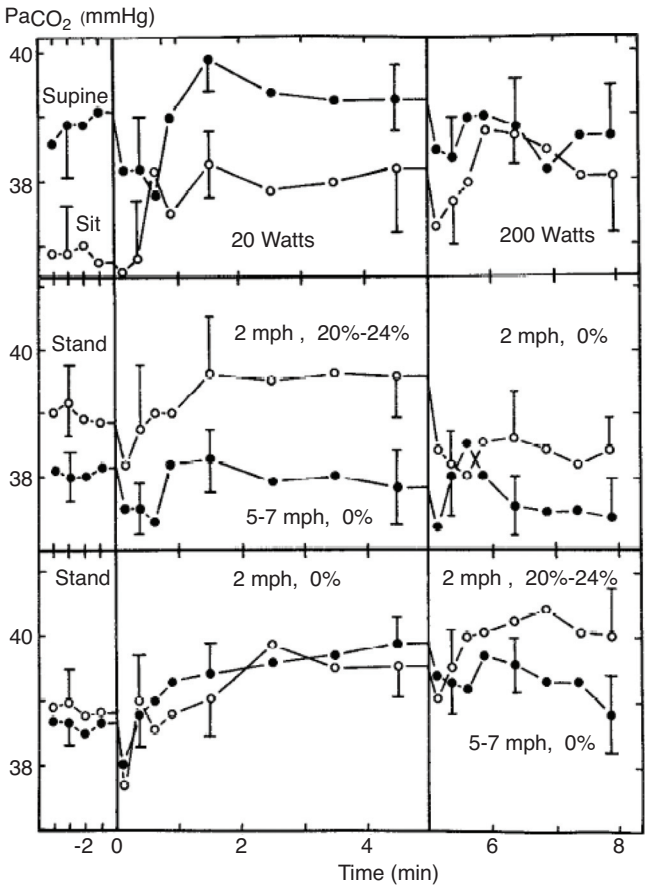

Figure 5 Temporal pattern of P_aCO_2 in humans ($n = 10$) from rest to work and work-to-work submaximal levels of exercise. All data were obtained without the subjects encumbered by a breathing valve system. Note the transient hypocapnia in the exercise transitions. The data are, with permission, from Forster et al. (126).

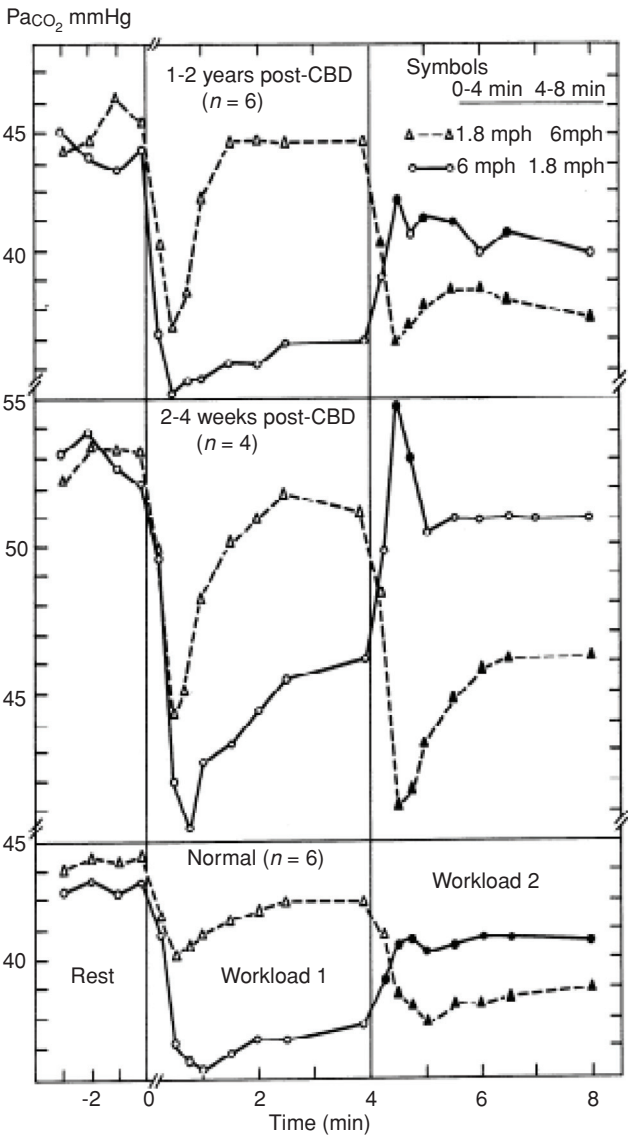

Figure 6 Temporal pattern of $PaCO_2$ in normal and carotid body denervated (CBD) ponies in rest to work and work-to-work transitions. The data were obtained without a mask needed to measure ventilatory parameters. Note the hypocapnia in rest to work transitions with some but not complete recovery, the changes in work-to-work transitions, and the exacerbation of the $PaCO_2$ disruptions after CBD. The data are, with permission, from Pan et al. (263).

90, 91, 126, 315, 316, 346) (Fig. 2). Homeostasis of Pao_2 is nearly maintained during mild, moderate, and heavy exercise (14, 84, 90). Exceptions are to be found in a minority of well-conditioned athletes who hyperventilate minimally during heavy exercise. In these individuals, $PaCO_2$ remains near resting levels and Pao_2 is reduced significantly below resting values (89, 168, 282, 288).

The relationship of $PaCO_2$ to work rate appears independent of the resting condition. During such conditions as chronic metabolic acidosis and alkalosis or hormonal changes when $PaCO_2$ is altered from normal, exercise results in $PaCO_2$ regulation to near the altered resting level (121, 259, 293). Hypoxia is unique in that $PaCO_2$ is lower during hypoxic exercise than at rest (87, 125, 293). In non-human species, $PaCO_2$ homeostasis is not maintained during submaximal exercise (Fig. 2) (47, 70, 116, 124, 130, 195, 203, 241, 263, 264, 281, 302, 319). Ponies (Fig. 6) (124, 263), goats (265), dogs (70), and rats (130) all decrease $PaCO_2$ in rest to work and low to moderate work transitions. Often there is some increase from the nadir in $PaCO_2$, but during steady-state conditions, $PaCO_2$ is always below rest in a workload-dependent fashion. Most species also hyperventilate during heavy exercise; in ponies, the exercise hypocapnia is a single function of workrate (Fig. 2) (264). In contrast to the declining $PaCO_2$, in the steady state of exercise, Pao_2 remains near resting levels in most species (70, 264, 302). Exceptional are horses during heavy exercise as they do not hyperventilate, thus $PaCO_2$ is at or above normal and Pao_2 is below normal (31, 322). An alveolar-capillary diffusion limitation combined with alveolar hypoventilation are primary contributors to the hypoxemia in horses (328).

Accordingly, a near "isocapnic hyperpnea" is not applicable to every species. However, exercise hypocapnia does not

contradict the idea of a coupling between $\dot{V}_E$ and metabolic rate. Moreover preventing hypercapnia and hypoxemia in the face of a several fold increase in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ represents a remarkable achievement by a regulatory system whose known sources of CO_2, O_2, and H^+ inputs (Fig. 1) appear incapable of providing a signal for the hyperpnea. Despite the complexity of the systems involved in the respiratory response to dynamic muscular exercise, $\dot{V}_E$ closely follows $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. This correlation does not imply causality. Although, we will present evidence that altering $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ does indeed affect breathing, there are also interventions wherein $\dot{V}_E$ is dissociated from $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Accordingly, what is (are) the signal(s) causing $\dot{V}_E$ to increase in proportion to O_2 uptake and CO_2 produced by the muscles and exchanged in the lung with no chemical error signal in the arterial blood? The properties of the respiratory control system accounting for these responses remain one of the most fundamental and yet unresolved question in respiratory physiology.

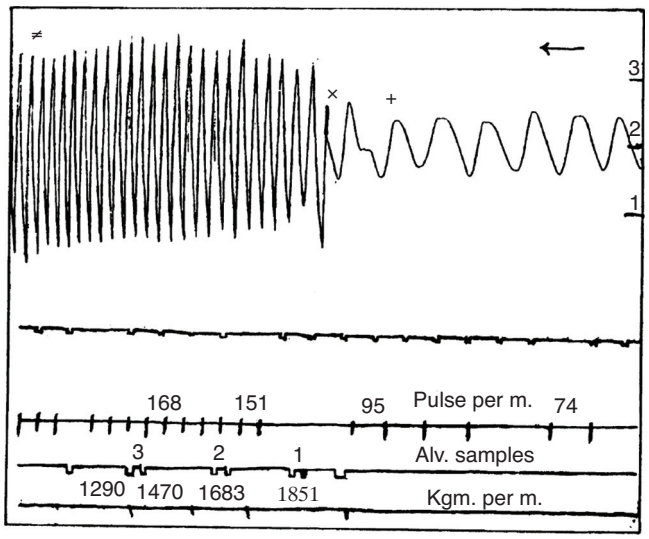

Figure 7 Recording of inspiration (upward deflection) and expiration in a human subject at rest and during moderate bicycle exercise. Onset of exercise indicated by x. Volume change indicated on right side and marks on the bottom indicate seconds. Adapted, with permission, from Krogh and Linehard (202).

Theories on the Mechanisms Mediating the Exercise Hyhperpnea

Historically, the hypotheses and studies on the exercise hyperpnea have been directed primarily to either submaximal exercise (<60% max $\dot{V}_{O_2}$) or near maximal exercise. This review will focus initially on submaximal exercise for which the majority of the hypotheses are grouped as: (i) neural feed-forward, (ii) neural feedback, and (iii) humoral (blood-born) feedback. The traditional rationale for the neural hypotheses is that the initial $\dot{V}_E$ response is too rapid to be mediated by an exercise metabolite transported in the blood to a receptor in the central circulation. The term neural feed forward is used to simply refer to a signal generated in the brain that initiates the hyperpnea simultaneous with or in advance of locomotion. Neural feedback refers to a signal generated in the locomotor limbs that reaches brainstem respiratory neurons via spinal afferents. The major rationale for the humoral hypotheses is the close relationship between the hyperpnea and metabolic rate.

Neural feed-forward mediation of the exercise hyperpnea

Rapid $\dot{V}_E$ response at the onset of exercise

The concept of a central neural mechanism mediating the exercise hyperpnea was discussed by Zuntz and Geppert in 1886 (368) and by Johansson in 1893 (183). One of the first detailed publications supporting this concept was by Krogh and Lindhard in 1913 (202). They studied the temporal pattern of $\dot{V}_E$ in human subjects during bicycle exercise (Fig. 7) and consistently found "a deep and rapid inspiration coinciding absolutely with the beginning of work." They concluded "it is obvious that changes which take place abruptly at the beginning of work or with a latent period-if any of less than 1 s cannot be brought about by any chemical regulation as a result of the processes in the working muscles." "The mechanism which shall produce the abrupt changes must be a nervous mechanism," and "we think that the evidence is in favor of an irradiation of impulses from the motor cortex" (202).

Several factors affect the rapid (phase I) $\dot{V}_E$ response at the onset of exercise. First, this response is greater for the same workload when it is achieved by treadmill speed rather than treadmill grade (32, 67, 78). Second, the behavioral or arousal state appears important as the rapid response is attenuated when humans at the onset of exercise are engaged in a complex cognitive task (34, 36). Furthermore, this response is attenuated in dogs by prior administration of a neural depressant (111, 112). Third, a peripheral, neural mechanism appears important as a rapid response occurs with passive limb movement (35). Fourth, as suggested by the effect of movement and posture on activity of respiratory muscles, a vestibule-respiratory reflex responding to head movement, at the onset of exercise, has been proposed to contribute to the rapid $\dot{V}_E$ response (366). Fifth, since pulmonary blood flow is less during the onset of supine versus upright exercise, it was postulated that a mechanism responding to an increase in pulmonary blood flow at the exercise onset mediated the rapid $\dot{V}_E$ response (340). However it was subsequently shown that during supine exercise by humans, the hypocapnia was not attenuated compared to upright exercise (Fig. 5). Another concern has been that the rapid response may reflect a "startle" or "anticipatory" response. However, Bell and Duffin (35) found that the fast $\dot{V}_E$ response was the same in transitions from rest to active exercise and from passive to active exercise. Finally, $\dot{V}_E$ phase I is virtually abolished when an increment in work rate is imposed from a background of exercise (345). Accordingly, it seems that a true fast (phase I) response occurs

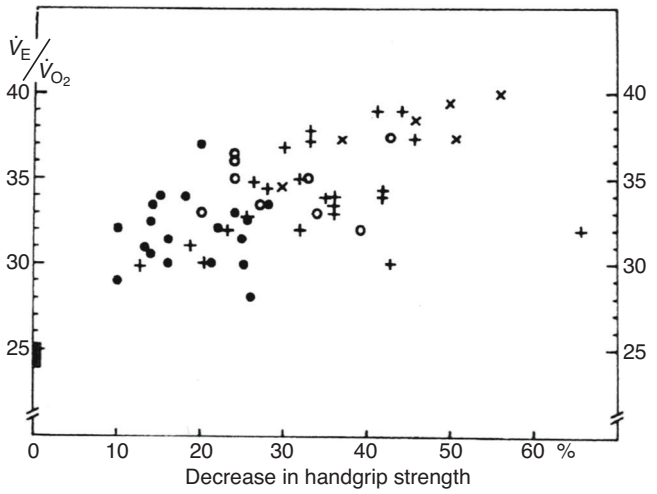

Figure 8 The ventilatory ($\dot{V}_E/\dot{V}_{O_2}$) response to exercise is increased as muscle strength is progressively weakened (decrease in handgrip strength) by injection of tubocurare. Adapted, with permission, from Asmussen et al. (14).

in rest to exercise transitions, but that there is evidence that the stimulus providing this fast response decreases during the course of exercise (182, 198).

The concept of a central neural drive was reinforced by studies of Asmussen and Nielsen. In one study on human subjects the circulation to the legs was blocked by pneumatic cuffs placed around the upper thighs which did not attenuate the rapid $\dot{V}_E$ response to bicycle exercise of different intensities (18). However, in the steady state of exercise, $\dot{V}_E$ during circulatory block was greater than during normal exercise, but at the cessation of exercise, $\dot{V}_E$ decreased in a normal manner in spite of the sustained muscle ischemia. Thus they concluded that the greater $\dot{V}_E$ with occlusion was not due to a muscle chemoreflex, but rather due to increased centrally driven neural activation of the muscles to compensate for the ischemia-induced decreased work capability of individual fibers. In a second study, human subjects exercised with and without prior administration of low doses of d-tubocurarine to attenuate neuromuscular transmission (15). The metabolic rate during bicycle exercise was not affected by curarization, but the exercise $\dot{V}_E$ response was much greater after curarization (Fig. 8). They reasoned that "as the curarization knocks out individual muscle fibers, mobilization of new ones or increased stimulation of the remaining ones take place to continue the work" and thereby metabolic rate is maintained. They postulated that increased "cortical irradiation" to maintain the work led to an increased "state of arousal" which led to the extra increase in $\dot{V}_E$ during curarization.

Central command suprapontine mediation of the exercise hyperpnea

Central command is commonly viewed as "a parallel, simultaneous excitation of neuronal circuits controlling the locomotor and cardiorespiratory systems, thus serving a feed-forward control mechanism"(330). Supposedly, a descending suprapontine neural signal projects to spinal locomotor neurons and to brainstem respiratory neurons to increase $\dot{V}_E$ simultaneously with the onset of locomotion. Supraspinal sites that project directly or indirectly to spinal locomotor rhythm generators include the primary motor cortex, the premotor and supplementary motor cortex and subthalamic, mesencephalic, and hypothalamic locomotor areas (330). Of these, the only area which when stimulated elicited both locomotion and $\dot{V}_E$ responses were the posterior (caudal) and dorsal hypothamamic areas (329). Eldridge et al. found that decorticate cats walk on a treadmill spontaneously or during electrical or chemical stimulation of the hypothalamic locomotor regions (Fig. 9), (109). Furthermore, in these studies, $\dot{V}_E$, heart rate (HR), and blood pressure increased before locomotion began. Most importantly, the responses were identical during spontaneous locomotion and when locomotion was prevented by paralysis of the cats (Fig. 9), (108). In the latter, paralyzed cats were studied while phrenic activity was monitored. The identical response in paralyzed and unparalyzed conditions was consistent with central command as opposed to feedback from exercising muscles.

Several other studies have found that electrical stimulation of hypothalamic sites in mammals evokes limb movement and an increase in $\dot{V}_E$, HR, and blood pressure, and that these responses were similar to spontaneous exercise (33, 93, 258, 289, 304). In addition, Thornton et al. found that electrical stimulation in the thalamus, subthalamic nuclei, and substantia nigra increased HR and blood pressure (320) in human subjects undergoing surgery for movement disorders. Also, there is evidence that neurons within the medullary retrotrapezoid nucleus (RTN) are part of the neural network through which hypothalamic locomotor areas affect breathing (128). In adult anesthetized rats, neurons in the perifornical hypothalamic locomotor area were stimulated by injection of the gamma-aminobutyric acid ($GABA_A$) antagonist, gabazine. After the injection, discharge frequency of RTN neurons and phrenic nerve activity both increased. It was concluded that RTN neurons probably contribute to "the feed-forward control of breathing associated with emotions and locomotion" (128). A major concern with all the hypothalamic stimulation studies is whether electrical or chemical stimulation of suprapontine sites truly mimic activation of pathways normally utilized during spontaneous exercise.

Two types of studies have attempted to directly test the hypothesis of central command mediation of the exercise responses. First, to determine whether indeed the signal for the exercise $\dot{V}_E$ and cardiovascular responses originate at hypothalamic sites, responses have been documented in mammals during exercise before and after lesioning the hypothalamus. A major limitation of all such lesioning studies is that it is highly unlikely that what remains in the postlesion condition is a truly unaltered control system. Two studies (166, 289) found attenuation of these responses in some animals after the lesions, but another study (258) found virtually identical responses before and after lesioning. A second

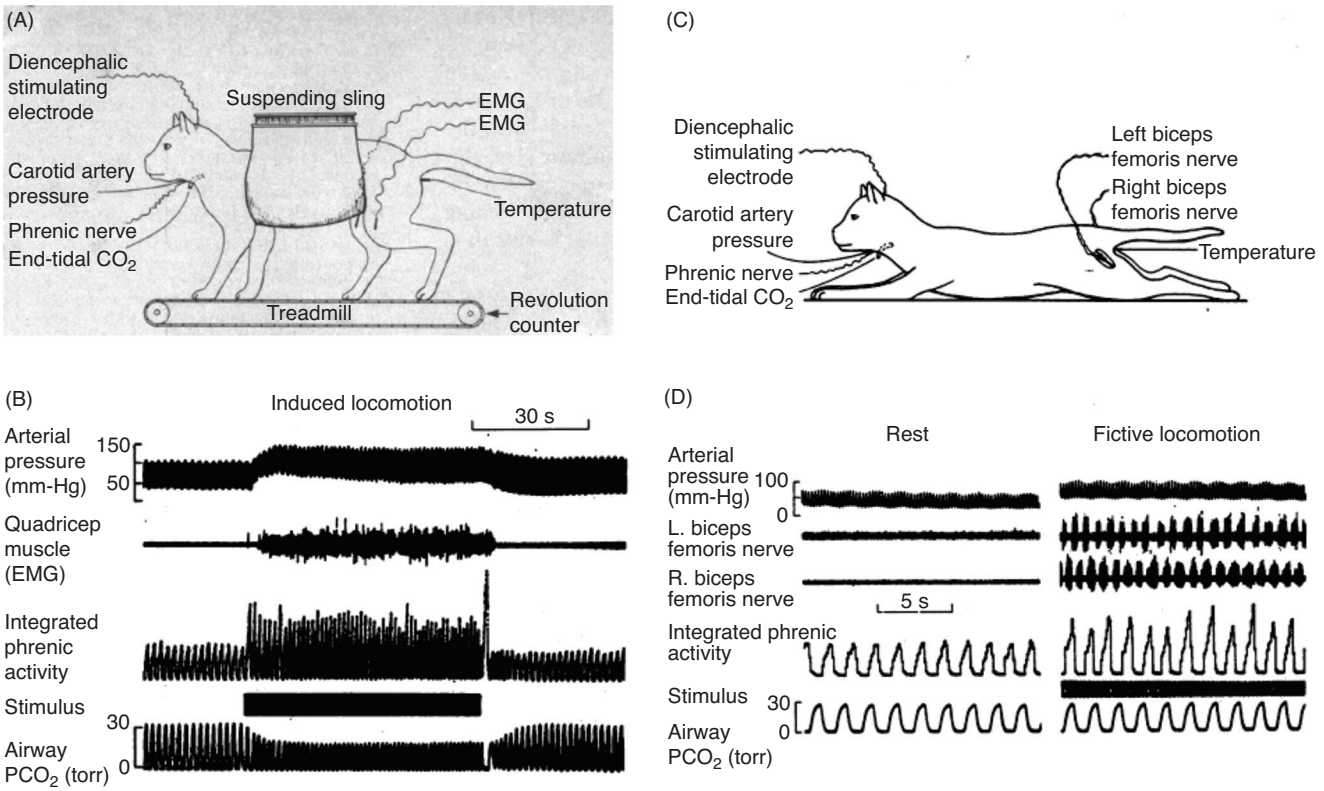

Figure 9 Data supporting concept that suprapontine mechanisms "central command" stimulates breathing. Shown (panel a) is a decorticate cat preparation used in studies when respiration (phrenic nerve activity) was measured during spontaneous locomotion and locomotion was induced by stimulation in the subthalamic locomotor region (panel b). Shown in panel c is decorticate paralyzed preparation used for spontaneous fictive locomotion which as shown in panel d elicited a respiratory response. Data are, with permission, from Eldridge et al. (109).

group of studies in humans (3, 19, 56) determined whether the $\dot{V}_E$ responses differed between normal voluntary muscle contraction and contractions of the leg muscles induced by an electronic stimulator. All three studies found virtually identical $\dot{V}_E$ responses to voluntary and electrically induced muscle contractions (Fig. 10). Each study provided evidence or reasoning that indeed central command was absent during electrically induced work, but there is no definitive proof of this point.

Neurocircuitry mediating cardiorespiratory responses to exercise

In attempts to gain insights into the neurocircuitry mediating the cardiorespiratory responses to exercise, studies have attempted to identify sites within the brain activated during spontaneous or imagined exercise (Fig. 11). Iwamoto et al. utilized c-fos expression as an index of neural activation (175, 178). They found that after 45 min of treadmill exercise in rats, there was increased c-fos expression in the hypothalamic/subthalamic locomotor regions including the posterior (caudal) and lateral hypothalamus. The authors concluded their "results from awake, exercising rats support those obtained previously" in decorticate animal preparations described above.

Fink et al. (115) used positron emission tomography (PET) to measure changes in regional cerebral blood flow (rCBF) which provided an index of increased neuronal activation. In humans during one-legged exercise that increased

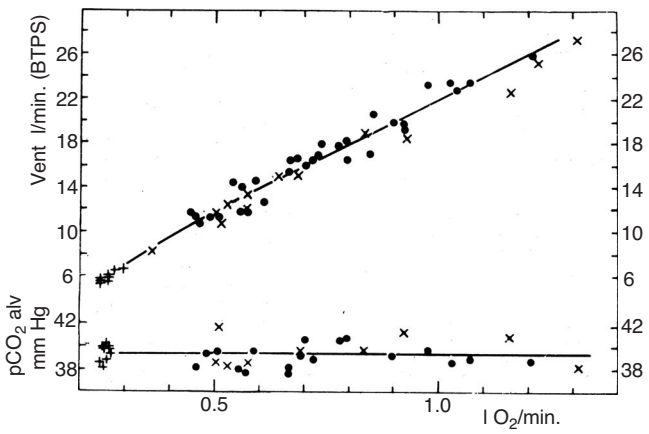

Figure 10 Effect of voluntary (circles) and electrically (x) induced exercise on pulmonary ventilation (vent) and alveolar PCO_2 (PCO_2 alv) relative to metabolic rate (l O_2 min). Note the near identical responses to the two exercise tasks interpreted as indicating "central command" is not obligatory for ventilatory response to exercise. Data are, with permission, from Asmussen et al. (14).

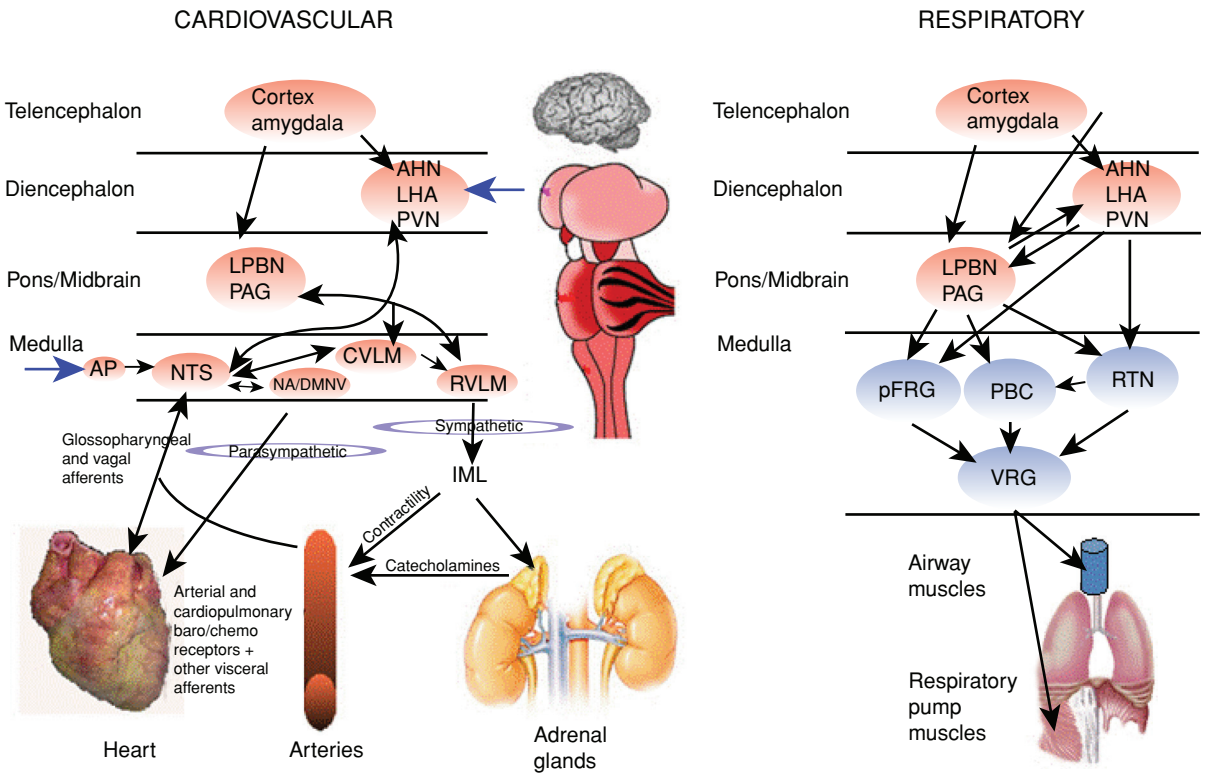

Figure 11 Schematics depicting multiple supramedullary structures potentially contributing to cardiovascular and respiratory control during exercise. The cardiovascular schematic was developed by Green and Paterson (139) and presented here with their permission. To our knowledge, no comparable schematic has been published for respiratory control; thus, since the cardiovascular and respiratory responses to exercise are usually qualitatively the same, we assume the supramedullary components are the same or at least similar for both responses. As detailed in the text, evidence suggests medullary respiratory neurons receive excitatory exercise-related inputs from suprapontine pathways that include the cortex, anterior (AHN) and lateral (LHA) hypothalamic nuclei, paraventricular nucleus (PVN), and periaqueductal gray (PAG). The respiratory rhythm originates within a brainstem oscillator which activates pattern generating neurons that provide for proper sequential activation of respiratory pump and airway muscles. The pre-Bötzinger (PBC) is the core site of rhythm and pattern generation with important contributions from the parafacial respiratory group (pFRG)/retrotrapezoid nucleus (RTN) as well as the pontine respiratory group including the lateral parabrachial nucleus (LPBN) (2, 303).

metabolic rate by 250%, they found increased rCBF in the left and right superlateral and supermedial primary motor cortex. These sites correspond to sites activated during volitional increases in breathing (72, 283). They also found increased activation in cortical and subcortical areas known to be involved in motor control (supplementary motor area, ventrolateral thalamus, cingulate gyrus, parietal and frontal cortex, globus pallidus, and cerebellum). Fink et al. also studied a second group of subjects after 15 min of bicycle exercise when breathing remained elevated but when there was no movement. They found rCBF was above control levels in the left supermedial motor cortex and in cortical and subcortical areas listed above, but they found no evidence for activation of any hypothalamic areas. Since the motor control areas remained activated post exercise, the authors speculated that "in postexercise hyperpnea and by implication even the hyperpnea during exercise, motor cortical involvement in control of breathing might be a behavioral or learned phenomenon" (115).

Subsequently, Thornton et al (321) also utilized PET scans to assess rCBF and found that in humans at rest during "imagined exercise" under hypnosis, $\dot{V}_E$ and HR increased along with increased activation in the right dorso-lateral prefrontal cortex, primary (PMA) and supplementary (SMA) motor areas, right premotor areas, superolateral sensorimotor areas, thalamus, and cerebellum. Similarly, Williamson et al. (353, 354) found, during actual and imagined exercise, increased activation of the anterior cingulate and insular cortexes which are part of the medial prefrontal cortex (196). In contrast, during voluntary hyperventilation, Thornton et al. (321) found significant activation primarily in the SMA and lateral sensorimotor areas. Since generation of movement based on working memory involves activation of the SMA and PMA, Thornton et al. concluded "these areas may encode a respiratory motor program (central command) that evolves as the motor task is learnt in development, interacting with classical error signals in real exercise" (321). Finally, since the insular and/or dorsolateral prefrontal cortex project to the SMA and PMA which project to the hypothalamus, the sites in the hypothalamus, which when electrically stimulated elicit a hyperpnea may normally be activated during exercise by the SMA and PMA which are activated by central command from the prefrontal cortex.

Finally, additional studies have been completed on humans undergoing treatment for movement disorders in which electrodes were implanted in specific suprapontine nuclei (29, 139, 141). A consistent finding has been increased neural activity in the periaqueductal gray (PAG) during anticipation of exercise and during different low levels of exercise. There also was increased activation during exercise in subthalmic nuclei but not in globus pallidus. The major conclusion from this series of studies is that the PAG "is an important area for the supraspinal control of exercise related cardiorespiratory changes but there is no evidence that it is involved in control of locomotion" (141).

The investigators of the studies summarized above readily point out the limitations of studies such as imaged exercise, use of patients with movement disorders, and measurements during levels of exercise that barely increase metabolic rate beyond normal physiologic variation. Nevertheless, as concluded by Guz (148) "such results have suggested motor cortical involvement in exercise-related hyperpnea", and even if the exact neurocircuitry has not been established, it seems intuitive that suprapontine sites (Fig. 11) are potential contributors to the exercise hyperpnea. Guz questioned whether some of these sites provide "the forms of irradiation—at cortical level-–suggested by Krogh and Lindhard." Or do other sites provide "a learned response providing an appropriate amount of central command?" Indeed, findings of past studies have been interpreted as indicative of a learned exercise hyperpnea (115, 321). This possibility is consistent with Somjen's reasoning that "the central nervous system (CNS) anticipates present and future needs on the basis of past experiences" (305). He postulates that negative feedback might be of vital importance during infancy when "by having successfully corrected errors, the CNS learns how to prevent them." Conceivably, central command (frontal cortex) may activate memory banks (SMA and PMA) which through the hypothalamus initiate locomotion and cardiorespiratory responses. Or memory banks may "employ principles different from all devices yet made by humans" (305).

Memory-like contributions to the control of breathing are also referred to as "associative or reinforcement learning" or long-term modulation (LTM) (240). Examples of LTM in goats (223, 325) and humans (356) was obtained by exercising them with increased external dead space and subsequently it was found that there was an augmentation of the hyperpnea during exercise without the added dead space. Similarly, in humans, repeated exercise with increased inspiratory resistance increases the tidal volume response to subsequent normal exercise (324). LTM is a serotonin-dependent mechanism which is associated with increased density of monoaminergic nerve terminals in spinal segements of the phrenic motor nucleus (240). Regarding its mechanism, LTM is similar to short-term modulation (STM) in that it is a serotonin-dependent response. STM is the "altered" stimulation that is required to maintain $PaCO_2$ during exercise at the same altered level as at rest during such conditions as metabolic acidosis and alkalosis (20, 239). Another example are aging humans with reduced lung elastic recoil resulting in uneven distribution of ventilation and an increased dead space to tidal volume ratio, yet because the overall $\dot{V}_E$ response is increased, the exercise $\dot{V}_E$ response remains isocapnic (186).

Sato et al attempted to test the "learned" hypothesis and found that the phase I and phase II responses were much faster in 12-year-old children than in 25-year-old adults (291). Others attempted to test this hypothesis by attenuating error feedback via denervating the carotid chemoreceptors (CBD) in 1-day-old goats. The $\dot{V}_E$ response to exercise at 3, 12, and 18 months later did not differ between CBD and sham CBD goats (127). These data do not support the Somjen hypothesis. They also do not invalidate the hypothesis because even if the CBD are important error sensors in the neonatal period, in their absence, the high degree of plasticity in neonates would likely have resulted in other mechanisms for development of "memory banks" (296).

Short-term potentiation contribution to the exercise hyperpnea

Brief stimulation of reflex arc afferents elicits a response that long outlasts the stimulus (299). Sherrington termed this an "afterdischarge" which has subsequently been demonstrated in many neuronal systems. This memory like effect develops rapidly, lasts for only seconds to minutes, and is known as short-term potentiation (STP). The effect is probably due to changes in the presynaptic membrane during repetitive firing resulting in gradually increasing neurotransmitter release and thus greater effects on the postsynaptic neuronal firing even though stimulation presynaptically is constant. STP could also be caused by increased excitatory neuromodulators altering membrane potential, or increased extracellular K+ causing further depolarization of the neurons. Respiratory STP has been demonstrated for several ventilatory stimuli including activation of carotid, vagal, and peripheral muscle afferents (103-105, 135), and it has been hypothesized that it is a component of the exercise hyperpnea. Waldrop et al. suggested that for exercise, STP "must make a sizable contribution to the ventilatory response" and that "its time course can explain much of the slow increase of ventilation after the onset of exercise"(330).

Conclusions regarding neural feed-forward mediation of the exercise hyperpnea

In 1913, Krogh and Lindhard stated "if the circulation and the respiration did not adapt themselves to the instantaneous and enormous rise in muscular metabolism, which is coincident with sudden and violent exertion, before the heart and the respiratory center were acted upon through the blood by the metabolites produced, then sudden and violent exertions on which the very life of most wild animals depends and which sometimes are very useful, at least, to civilized man himself, could not possibly be sustained for more than a fraction of a minute (202). The ideal condition would be of course that the

circulation and respiration were adapted to the changing needs as instantly as the muscles themselves" (202). Indeed, neural feed-forward mediation of the exercise hyperpnea seems intuitive as volitional exercise requires activation of the CNS, and there is evidence that suprapontine sites activated during exercise project to medullary respiratory nuclei. However, definitive testing of the central command hypothesis during physiologic exercise has been a challenge. The evidence from animal studies for central command is strong but inconclusive as these studies may not mimic "real" exercise or real central command. The evidence from human studies is more limited and somewhat indirect. Based on the evidence to date, central command MUST exist and it must play a significant role in intact humans. It remains for investigators to demonstrate its contribution in a "neurally intact" animal or human with a normal control system. With further development of the technology for recording and altering of neural activity at various CNS sites during different levels of spontaneous exercise, the suggestive findings of past studies could be established, expanded, and become definitive. Nevertheless, we conclude that currently it remains questionable whether there is indisputable evidence for or against central command mediation of the exercise hyperpnea.

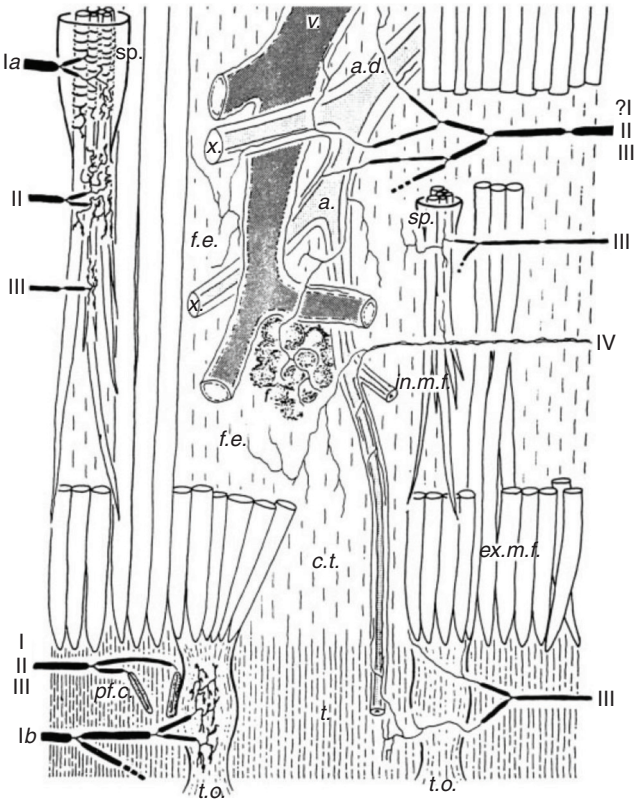

Figure 12 Anatomical distribution of the afferent innervation of the cat skeletal muscle. Most of the group III and IV afferents fibers are found in association with arterioles (a.) and the venous and venular structures (v.) of the muscles. Data are, with permission, from Stacey et al. (308).

Neural feedback mediation of the exercise hyperpnea

The concept that neural feedback from contracting muscles contributes to or mediates the exercise hyperpnea is attractive because: (a) there are several sensory (afferent) nerves within the muscles or surrounding tissue that are affected by muscle contraction (Fig. 12) and (b) activity of these receptors is transmitted via spinal pathways with sufficient speed to account for the rapid increase in breathing at the onset of exercise (44, 231) (Fig. 13). The sensory nerves are labeled I through IV with two subtypes Ia and Ib. The distinction between these is based on fiber size and degree of myelination which determine the conduction velocity of the nerve fiber. The highly myelinated group Ia and Ib generally conduct impulses from muscle spindles and Golgi tendon organs, respectively. The Ia fibers signal the rate of muscle stretch or lengthening while the Ib fibers signal both stretch and contraction. Some group II afferents are also myelinated and are activated by muscle stretch but do not signal the rate of stretch. Other group II afferents signal muscle distortion but not muscle stretch. The contribution of the group 1 and II afferents to the normal $\dot{V}_E$ response to exercise (42, 43) appears to be negligible (231). Group III are thinly myelinated conducting impulses from free nerve ending receptors in tendons (261, 287). Group IV afferents or C-fibers are not myelinated and they conduct impulses also from free nerve endings at widespread locations

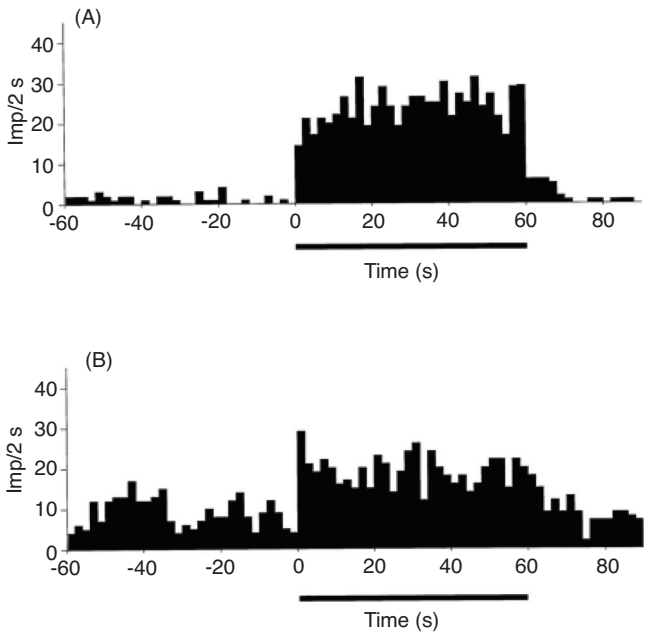

Figure 13 Exercise activates group III and group IV muscles afferents. Shown are cumulative histograms for 24 group III afferents (A) and 10 group IV afferents (B) before, during, and after time that cats performed dynamic exercise, which was induced by stimulation of mesencephalic locomotor region. Exercise period is denoted by horizontal bars. Note maintained response to dynamic exercise by both group III and group IV afferent impulses. Data are, with permission, from Adreani et al. (4).

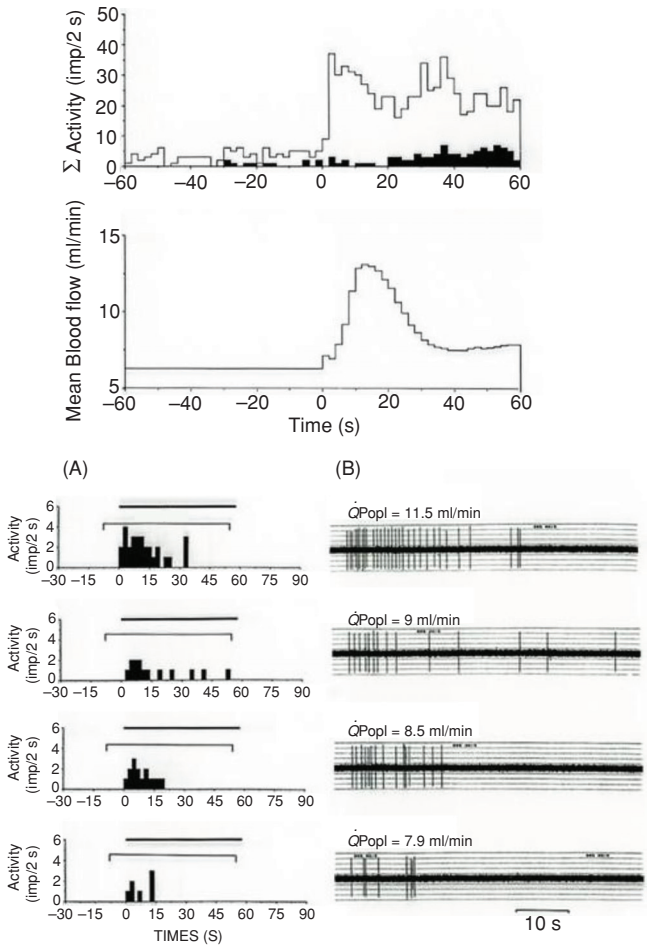

Figure 14 Increased muscle blood flow activates group III and group IV afferents. Shown in the top panel are the temporal profiles of cumulative histogram of the activity of 15 group IV (open bars) and 3 group III (solid bars) fibers of the cat triceps surae, responding to papaverine (top) and mean popliteal blood flow (bottom). Shown in the bottom are the effects of venous obstruction on the discharge of a group IV muscle afferent fiber originating in the triceps surae of the cat at different flow levels after an injection of isoproterenol. The higher the level of flow before occlusion the greater the neural response to venous distension. Data are, with permission, from Haouzi et al. (156).

including venous and lymph vessels and in connective tissue. The group III and IV afferents are supposedly activated by: (a) distortion of their receptive field, (b) metabolic by-products of muscle contraction (H^+, K^+, and lactate), (c) local inflammation, (d) a change in tissue temperature, and (e) factors that cause muscle pain (163, 190-192, 234, 235). Moreover these receptors respond to the distension of the vessels, predominately at the venule level; thus they could monitor the level of muscle blood flow through which they may activate the cardiovascular and respiratory systems (Fig. 14) (156).

Several different preparations and techniques have been utilized to gain insight into the contribution of spinal afferents to the exercise hyperpnea. Even though the bulk of evidence indicates muscle contraction leads to increased breathing, the role of spinal afferents in exercise hyperpnea remains controversial.

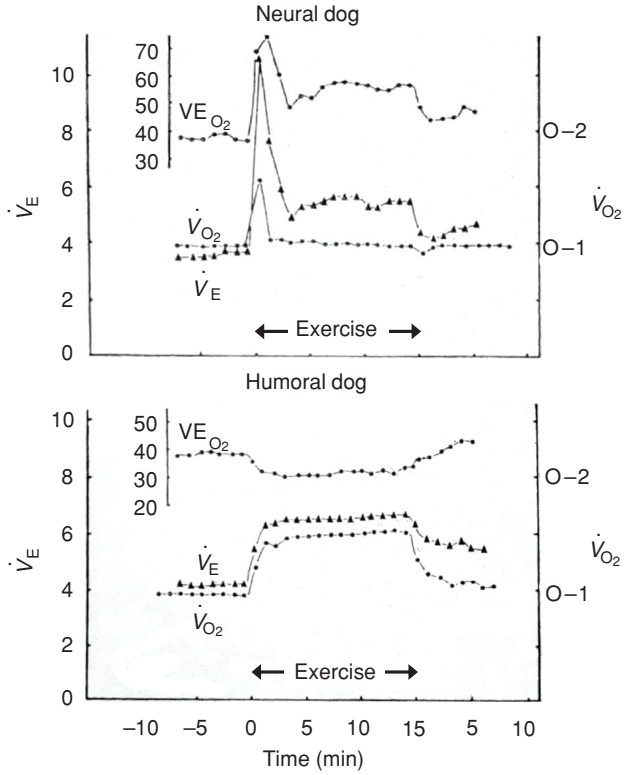

Figure 15 The time course of pulmonary ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), and the $\dot{V}_E/\dot{V}_{O_2}$ ration ($\dot{V}_EO_2$) in an anesthetized (neural) dog when the hindlimb muscles were induced electrically to contract and the venous blood from the hindlimbs was delivered to another non exercise (humoral) dog. Note the brisk hyperpnea at the onset of contraction in the neural dog and the delayed response in the humoral dog. Data are, with permission, from Kao et al. (189).

Responses to electrically induced muscle contraction

Comroe and Schmidt in 1943 electrically induced muscle contraction in the hindlimbs of dogs and cats by stimulating the ventral roots (74). In both species, $\dot{V}_E$ increased immediately with the onset of contraction and this response was abolished in dogs but not in cats by spinal cord transection. Years later, Kao et al. completed similar studies, but they not only isolated the effect of muscle afferents from central command but also isolated humoral or blood-borne stimuli (189) (Fig. 15). They electrically induced contraction of the hindlimbs of one dog (neural dog) while perfusing the hindlimbs of this dog with blood from a second dog (humoral dog) through anastomoses of the arteries and veins of the two dogs. The $\dot{V}_E$ of the neural dog increased immediately at the onset of contraction, but there was no sustained increase in metabolic rate of this dog; thus this dog became hypocapnic. This hyperpnea was eliminated by ablation of the lateral spinal columns or by transection of the spinal cord. In the humoral dog, there was a hyperpnea which was delayed until Pao_2 decreased and $PaCO_2$ increased. Kao et al. thus concluded that "there is certainly a peripheral neurogenic drive which must be considered as the, or one of the mechanism of exercise hyperpnea" (189).

Subsequently, in agreement with Kao et al., others (38, 231, 243, 295, 323) have shown that electrically induced muscle contractions elicit a rapid increase in $\dot{V}_E$ dependent on an intact spinal cord. In contrast, still others (77,207,208,341) showed that electrically induced contractions elicited a rapid hyperpnea independent of an intact spinal cord. Levine (208) concluded that "muscular exercise can stimulate $\dot{V}_E$ via humoral factors" while Weissman et al. (341) concluded that "reflex discharge of afferent nerves from the exercising limbs was not requisite for the matching of ventilation to metabolic demand during exercise." These conclusions were not supported by studies of Haouzi and Chenuel (153) who, in anesthetized sheep, electrically induced muscle contractions while using an isolated perfusion system to maintain $PaCO_2$ constant, or in other studies which blocked venous return to the lung (Fig. 16A). Their data led to the conclusion that the $\dot{V}_E$ response to electrically induced contractions was via spinal afferents initiated by a mechanism described below. Accordingly, all studies using electrical stimulation of muscle contraction in anesthetized animals found an increase in $\dot{V}_E$, but there is disagreement on whether the increase is through spinal afferents.

An isocapnic hyperpnea is elicited during electrically induced contractions in paraplegic humans (3, 19, 55, 57) These data appear inconsistent with mediation of the hyperpnea by spinal afferents, and since in spinal cord intact humans, the $\dot{V}_E$ response to electrically induced and voluntary contractions does not differ, it would appear that a humoral mechanism mediates the hyperpnea. A major limitation of these studies is that the 50% to 100% increase in metabolic rate is within the physiologic variation that occurs at rest. In addition, the small increase in $\dot{V}_E$ could be explained by small undetectable increases in $PaCO_2$.

Effects of occlusion of blood vessels to/from the muscles

Comroe and Schmidt (74) found in anesthetized cats and dogs that electrically induced muscle contractions elicited a hyperpnea which subsequently was attenuated in cats but not dogs when blood flow to the legs was occluded. Others also tested the peripheral chemoreflex hypothesis by: (i) perfusing the legs with hypercapnic, acidotic, and hypoxemic blood or venous blood collected previously from exercising legs, (ii) intra-arterial injections of chemical agents that change during exercise, and (iii) vascular occlusion postexercise thereby trapping metabolites in the muscle. The data from these studies do not support a muscle chemoreflex-induced hyperpnea (85, 158, 176, 287). Indeed, the trapping of exercise metabolites in the muscles at the end of exercise results in a return of $\dot{V}_E$ to resting levels more quickly than normal (Figs. 4 and 16B). In addition, the increase in afferent nerve fiber activity during ischemic contractions occurs after a delay of nearly a minute (192). In other studies, there was a decrease in activity of a population of fibers during contraction when the arterial circulation was occluded (235). These findings are inconsistent with a muscle chemoreflex contributing to the exercise hyperpnea.

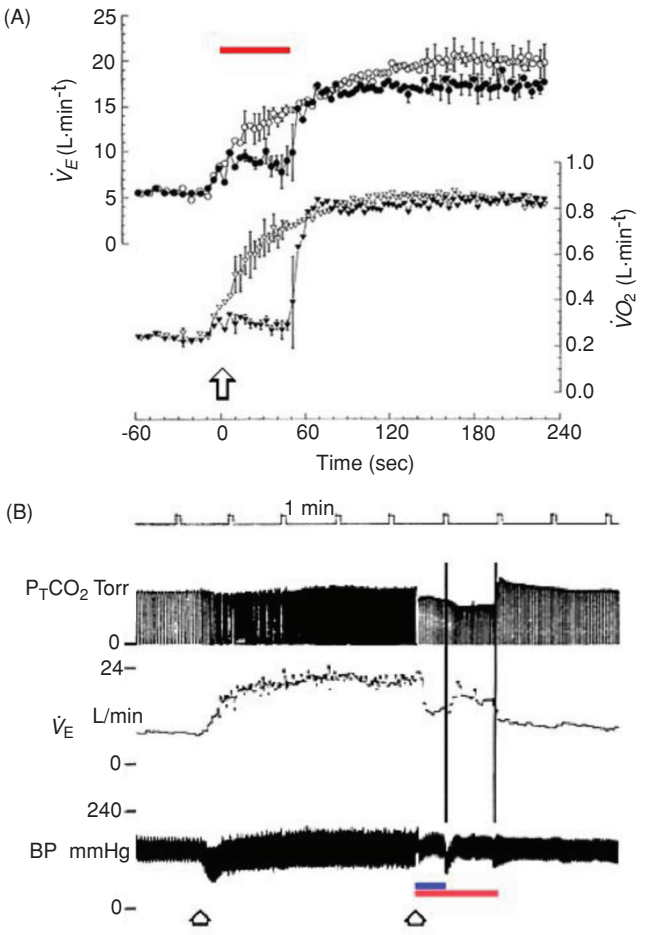

Figure 16 Blood flow in muscles has an effect on ventilation. Shown in panel A are the effects of the occlusion of the iliac arteries on the $\dot{V}_E$ and $\dot{V}_{O_2}$ responses at the onset of electrically induced muscle contractions in anesthetized dogs. The arrow indicates the onset of exercise. The arterial occlusion was maintained during the period depicted by the horizontal bar. Responses in control condition are depicted with open symbols while the responses to occlusion and release are shown using closed symbols. Note that impediment of the arterial supply to the contracting muscles prevented the normal increase in $\dot{V}_{O_2}$ and reduced dramatically the magnitude of the normal $\dot{V}_E$ response to exercise. Shown in panel B are the $\dot{V}_E$ effects of the occlusion of the lower abdominal aorta and inferior vena cava at the cessation of electrically induced hindlimb muscle contractions in an anesthetized dog. At the cessation of the contractions (second vertical arrow), both the arterial and venous balloons were inflated (first and second horizontal bar, respectively). The arterial balloon was deflated at the first vertical line, whereas venous return from the hindlimb remained blocked. This change caused $\dot{V}_E$ to increase despite the drop in $PETCO_2$ and the lack of sustained change in systemic blood pressure (BP). When the venous balloon was deflated, note that $\dot{V}_E$ decreased despite the ensuing hypercapnia. Data are, with permission, from Huszczuk et al. (174).

Vascular occlusions of exercising muscles have also been completed in humans. As summarized in section *Neural feedforward mediator of the exercise hypernea*, Asmussen (18) found in humans that occlusion of blood flow to exercising muscles increased breathing during exercise. Similarly, others (57, 102, 355) also found occlusion of blood flow increased

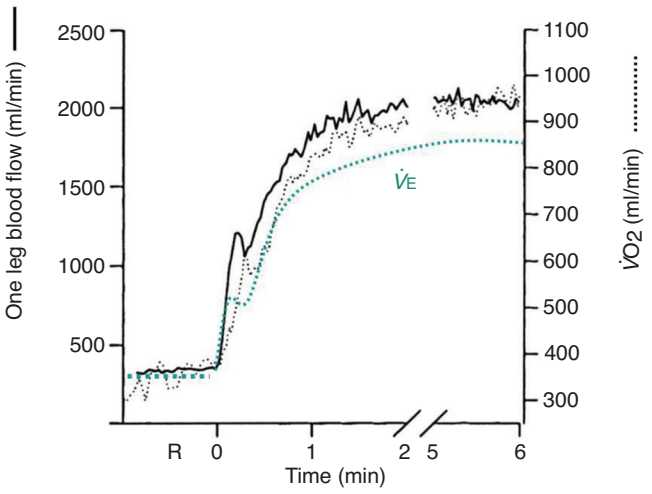

Figure 17 Rapid muscle blood flow response to exercise. Shown are oxygen consumption (dotted line, $\dot{V}_{O_2}$) and leg blood flow (solid line) response to constant work rate exercise in supine position (40 W). Note the immediate increase in blood flow (as soon as the exercise starts) and the exponential increase in blood flow preceding $\dot{V}_{O_2}$ phase II and reaching a steady state within 2 min. The ventilatory responses have been added based on the characteristics presented by MacDonald et al. (220).

breathing. This increase was attributed to increased activation of a muscle chemoreflex or increased central command to compensate for reduced muscle contractile capability and/or increased pain.

In summary, the animal and human data on vascular occlusion during exercise does not provide strong support for the hypothesis that a peripheral chemoreflex contributes to the hyperpnea during submaximal exercise.

The vascular distension hypothesis

Group III and IV endings appear to respond to the distension of the vessels, predominantly at the venule level, and thus could monitor the level of muscle blood flow by encoding the degree of recruitment of the postcapillary network (Fig. 17) (156). Type III and IV afferent fibers are found in the vicinity of and in the adventitia of the arterioles and the venules (Fig. 12) (327). Direct recording of their activity showed that group IV muscle afferent fibers are stimulated by venous occlusion and by injection of vasodilatory agents (156). This change in neural activity has implications for the respiratory responses to muscle contractions. For instance, arterial occlusion of the hindlimb muscles prevents the normal increase in O_2 uptake and $\dot{V}_E$ at the onset of electrically induced hindlimb muscle contractions in dogs (Fig. 16A). More importantly, releasing the arterial occlusion while maintaining the venous occlusion stimulates $\dot{V}_E$ to decrease $PaCO_2$ despite little or no changes in the central circulation downstream of the occlusion (155, 171). Finally, impeding only the circulation from (venous side) or to (arterial side) the hindlimbs during electrically induced muscle contractions has opposite ventilatory outcomes (158,171). Indeed, despite a similar reduction in O_2 uptake resulting from obstructing the caudal vena cava or the distal abdominal aorta, $\dot{V}_E$ typically rises in the former and decreases in the latter (158).

Based on these experiments, it was proposed that by encoding the extent of the postcapillary vascular bed being perfused, a signal reflecting the change in local metabolism could be transduced via the change in the vascular status in the muscle (155, 157). It was proposed that this regulatory system anticipates the chemical changes that occur in the arterial blood during increased metabolic load and attempts to minimize them by adjusting $\dot{V}_E$ to muscle perfusion, thus matching the magnitudes of the peripheral and pulmonary gas exchange. The increase in muscle perfusion with exercise elicits an increase in $\dot{V}_E$ sufficient to potentially explain the exercise hyperpnea. The known temporal profile of the muscle blood flow changes (220), with its abrupt increase at the onset of exercise, is compatible with and could account for the phase I immediate increase in $\dot{V}_E$ (Fig. 17). Muscle blood flow phase II has a temporal profile similar to $\dot{V}_{O_2}$ measured at the mouth and these are faster than the $\dot{V}_E$ response. A model through which $\dot{V}_E$ follows the change in pulmonary gas exchange via a peripheral signal of a circulatory nature, proportional to the local flow of blood, could account for the characteristic $\dot{V}_E$ responses to step, impulse, and sinusoidal exercise. However, it remains to be established whether this venule signal is sufficiently strong to account for a significant portion of the exercise hyperpnea. Also, unknown is the temporal pattern of venule blood flow and its relationship to cardiac output. It is known that during exercise, the kinetics of cardiac output are much faster than for $\dot{V}_E$. Furthermore, there is no close temporal relationship between changes in $\dot{V}_E$ and cardiac output during exercise (Fig. 18) (262, 316); thus if venule blood flow explains the exercise hyperpnea, then its regulation must be independent of cardiac output.

Effects of attenuation of muscle afferents in awake humans and animals

The objective of these studies was to determine whether attenuation of spinal afferents would alter the exercise hyperpnea. Hornbien et al. injected 15 to 20 ml of lidocaine into the lumbar peridural space which selectively blocked gamma efferent fibers while larger alpha fibers were spared (170). They found that the injection had no effect on the hyperpnea during the onset or steady state of exercise at a $\dot{V}_{O_2}$ of 2 l/min. They concluded that muscle spindle afferents do not contribute to the exercise hyperpnea. Fernandes et al. injected bupivacaine at the L3-L4 vertebral interspace in humans to induce sensory analgesia below T10-T11 (114). This injection reduced arterial blood pressure during exercise, but it did not affect the HR and $\dot{V}_E$ responses to exercise; thus, this study does not provide evidence of a spinal afferent contribution to the exercise hyperpnea. In another study, Strange et al in humans created cutaneous sensory anesthesia below T8-T10 through epidural anesthesia (313). They electrically induced dynamic knee extension which doubled $\dot{V}_E$ and metabolic rate and caused

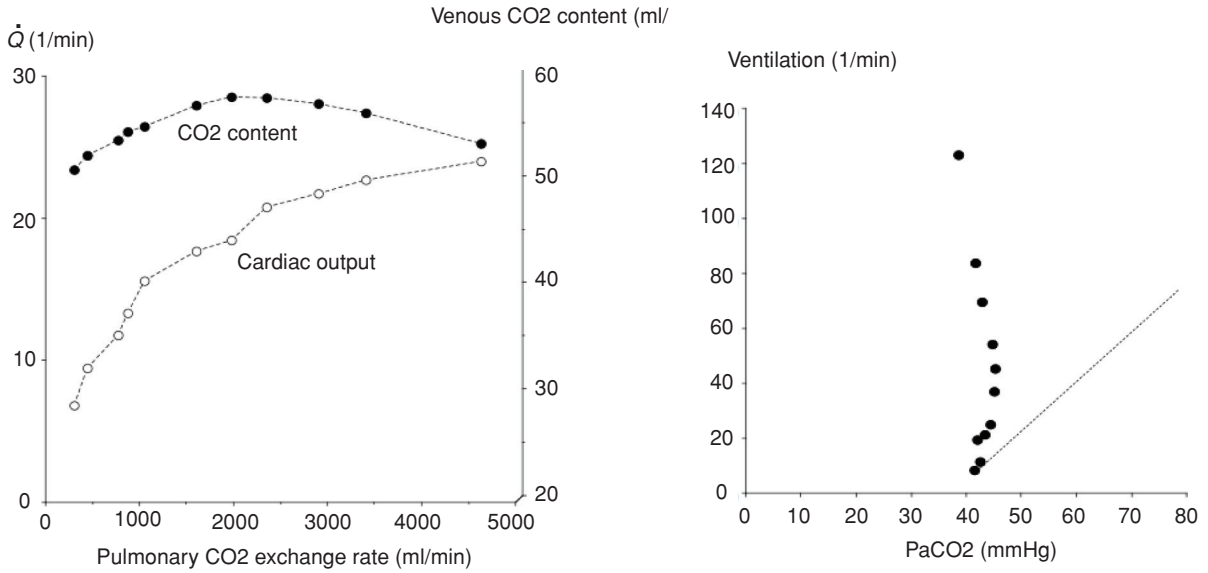

Figure 18 The isocapnic ventilatory response (right panel) to exercise does not correlate with changes in cardiac output and mixed venous CO_2 content (left panel) during ramp-like exercise in healthy humans. Note that as cardiac output and ventilation increase dramatically, there is only a small change in mixed venous CO_2 content; thus, it is unlikely CO_2 content provides a major signal for the blood flow and ventilatory responses. Data are, with permission, from Sun et al. (316).

a 2 to 3 mmHg hypocapnia. They concluded that a neural reflex mechanism is not essential for the $\dot{V}_E$ response to this type of muscle contractions. Finally, Amann and Dempsey injected 0.5% lidocaine into the L3-L4 vertebral interspace of trained human cyclist to determine whether somatosensory feedback from muscles had an inhibitory influence on central command (8). They found that epidural lidocaine reduced the power output by 9%, but the integrated electromyogram of the vastus lateralis was increased and $\dot{V}_E$ was increased out of proportion to a reduced metabolic rate and power output. They concluded that somatosensory feedback during high-intensity exercise inhibits central command. Attenuating this feedback accentuates central command which in turn increases the exercise hyperpnea.

Epidural block with lidocaine attenuates both spinal afferents and efferents. The effect on the efferents likely elicits a compensatory increased central command (as postulated by Asmussen et al. (15) after injection of tubocurare) which would mask the effect on breathing of a reduction in spinal afferents (8). Accordingly, Amann and Dempsey attenuated only the afferent limb with no effect on limb muscle maximum strength by injecting the opioid agonist fentanyl into the L3-L4 vertebral interspace of trained cyclist before a 5-km time trial (9). During the first 2.5 km of the trial with blocked afferents, the integrated electromyogram of the locomotor muscles and the power output were above control time trials. These data are in agreement with their previous studies "emphasizing the critical role of somatosensory feedback from working muscles on the centrally mediated determination" (8) of central motor drive. They also found that during the first 2.5 km with blocked afferents, there was an approximate 6 mmHg hypoventilation which "may have occurred due to the absence of feedback from muscle metaboreceptors and/or mechanoreceptors" (9). Finally, during bicycle exercise in the laboratory, Amann et al. found that fentanyl-induced afferent blockade versus placebo at several equal steady-state exercise work rates and reported fentanyl induced similar degrees of hypoventilation (Fig. 19) (7). This hypoventilation provides strong support for a major role of spinal afferents in the exercise hyperpnea. Further, this significant role for muscle afferent feedback was shown to occur during rhythmic (cycling) exercise with presumably normal muscle blood flow.

Another attempt to gain insights into the spinal afferent contribution to the exercise hyperpnea was achieved by studying the $\dot{V}_E$ response of ponies to treadmill exercise before and 3 to 4 weeks after surgical lesions of the dorsal lateral spinal pathways at the first lumbar level (267). The hypocapnia that normally occurs in ponies at the onset and during the steady state of treadmill walking in ponies was attenuated by about 2 mmHg after spinal lesioning. In addition, breathing frequency during exercise was less after compared to before lesioning. These small changes may have underestimated the role of spinal afferents in the exercise hyperpnea because: (a) it could not be determined whether hindlimb afferents were totally eliminated and (b) afferent innervation of the forelimbs remained intact; thus, the lesions were incomplete. Moreover, the postlesion studies were 3 to 4 weeks after surgery simply because initially after surgery, the ponies could not stand let alone walk. Finally, before surgery the ponies were able to walk and run well on the treadmill with only the hindlegs. However, after surgery, they were unable to perform two-legged exercise. This finding and the long recovery time suggest a relearning or reconfiguration of neural pathways using forelimb afferents to perform exercise.

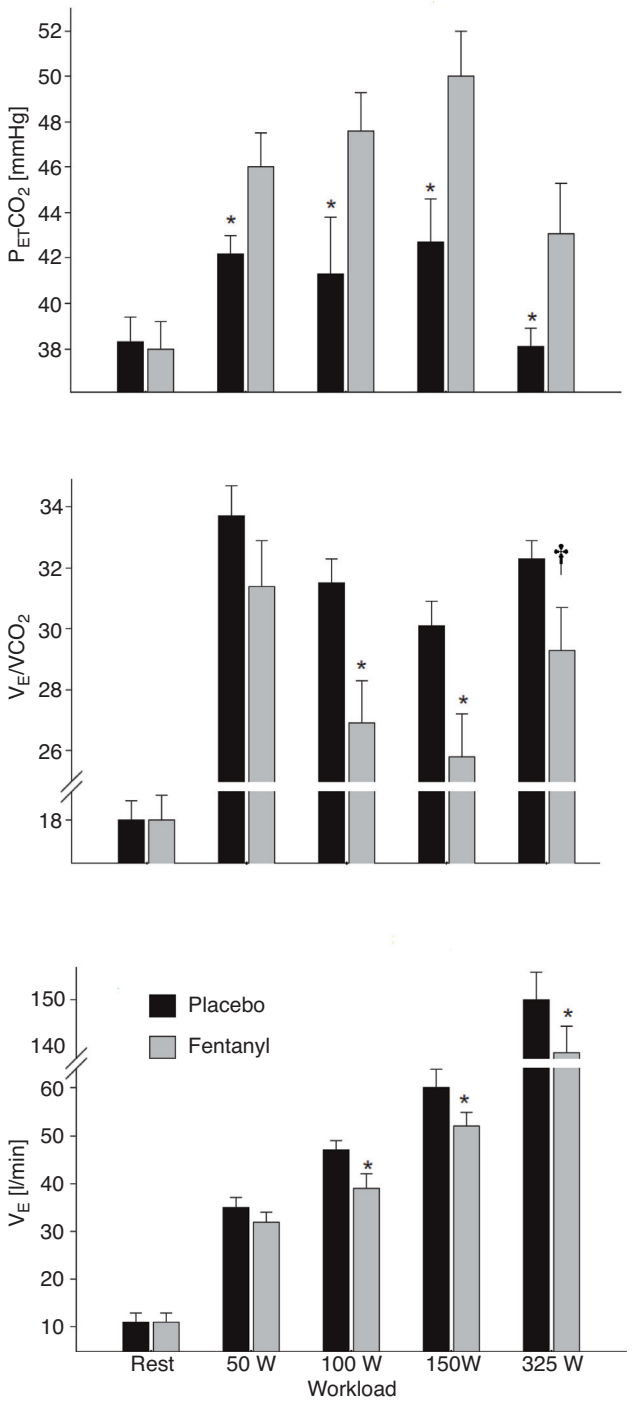

Figure 19 Effect of blockage of μ-opioid sensitive type III-IV muscle afferents via intrathecal Fentanyl on the steady-state ventilatory response to 3 min of cycling exercise at each of four work rates. (*$P<0.05$, $P<0.8$). The Fentanyl-induced hypoventilation was due to a reduced breathing frequency. Heart rate and mean arterial blood pressure (data not shown) along with $\dot{V}_E$ were significantly reduced at each work rate. Taking into account the reduced exercise $\dot{V}_E$ with Fentanyl plus the ventilatory equivalent of the concomitant rise in $PETCO_2$, it is estimated that the partial blockage of muscle afferents accounted for 47%, 45%, and 15% of the total exercise hyperpnea at 100, 150, and 325 W, respectively. Data adapted, with permission, from Amann et al. (7).

Accordingly, there also may have been a reconfiguration or relearning within the $\dot{V}_E$ control network to minimize the effect of attenuation in hindlimb spinal afferent input to the control network. Although this study provides support for the concept of a spinal afferent contribution to the exercise hyperpnea, it is also important in its illustration of the limitations and difficulty of creating lesions to gain insight into the exercise hyperpnea. Finally, the study also demonstrates the high degree of plasticity within the neural control pathways.

Breathing frequency and limb-movement frequency

A stimulus for breathing related to limb movement is suggested by the increase in breathing with passive movement of the legs (35, 82, 136, 250, 291). Moreover several investigators have found that for the same increase in metabolic rate, the tachypnea and hyperpnea are greater when the treadmill speed or cycling frequency is increased as opposed to an increase in treadmill grade or cycling resistance (5, 32, 53, 67, 179, 193, 194, 242). Furthermore during sinusoidal changes in work rate, investigators have found greater amplitudes and lower phase lags for ventilation when limb-movement frequency is varied compared to variations in treadmill grade or cycle resistance (64, 65, 342). In addition, several mammals, including humans demonstrate entrainment or coupling of breathing frequency with limb movement frequency (31, 32, 177). Entrainment refers to a defined relationship between limb movement frequency and breathing frequency. This relationship can be 1 to 1 as in galloping equines or there can be harmonic locomotor-respiratory coupling (e.g., 2:1, 4:1, 3:2, etc). The 1:1 coupling can be the mechanical consequence of visceral mass motion during quadrupedal locomotion in the horizontal position. However, this "visceral piston" can not apply to harmonic coupling observed in bipeds. Thus, the coupling and the effect of limb-movement frequency on breathing frequency in humans is probably neurogenic. However, in nonhuman mammals, limb-movement frequency is not a determinate of the $\dot{V}_E$-$\dot{V}_{O_2}$ relationship and exercise $PaCO_2$ (124,242). In ponies, the exercise hypocapnia at the onset and steady state of exercise is related to metabolic rate during both four-legged and two-legged exercise (124). In contrast, humans who are nearly isocapnic during submaximal bicycle exercise and treadmill walking are hypocapnic during treadmill running (150, 232). In summary, limb-movement frequency clearly affects breathing frequency and in humans it also affects the $PaCO_2$ during exercise. The degree of entrainment of breathing frequency and limb-movement frequency is inversely related to the hypoxic drive to breathing suggesting that chemoreceptors affect entrainment (271) mechanisms are deferring to the respiratory demands during hypoxia (271).

One concept of entrainment is that it is mediated via coordination between respiratory and locomotor pattern generators which seems feasible based on the evidence that there is coordination between separate hindlimb and forelimb pattern generators for quadrupedal locomotion (21). Different

preparations have been utilized to determine the influence of limb pattern generator activation on respiration (97,245,280). In an *in vitro* preparation, fictive locomotion induced by pharmacological activation of lumbar locomotor generators increased spontaneous respiratory rate but there was no evidence of coupling. However, they found that respiratory motor activity was entrained 1:1 with locomotion over a range of periodic electrical stimulation applied to low-threshold sensory pathways originating from contracting hindlimb muscles. Subsequently, Potts et al. (280) confirmed and extended these findings utilizing an *in situ* preparation on 6- to 8-week-old rats. They activated somatic afferents innervating the forelimbs by direct stimulation of forelimb flexors muscles. They found 1:1 coupling between respiratory rhythm and forelimb contraction over a range of contraction frequencies but this occurred only if the contractions were during the expiratory phase. Inhibition of the lateral parabrachial nucleus with injections of isoguvacine eliminated the coupling, but did not affect the overall increase in respiratory frequency during somatic afferent stimulation. The authors concluded that "somatic afferent stimulation modulates respiratory activity by at least two independent neural circuits: (i) a spinopontomedullary pathway controlling the phase of inspiration relative to an afferent stimulus and (ii) a neural circuit that mediates tachypnea" (280). The data from these studies are thus supportive of the concepts that spinal afferents affect breathing frequency and entrainment of breathing and limb-movement frequencies.

Conclusions regarding neural feedback mediation of the exercise hyperpnea

Numerous studies under unphysiologic conditions have provided conflicting evidence regarding the role of spinal afferents in the exercise hyperpnea. On the other hand, there is strong evidence that Group III and IV afferents sensing venous volume could provide a signal for the hyperpnea. Moreover, studies during physiologic exercise in humans and ponies indicate that spinal afferents contribute to the hyperpnea. Indeed, the most convincing support for this hypothesis are the data indicating the marked attenuation of the exercise hyperpnea in humans after selective partial attenuation of spinal afferents (Fig. 19) (7).

Caveats with neural feed forward and feedback hypotheses of the exercise hyperpnea

Implicit in neural feed-forward and feedback mediation of the exercise hyperpnea is motor activity. In an attempt to gain insight into the importance of motor activity to the exercise hyperpnea, investigators have applied a simple engineering technique relying on the principle of linearity that allows for the "dynamic isolation" of many putative stimuli to breathe (131, 132). This approach offers a different perspective on the ventilatory response to exercise. For example, one can separate the effects of the motor act from $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ through sinusoidal changes in work rate (Fig. 20). Indeed, if a sinusoidal input is applied to a linear system, the output will vary sinusoidally at the same frequency as the input. However, the amplitude and the phase lag of the fundamental component of the output will change according to the input frequency and the dynamic properties of the system (time constant and time delay) (64,66,151,342). Therefore, by varying the work intensity in a sinusoidal manner (Fig. 20), it is possible to isolate the of $\dot{V}_E$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ responses. These responses have a 30 to 50 s time constant response compared to a virtually flat frequency response of motor activity. As expected, when the period of the work rate oscillations are decreased from 10 to 1 per min, the amplitude of the $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ responses decrease and the phase lags between work rate and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ increase, despite a similar amplitude of motor or locomotion activation. At periods shorter than 2 min, the changes in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are virtually abolished and $\dot{V}_E$ temporally follows the same pattern as $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ (Fig. 20). In other words, when conditions are created where work rate changes with no concurrent change in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, $\dot{V}_E$ follows factors related to gas exchange rate and not to the motor activity (151, 154).

These results appear to conflict with the previous conclusions that signals related to motor activity, which includes central command, are likely to contribute to the overall exercise hyperpnea. However, the meaning of the $\dot{V}_E$ changes during sinusoidal changes in work rate must be understood in keeping with the frequency domain which is studied. During sinusoidal submaximal exercise, the $\dot{V}_E$ responses are likely most comparable to Phase II responses to a step change in exercise. If motor activity/central command contribute primarily to the fast or phase I $\dot{V}_E$ response to submaximal exercise, then this contribution would be absent during sinusoidal exercise. This view is suggested by the findings that: (a) there is no fast response in work to work transitions (345) and (b) the fast $\dot{V}_E$ off-transient from constant load exercise is less than the fast $\dot{V}_E$ on-transient indicating that during constant submaximal exercise, there is a waning of the signal that caused the fast on-transient (181, 198). Accordingly, during sinusoidal changes in work, there would be no or minimal contribution to the changes in breathing from the signal(s) (motor activity/central command) that normally contribute to the fast $\dot{V}_E$ response to work initiated from rest. On the other hand, if the command and control of movements and muscle contractions are an important mechanism involved in exercise hyperpnea beyond the transition from rest, then it remains to be elucidated why responses obtained from sinusoidal exercise are in apparent conflict with central command/motor activity.

In summary, despite the complexity of the systems involved in the respiratory response to dynamic muscular exercise, $\dot{V}_E$ temporally follows $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ irrespective of the type of work rate forcing (131, 132). Although this correlation does not imply causality, it provides rationale for considering mechanisms unrelated to the motor act such as humoral factors to explain the link between $\dot{V}_E$ and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

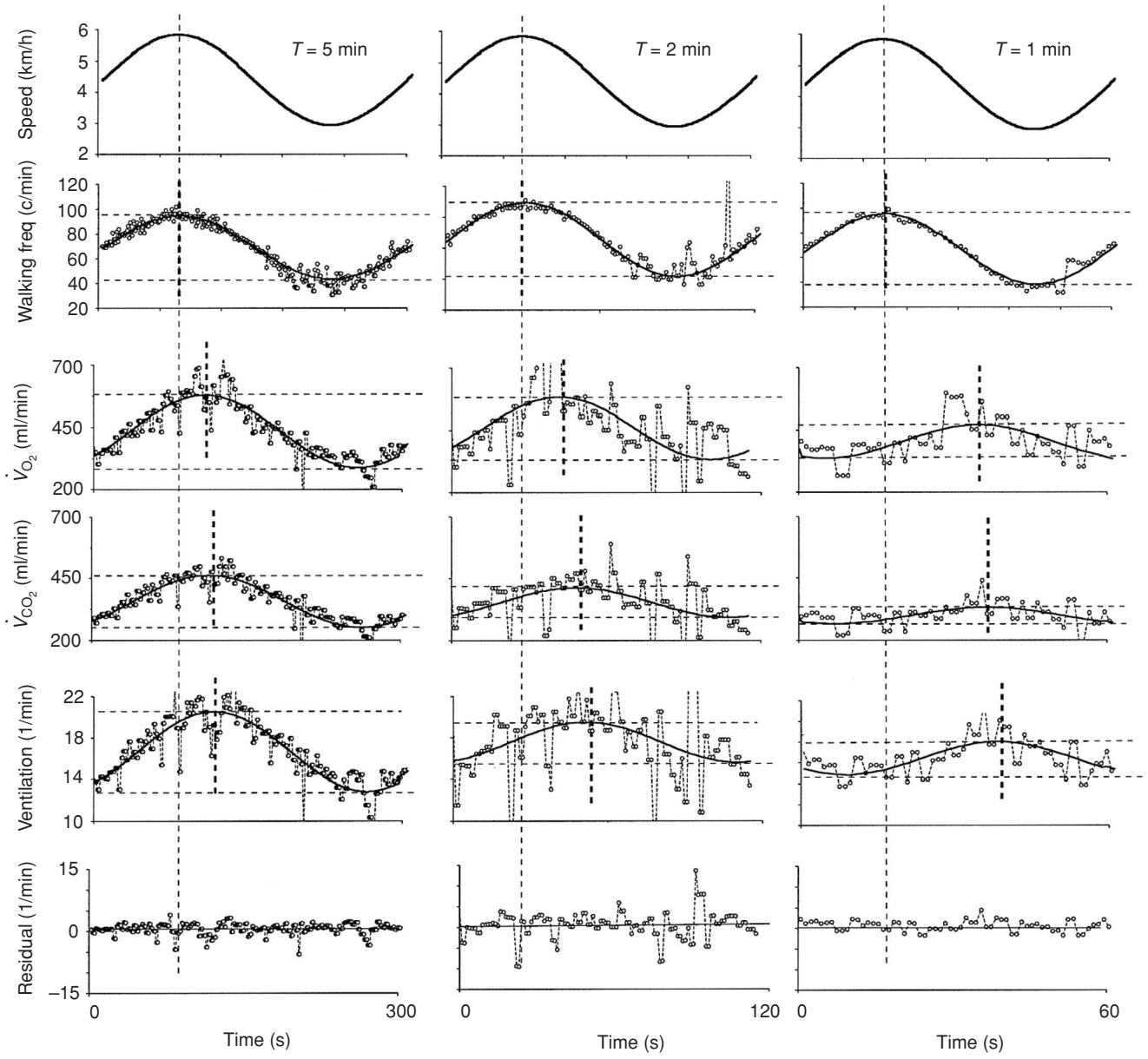

Figure 20 Example of changes in oxygen consumption ($\dot{V}O2$), CO_2 excretion ($\dot{V}_{CO_2}$), and ventilation when the period of sinusoidal changes in treadmill speed is shortened from 5 to 2 and then to 1 min. The fundamental component of the responses computed by Fourier analysis is superimposed on the raw data. Note that the changes in walking frequency are in phase with the sinusoidal changes in the speed of the treadmill and that there is no reduction in amplitude when the frequency of oscillations of the treadmill speed increases. There is a clear reduction in amplitude of both pulmonary gas exchange and ventilation when the oscillation period decreases whereas the phase lag between walking frequency and the respiratory parameters increases. Data are, with permission, from Haouzi et al. (151).

Humoral mediation of the hyperpnea during submaximal exercise

Among the first to propose a humoral mechanism were Zuntz and Geppert in 1886 who proposed that unknown blood substances produced by the exercising muscles provided the stimulus for the exercise hyperpnea (368). In 1905, after Haldane and Priestly had documented the important role of $PaCO_2$ and Pao_2 in regulation of breathing, they proposed that the increased CO_2 production during exercise could mediate the exercise hyperpnea (149). However, Douglas and Haldane observed in 1909 that $PaCO_2$ did not change sufficiently during exercise to account for the increased breathing (96). Indeed, as shown in Figure 2, numerous studies have confirmed the near homeostasis of $PaCO_2$ during mild and moderate exercise in humans. In addition, it has also been shown that cerebral spinal fluid PCO_2 and $[H^+]$ do not increase in ponies during exercise (46). Moreover, the $\dot{V}_E$ response to electrically induced muscle contraction in anesthetized sheep is coupled to $\dot{V}_{CO_2}$ even when cephalic perfusion is separately controlled (153). Nevertheless many investigators have proposed and attempted to identify variables which are changing along the gas

exchange pathway that could stimulate breathing without an error signal in the mean stimulus level at the known chemoreceptors. This search for a humoral stimulus to maintain a near isocapnic hyperpnea during exercise has also been suggested by findings during numerous nonexercise conditions (including cold-induced thermogenesis, hypoxic hypometabolism, circadian oscillations, changes in body weight, and gas exchange in the avian hatching period) during which $\dot{V}_E$ changes are closely coupled to changes in metabolic rate to maintain PCO_2 homeostasis (129,134,233,246,248,276,294). We will thus review several humoral theories that relate specifically to the exercise hyperpnea.

Increased CO_2 sensitivity mediation of the exercise hyperpnea

One of the first proposed theories by which PCO_2 could mediate the exercise hyperpnea was that sensitivity to CO_2 increased during exercise. For example, Krogh and Linhard suggested that cortical irradiation mediated the rapid $\dot{V}_E$ response to exercise by suddenly increasing the sensitivity of the respiratory center to hydrogen ions (202). However, Duffin et al. found that the phase I rapid response to exercise was not associated with a change in the threshold or sensitivity of peripheral and central CO_2-H^+ chemoreceptors (68, 99). In addition, several studies have tested whether steady-state CO_2 sensitivity increases during exercise and it appears the exercise and CO_2 stimuli have an additive effect on breathing (Fig. 21) (14, 17, 69, 98, 278, 339). Noteworthy were studies in anesthetized preparations that found spinal afferent (107) and central command (128) stimuli, respectively, do not increase the respiratory response to CO_2. Moreover, since there is a workload-dependent hypocapnia in non-human mammals during exercise, it does not seem intuitive that the control system would be designed to increase sensitivity to CO_2 to create a progressive reduction in the absolute level of the CO_2.

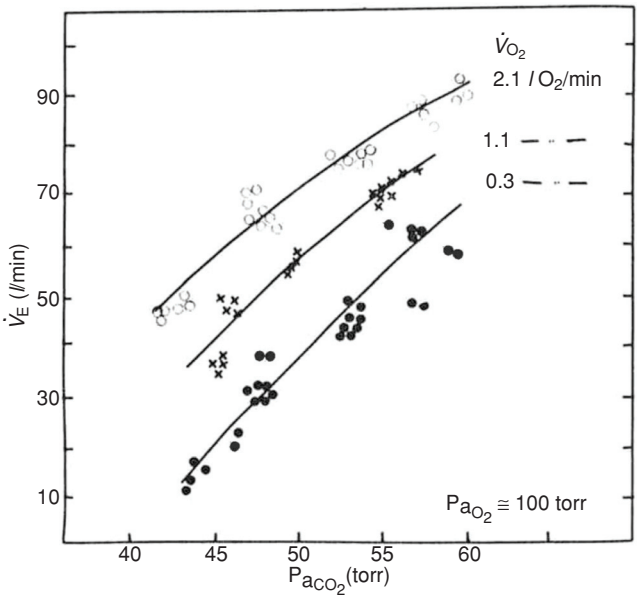

Figure 21 Ventilatory sensitivity to increases in $PaCO_2$ at rest and during two levels of bicycle exercise in a normal human. Note that exercise did not change the slope of the relationship indicating an unchanged sensitivity to CO_2 during exercise. Data are, with permission, from studies by Asmussen et al, (17).

Venous CO_2 content as a signal for the exercise hyperpnea

There are four major pulmonary receptors (290, 350). The slowly adapting stretch receptors (SASRs) in the extrapulmonary and intrapulmonary airways are activated as the lung inflates. The SASRs provide an input via the vagus nerve to the central network that has a major role in terminating inspiration. The activity of these receptors is altered by changes in airway CO_2 (28,73); thus, a pulmonary CO_2 sensory mechanism has been postulated to mediate the exercise hyperpnea. The primary role of a second set of receptors, the rapidly adapting stretch receptors (also known as irritant receptor) is to initiate airway protective reflexes such as a cough that clears the airway. Two final receptors are the pulmonary and bronchial C-fibers which are located deep within the lung near alveoli and capillaries. Their role is primarily to initiate reflexes that are related to defense of the airways.

The close relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ during steady state submaximal exercise suggests the hypothesis that a mechanism in the lung senses delivery of CO_2 and stimulates breathing proportionately to provide an isocapnic hyperpnea. However, studies prior to about 1960 indicated that this coupling was not causal. For example, Heymans and Heymans found that $\dot{V}_E$ did not increase when isolated dog lungs were perfused with acidotic, hypercapnia, and hypoxemic fluids (164). Cropp and Comroe infused blood into the right ventricle with PCO_2 levels ranging from 5 to 50 mmHg in anesthetized dogs and cats and unanesthetized dogs which only increased $\dot{V}_E$ when $PaCO_2$ increased above normal (76). These data were confirmed by different studies supporting the conclusion that "there are no CO_2 receptors in the precapillary pulmonary circulation of importance in the physiological regulation of respiration" (76). This conclusion was compatible with Kao's subsequent findings that the chemoreceptors could not account for the rise in $\dot{V}_E$ during electrically induced muscle contractions (189).

However, the possible role of chemical factors in maintaining $PaCO_2$ homeostasis during exercise regained interest in the 1970s after Yamanoto's findings that $\dot{V}_E$ rose isocapnically when venous CO_2 content was increased in resting rats by infusing intravenously blood enriched in an extracorporeal system with 100% CO_2 (363). They proposed the sensing mechanism was the carotid body (CB) responding to the increased $PaCO_2$ or pH oscillations when venous CO_2 increased. Accordingly, in the latter part of the 20th century, several studies tested this hypothesis and/or the hypothesis that a mechanism sensed the amount of CO_2 delivered to the lung. These studies used an extracorporeal gas exchanger to increase or decrease venous and

thus delivered CO_2. In several studies on anesthetized animals, it was claimed that $\dot{V}_E$ changed in proportion to the change in CO_2 delivery to maintain homeostasis of $PaCO_2$ (206, 214, 274, 314, 338). In contrast, in an equal number of studies, there was a change in $PaCO_2$ sufficient to account for the hyperpnea or hypopnea during CO_2 loading and unloading (39, 118, 138, 171, 209, 277, 284, 300). Similar studies on awake sheep found that venous CO_2 loading that increased pulmonary CO_2 excretion up to 350% also increased $\dot{V}_E$ to the same extent as exercise induced increases in CO_2 excretion (275). Removal of CO_2 during exercise to equal the resting metabolic rate decreased $\dot{V}_E$ to sustained apnea.

There are several reasons for questioning whether the venous CO_2 loading and unloading studies provide a valid test of the pulmonary CO_2 receptor and arterial oscillation theories of the exercise hyperpnea. First the increase in $\dot{V}_{CO_2}$ in humans and ponies during exercise is associated with a moderate (315) or no (262) change in venous CO_2 content (Fig. 18) and the temporal pattern of CO_2 delivery does not correlate with $\dot{V}_E$. Thus, the large change in CO_2 load in some studies provided larger changes in P_aCO_2 and pH oscillation than are experienced during exercise. Second, the apparent isocapnic nature of the response to loading and unloading was hypercapnic and hypocapnic after carotid body denervation (CBD) (273). This finding not only indicates that lung receptors do not account for the responses, but also is contradictory to evidence summarized in a subsequent section indicating that the CB does not provide an unique exercise stimulus. Third, the contention of $PaCO_2$ homeostasis during loading and unloading was challenged on statistical grounds by Bennett et al. (39), who showed that the use of pooled data was inadequate to determine whether there was a significant deviation in $PaCO_2$. Finally, as pointed out by Ponte and Purves (277), Yamamoto was unable to prevent large changes in cardiac output and blood volume during CO_2 loading. As described below, these and other authors have shown that such circulatory changes could *per se* stimulate breathing. We are therefore left with no clear evidence suggesting that the change in venous CO_2 content could, within the range of physiological changes during exercise, provoke an isocapnic increase in breathing.

Pulmonary blood and CO_2 flow as a signal for the exercise hyperpnea

Several investigators have studied whether receptors sensing pulmonary blood and CO_2 flow mediate the exercise hyperpnea (142, 173, 277, 298, 300). These studies used an extracorporeal gas exchange system to alter either CO_2 content, blood flow, or both to the lung independent of arterial CO_2 and blood flow. For example, Huszczuk (171) studied the effects of changing the CO_2 content of the venous blood and, in another series of experiments (173), diverted the venous return after arterialization away from the right heart into the lower aorta at rest and during electrically induced exercise. From these studies the authors concluded that "the results support the suggestion of CO_2 flow-related hyperpnea both at rest and during muscular exercise" (173). However, the apparent flow related stimulus was small relative to the exercise hyperpnea. Moreover, Pan et al. found in ponies during normal treadmill walking or running that the $\dot{V}_E$ response did not correlate temporally with pulmonary blood flow, pulmonary CO_2 delivery, or pulmonary CO_2 excretion indicating that the exercise hyperpnea is not mediated by a pulmonary flow and CO_2 mechanism (262).

Effects on the exercise hyperpnea of attenuating pulmonary vagal feedback

Several studies have tested the pulmonary CO_2 hypothesis by evaluating the effect of attenuating pulmonary vagal feedback. Humans have been studied after lung transplant (26); dogs were studied after anesthetic or cold block of the vagi (6,275); and dogs and ponies were studied after sectioning the hilar branches of the vagus nerves which specifically innervate the lungs (71, 110, 113, 117, 120, 123). As predicted from the role of SASRs in control of breathing, attenuation of vagal feedback increased tidal volume and reduced breathing frequency at rest and during exercise. In these studies in the awake state, during mild and moderate exercise, the changes in $\dot{V}_E$ and $PaCO_2$ were not altered by lung denervation. Thus, this series of studies strongly suggest that a pulmonary CO_2 sensing mechanism is not obligatory for the exercise hyperpnea.

From all the data summarized on venous CO_2 loading and unloading, pulmonary CO_2 delivery, and pulmonary blood flow, the data supportive of these concepts were primarily obtained on anesthetized animals in which small changes in $\dot{V}_E$ were elicited. It is questionable whether these changes occurred without changes in $PaCO_2$. If indeed there is a pulmonary mechanism that can stimulate $\dot{V}_E$, there is no available evidence that it could stimulate $\dot{V}_E$ in a manner to explain the hyperpnea of exercise. However, a pulmonary mechanism could be important to the coupling of $\dot{V}_E$ to metabolic rate during nonexercise conditions such as with weight loss, changes in state of arousal, and circadian variations (246, 247).

Cardiac afferent mediation of the exercise hyperpnea

Mechanoreceptors in the heart are activated by changes in atrial or ventricular volume or distention which contribute to autonomic control of cardiac function and arterial blood pressure (13). In addition, these receptors may also affect breathing. Passive distention of the right ventricle and increases in ventricle pressure and pulmonary artery pressure increase breathing in anesthetized preparations (188, 199, 200, 215, 326). To further test the role of cardiac receptors, Brown et al. increased cardiac output in anesthetized dogs by intravenous injections of isoproterenol and decreased cardiac output in awake humans by propranolol infusions (58,336). In both studies, $\dot{V}_E$ changed in proportion to the change in cardiac output thus maintaining homeostasis of $PaCO_2$. When the cardiac responses were blocked by

drugs, then there were no $\dot{V}_E$ responses to isoproterenol and propranolol. Also supportive of a cardiac receptor mediated stimulus for breathing were data showing a brisk hyperpnea upon release of cuffs that occluded venous return after exercise (84,176,287). As a result of this body of work, Wasserman et al. proposed a theory known as "cardiodynamic" mediation of the exercise hyperpnea.

However, data from other studies did not support cardiodynamic mediation of the exercise hyperpnea. In normal humans and ponies, the temporal pattern of circulation and $\dot{V}_E$ during exercise are not correlated in a manner suggesting interdependence (Fig. 18) (244, 262, 316). Moreover, the cardiovascular responses to exercise are slower than normal in human heart and heart-lung transplant patients, but their $\dot{V}_E$ responses to exercise are normal or exaggerated (26,101,292). Similarly, in goats studied before and after cardiac denervation, the cardiac response was sluggish after denervation, but $\dot{V}_E$ and $PaCO_2$ were unaffected (54). Finally, $\dot{V}_E$ did not change directionally with steep changes in cardiac output during voluntary exercise in animals with artificial hearts (172). Accordingly, even though in specific experimental preparations activation of cardiac afferents and/or pressure along the length of the pulmonary vasculature can alter breathing, all known test of the cardiodynamic theory using voluntary exercise indicate that cardiac afferents are not critical for the exercise hyperpnea.

Carotid afferent mediation of the exercise hyperpnea

The carotid bodies (CB) are small bilateral organs located near the bifurcations of the common carotid arteries (204, 253). They consist of two cell types, I (glomus or sensory) and II (glial-like). The glomus cells are innervated by the sinus branch of the IX cranial nerve. The sensory mechanisms within the glomus cell for hypoxia, hypercapnia, and acidosis have not been established. These stimuli induce an increase in intracellular Ca^{2+} which results in neurotransmitter release that initiates events at the nerve ending leading to propagated action potential in the sinus nerve. At normal levels of arterial blood gases, there is a low-level activity pattern in the sinus nerve. The sinus nerve activity response to hypoxia is hyperbolic with a sharp increase in activity at a Pao_2 of 40 to 50 mmHg (205). The nerve activity response to hypercapnia is linear and relatively flat (205). The sensory responses are fast enabling detection of breath to breath oscillation in arterial blood gases. Moreover, as indicated by the severe hypoventilation that occurs after CBD, the tonic activity of the carotid body provides a major stimulus for eupneic breathing (48, 51, 167, 265, 285).

As shown in Figures2 and 4, Pao_2, $PaCO_2$, and H^+ stimulus level at the CB clearly do not increase in a manner expected to account for the hyperpnea during submaximal exercise. Nevertheless, various mechanisms have been postulated by which these chemoreceptors could mediate the hyperpnea. One postulate is that there is increased gain of the CB during exercise (45). A second postulate is that during exercise the increased amplitude of breath-to-breath oscillations in blood gases provides a signal beyond that of average values of blood gases (22, 137, 363). A third postulate is that the medullary respiratory controller functions as an integral controller; thus a postulated slight transient hypercapnia at the onset of exercise increases breathing which remains elevated until the chemoreceptor activity is again altered (335). A fourth postulate is that the workload-dependent increase in plasma $[K^+]$ progressively increases the activity of the sinus nerve (270). The rationale and supportive data for each of these hypotheses are controversial (122, 333) and the effects are too small to account for any appreciable portions of the exercise hyperpnea.

Investigators have attempted to gain insights into the role of the CB in the control of breathing by inhalation of hyperoxic gas mixtures to attenuate chemoreceptor activity. Complicating interpretation of these data is the effect of hyperoxia on CO_2 transport and the effects of superoxide on neurons, which after a few minutes of hyperoxia will increase stimulus level at the intracranial CO_2-H+ and/or increase neuron excitability (80). As a result, Dejours proposed years ago that only a few breaths of hyperoxia is the best way of assessing the contribution of the CB to the control of breathing. He found that in humans "in normoxia, the 'O_2 test' shows that ventilation decreases by about 10% after a delay of 10 s in the resting subject and after a delay of 5 s during moderate exercise" (83). St. Criox et al. (307), Masuda et al. (227), and Jeyaranjan et al. (180) found for humans that the transient O_2 test decreased breathing by 15% to 20%, respectively. These data show that the CB are stimulating breathing at rest and probably even more during exercise. The apparent sensitizing effects of exercise on carotid chemoreceptor responsiveness are consistent with the aforementioned hyperventilatory responses of hypoxia-exercise combination even when both are at relatively mild levels (Fig. 22) (45). A caveat here is that the contribution of these chemoreceptors might be underestimated because hyperoxia only attenuates and does not eliminate chemoreceptor activity (205). An additional indication of a carotid contribution are data showing that hyperoxia slows the kinetics of $\dot{V}_E$ and gas exchange during exercise (143, 332). The complicated effect of prolonged hyperoxia was shown by Haouzi et al. as during exercise in dogs the transient O_2 test increased $PETCO_2$ nearly 3 mmHG while prolonged hyperoxia only increased $PETCO_2$ 0.5 mmHG (152). These authors proposed that "changes in CO_2 stores in the exercising muscles could contribute to O_2-induced stimulation during exercise, possibly through stimulation of muscle afferents responding to local circulatory changes" (152).

Another approach to studying the contribution of the CB is through determining the effects of CBD. For example, Wasserman et al. (337) and Honda et al. (169) studied the $\dot{V}_E$ response to exercise of asthmatic humans who years earlier underwent CBD in an attempt to alleviate their dyspnea. These studies found that the time constant of $\dot{V}_E$ in response to exercise was greater than in age-matched control subjects.

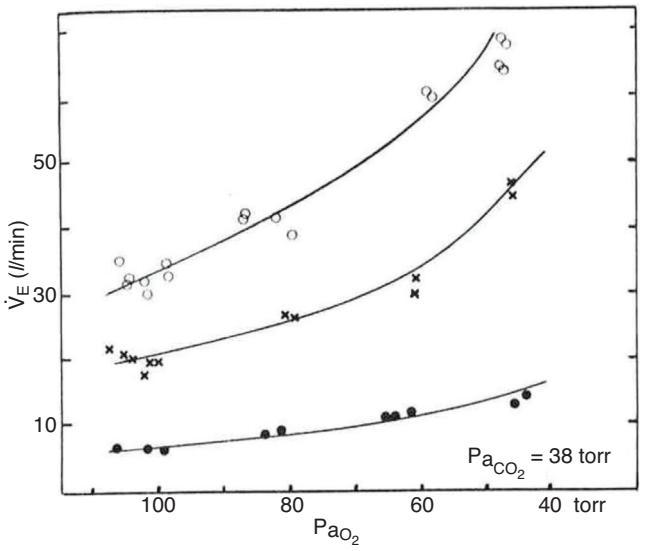

Figure 22 Effect of exercise on ventilatory ($\dot{V}_E$) sensitivity to hypoxia in a normal human. The closed symbols were obtained at rest and the additional data were obtained during two levels of submaximal exercise. Note that exercise increased the response to hypoxia. Data are, with permission, from Asmussen et al. (17).

As a result, there was a transient hypercapnia in these subjects but not in the normal subjects. Wasserman et al. also found that there was an inverse relationship between the $\dot{V}_E$ time constant during exercise and induced presumed changes in carotid chemoreceptor activity (143, 259). They thus concluded that the CB "are responsible, in part, for the rate of increase in $\dot{V}_E$ to steady-state exercise" (337). A major concern with these CB data is that it was assumed that CBD rather than asthma caused the abnormal response in the asthmatics. It was not reported whether the CBD patients had normal pulmonary mechanics. Increased airway resistance in normal humans can cause hypoventilation during exercise which is accentuated when carotid chemoreceptor activity is attenuated by hyperoxia (119). Asthmatics with intact chemoreceptors tend to hypoventilate during exercise; thus, this hypoventilation in the CBD asthmatics has been argued to be related to the asthmatic disease rather than the effects of CBD (119).

In otherwise healthy animals, CBD ponies (263, 264), goats (47,265), and dogs (51) hypoventilate at rest and during exercise for days after CBD. At the onset of exercise, these animals decrease their $PaCO_2$ more than the decrease before CBD (Fig. 6). This finding suggests the CB normally serve to partially dampen a hyperventilatory drive to breath during exercise. In the steady state of exercise, $PaCO_2$ has returned toward resting levels and the difference between the rest and exercise hypercapnic levels is nearly the same as before CBD. For example, Bouverot et al. found in dogs prior to CBD, a $PaCO_2$ of 36.6 mmHg a rest and 32.4 mmHg during treadmill exercise at a metabolic rate five times rest (51). Four days after bilateral CBD, the rest and exercise values were 51.9 and 46.3 mmHg, respectively. Similarly, Pan et al. found in ponies prior to CBD, a $PaCO_2$ of 44.5 mmHg at rest and 43.1, 42.3, and 40 mmHg during treadmill exercise at metabolic rates two, four, and eight times rest (263). Two to four weeks after CBD, $PaCO_2$ was 54 mmHg at rest and 52.7, 51.7, and 46.8 mmHg during the three respective work rates. Bisgard et al. (47) and Pan et al. (265) also found in goats nearly the same rest to exercise difference in $PaCO_2$ before and after CBD even though the goats were hypoventilating after CBD. These findings are consistent with the emerging concept that the CB provide a major excitatory drive for breathing (127, 301) which is equally important at rest and during exercise. Thus, in conclusion the CB do not provide an unique "exercise-related" drive for breathing. However, as indicated by both the single breath O_2 tests and by the CBD data on healthy mammals, these receptors provide an excitatory drive needed for the controller mechanisms to meet the demands imposed by different levels of metabolic rate. Furthermore, these receptors also "fine-tune" alveolar ventilation to the metabolic demands.

Conclusions regarding humoral mediation of the exercise hyperpnea

Krogh and Lindhard (section *Neural feed-forward mediation of the exercise hyperpnea*) concluded it is not intuitive that humoral factors provide a major stimulus for the exercise hyperpnea. Tests of this hypothesis have yielded a great deal of conflicting data which is in part due to the unphysiologic conditions (electrically induced muscle contractions or venous CO_2 loading in anesthetized animals) of many studies. It seems clear though that none of the postulated humoral mechanisms could account for the temporal pattern or magnitude of the exercise hyperpnea. However, the CBD serve the same role as at rest in providing a major source of tonic excitatory input to the brainstem respiratory control network and in "fine tuning" alveolar ventilation to metabolic demands.

Mediation of the hyperpnea during submaximal exercise by multiple mechanisms

Neurohumoral theory

Dejours was one of the first investigators to propose that the multiple mechanisms contribute to the hyperpnea during submaximal exercise (84). His "neurohumoral theory" was based primarily on the temporal pattern of the hyperpnea. Similar to previous investigators, he found that within seconds after the onset of exercise, the hyperpnea reached about 50% of its steady-state value (Fig. 4). He reasoned this response was too rapid to be mediated by a muscle metabolite transported by the blood to a receptor outside the muscle; thus he concluded this increase was neurally mediated by either central command or spinal afferents. He further felt the subsequent increase to the steady state was inconsistent with a neural mechanism but was consistent with a gradual increase in some unidentified muscle metabolite acting outside of the muscle. Time-dependent increases in plasma $[K^+]$, catecholamines, and core temperature might be additional stimuli that contribute to this phase

of the hyperpnea. However, as detailed earlier, if there indeed is a humoral contribution to the phase II $\dot{V}_E$ response to exercise, it is unlikely from lung, cardiac, carotid, or central chemoreceptors, but conceivably it is from vascular receptors in the working muscles.

Role of short-term potentiation

As summarized in section *Neural feed-forward mediation of the exercise hyperpnea*, Waldrop et al. also proposed that multiple mechanisms mediate the hyperpnea during submaximal exercise (331). Their studies provided support for the concept that central command could contribute to the exercise hyperpnea. In addition, because respiratory STP occurs with several other respiratory stimuli in mammals, they reasoned that it is likely that the central command neural stimulus would also elicit STP. In support of their ideas, they observed a slow rise in $\dot{V}_E$ (i.e., STP) after the rapid rise during locomotion in nonparalyzed dogs, and also after fictive locomotion in paralyzed dogs (106). However the time constants of STP are too rapid to fully account for the phase II on- and off-transient responses to exercise.

Redundant mechanism mediation of the exercise hyperpnea

Yamamoto proposed a different version of multiple mechanisms for mediation of the exercise hyperpnea (362). He reasoned that there likely are "many sufficient mechanisms, each of which in a given isolated circumstance, explains the whole phenomenon. When they act simultaneously, they mask each other." Conceivably, this "redundancy" may reconcile the widely differing theories that appear capable of mediating the hyperpnea.

There are at least three mechanisms that could create redundancy in a control system (147). One is occlusion that prevents summation of two different excitatory inputs to a neuron. For example, humoral and peripheral neurogenic afferents could both excite the same brainstem respiratory neuron. In the absence of summation, activation of respiratory neurons and thus the exercise hyperpnea are the same whether both or only one of the afferents are functional. A second possible mechanism could be presynaptic inhibition whereby one excitatory input to a respiratory neuron blocks another excitatory input before both synapse at the same respiratory neuron. For example, two peripheral neurogenic afferents could synapse on the same neurons but one presynaptically inhibits the other. Chemoreceptor feedback could be a third mechanism of redundancy. For example, in the absence of primary drives (central and/or peripheral neurogenic), arterial blood gas would change and the resultant changes in carotid and intracranial chemoreceptor activity would result in a hyperpnea.

Waldrop et al. tested Yamamoto's hypothesis in anesthetized cats (331). They found that the summed $\dot{V}_E$ response to separate activation of central command and peripheral neurogenic feedback exceeded the response when the two were activated simultaneously (331). These data thus appear consistent with redundancy by occlusion.

Pan et al. tested the possibility of redundancy of exercise stimuli in awake ponies (266). They determined whether the effects on breathing and $PaCO_2$ regulation after CBD, hilar nerve denervation (HND), and partial spinal lesions (SL) in the same animal were predictable from the effects of these lesions individually. Alone CBD, HND, and SL do not affect or slightly attenuate the normal exercise hyperventilation in this species. They predicted that if redundancy exists among these pathways, the exercise hyperventilation would be attenuated conceivably to exercise hypoventilation. However, they found that after all three lesions, the exercise hyperventilation was greater than with any single lesion; thus, this study does not support the hypothesis of Yamamoto. The caveat with the studies of Pan et al. is that any single chronic lesion and possibly more so with multiple lesions, the control system has been altered in a way that the data may not provide insight into the normal contribution of the pathway.

The differences in conclusion of Waldrop's and Pan's studies could relate to use of anesthetized cats in Waldrop's study versus awake ponies in Pan's studies. Alternatively, the difference in conclusions could relate to the different pathways studied. Conceivably, the key component might be central command which was studied by Waldrop but not by Pan.

Redundancy in physiologic regulatory mechanisms seems common and intuitive. Moreover, redundancy is well documented for other components of the ventilatory control system (chemoreception, neuromodulation, respiratory rhythm, and pattern). Accordingly, it seems feasible that multiple stimuli contribute to the exercise hyperpnea, and that when any one stimulus is attenuated, other stimuli are capable of compensation to maintain a normal hyperpnea.

The Hyperventilation of Heavy Exercise

When $\dot{V}_A$ increases out of proportion to $\dot{V}_{CO_2}$

As exercise intensity increases beyond 50% to 60% of maximum $\dot{V}_{O_2}$, $\dot{V}_E$ increases out of proportion with respect to $\dot{V}_{O_2}$ (causing alveolar PO_2 to rise) and then at a slightly higher workload disproportionately more with respect to $\dot{V}_{CO_2}$ (causing alveolar PCO_2 to fall). At maximal exercise, the degree of hyperventilation can be sufficient to drive $PaCO_2$ 8 to 15 mmHg below and to raise alveolar PO_2 20+ mmHg above resting values. This hyperventilatory response has several important implications for exercise performance in that it: (i) provides an important (partial) compensation for arterial pH regulation in the face of a progressive metabolic acidosis, (ii) is critical to preventing arterial hypoxemia in the face of progressive widening of the alveolar to arterial PO_2 difference, (iii) requires that a significant share of the total cardiac output be devoted to the respiratory (vs. limb locomotor) musculature, and (iv) causes a hypocapnic-induced cerebral

vasoconstriction and reduced cerebral blood flow with potential implications for an altered brain metabolism (252, 254).

What mechanisms mediate this "extra drive" to breathe? The popular choice for the past 60+ years or so has been a metabolic acidosis, because arterial plasma lactic acid and H^+ begin to rise coincident with the onset of the hyperventilatory response. Reasonably, the hyperventilation is viewed as a ventilatory compensation for a primary metabolic acidosis. Furthermore, since CB are exposed to the metabolic acidosis [whereas the brain interstitial fluid which bathes the medullary chemoreceptors is protected to a significant extent from circulating lactic acid by the blood brain barrier (48)], they are the logical choice as the main transducer of the metabolic acidosis and the hyperventilatory response. Two types of clinical models also support this hypothesis. Neither the mildly asthmatic patient with denervated carotid bodies (217) nor the patient with congenital hypoventilation syndrome and a demonstrated absence of ventilatory response to chemoreceptor stimuli (CO_2 or hypoxia) at rest (297) show a hyperventilatory response to heavy exercise even though both of these types of patients show a normal isocapnic hyperpnea during mild intensity exercise. Thus, unlike the dilemma of moderate intensity exercise *hyperpnea*, the *hyperventilation* of heavy exercise would at first glance appear to have a clearly defined stimulus and reflex receptor site.

On the other hand, there are several lines of evidence that preclude such a clear cut conclusion. First, neither metabolic acidosis nor the carotid bodies were shown to be required for the hyperventilatory response to heavy exercise. When dietary-induced glycogen depletion was used to prevent almost all of the exercise-induced increase in lactic acid, a normal hyperventilatory response persisted (161). Furthermore, when exercising animals were studied before and after CBD, the animal's $\dot{V}_E$ response to heavy exercise was, if anything, slightly *greater* following CBD, despite similar levels of metabolic acidosis (264). These experimental data conflict with the cross-sectional evidence in the CBD asthmatic humans cited above. Inspiring hyperoxic gases, which are known to greatly reduce the tonic activity and responsitivity of the CB, caused transient reductions in $\dot{V}_E$ during heavy exercise. However, similar thresholds of exercise intensity were shown to exist for the onset of hyperventilation in hyperoxic as well as normoxic exercise (68,180,297). Unfortunately hyperoxia, after being present for only a few minutes, has a secondary central stimulatory effect on breathing (80). Thus, this dual inhibitory/excitatory influence of hyperoxia confounds the interpretation of the results of steady-state hyperoxia interventions.

What can we conclude from these conflicting data? Given the well-described $\dot{V}_E$ response of the CB to circulating hydrogen ions (205), it is safe to say that the CB are involved to a significant extent in the $\dot{V}_E$ response to heavy exercise. However, during high intensity exercise, the metabolic acidosis alone is unlikely to be a sufficiently strong stimulus to explain the 20% to 30% or 20 to 40 l/min "extra" increase in $\dot{V}_E$ in healthy young subjects (92). There are additional carotid body stimuli, such as increasing concentrations of norepinenephrine, potassium, adenosine, angiotension, and temperature which occur in heavy exercise and might play a role in sensitizing the carotid chemoreceptor to circulating [H+] (269).

However despite several attempts, the literature is quite unclear on whether exercise, *per se*, somehow "sensitizes" carotid chemoreceptor responsiveness. On the one hand, the $\dot{V}_E$ response to such carotid chemoreceptor stimuli as progressive hypoxia, are markedly augmented even in mild intensity exercise (Fig. 22) (88, 339). Furthermore, exercise-induced sympathetically-mediated vasoconstrictor influences on the limb muscle vasculature are markedly attenuated by selective inhibition of the CB during even mild exercise in the canine and human (310, 311). However CB inhibition via transient hyperoxia or dopamine infusion in humans failed to reveal any effects of exercise intensity on CB responsiveness (344). Thus, while the responsiveness to transient CB inhibition is clearly enhanced during exercise versus rest, increased exercise intensity does not appear to further enhance CB sensitivity. Furthermore, studies differ substantially in the timing of acute hyperoxia effects on $\dot{V}_E$ during heavy exercise, with some findings supporting a rapid, substantial decline in $\dot{V}_E$ within two breaths of hyperoxia (180, 334).

A potential role for "central" medullary chemoreceptors in controlling ventilation during heavy exercise has many complexities and considerations. First, given the tight junctions in the blood brain barrier, little if any of the lactic acidosis in systemic blood is likely to be transported to brain extra cellular fluid especially during exercise of short duration (46). On the other hand, the hyperventilatory response itself will cause an immediate reduction in systemic as well as brain extracellular fluid (ECF) PCO_2 and a central alkalosis will accompany this hypocapnia. To date, this central alkalosis has only been inferred from measurements made in cisternal CSF during exercise in hyperventilating animals (46). Since hypocapnia also causes marked cerebral vasoconstriction and reduced cerebral blood flow during exercise, the reduction in brain PCO_2 will be less than that in arterial PCO_2 thereby protecting against more marked brain hypocapnia and alkalosis. Despite the cerebral vasoconstriction limited measurements have indicated that brain mitochondrial PO_2 is unlikely to be reduced sufficiently to elicit brain tissue anaerobiosis (252). Thus, it seems unlikely that the central chemoreceptors ECF ionic environment would change in a direction which presents a significant stimulus to central chemoreceptors during heavy exercise. On the other hand, recent findings suggest that evaluating peripheral or central chemoreceptor contributions to breathing based on the conventional model of purely separate inputs to the respiratory controller from the peripheral *or* the central chemoreceptors maybe in error. First, Stornetta et al. have demonstrated a neuroanatomical linkage of carotid chemoreceptor afferent input through the nucleus of the solitary tract to the chemosensory neurons in the RTN (312). Furthermore, recent experiments in the resting, unanesthetized neurally intact canine have shown that changing the level of

carotid chemoreceptor stimulation/inhibition has marked hyperadditive effects on the ventilatory sensitivity to CO_2 of the central chemoreceptors (49, 50). Accordingly, we speculate that the likely stimulation of CB via circulating humoral stimuli in heavy exercise will contribute to the hyperventilatory response by *both:* (i) increasing the sensory input to the respiratory controller via the CB themselves and (ii) through the augmenting effects of increased peripheral sensory input on the chemosensitive gain of the central chemoreceptors. Quantifying this effect of the dual, interdependent role of peripheral chemoreceptor input during exercise presents a substantial challenge.

Other powerful locomotor-linked, nonchemoreceptor stimuli are likely to contribute to heavy-exercise-induced hyperventilation, because as locomotor muscle fatigue occurs in heavy exercise, more central command must be generated to maintain locomotor muscle force. There is no direct evidence to support this suggestion, but in exercising humans electromyogram (EMG) of the limb locomotor muscles showed a marked curvilinear increase in activity versus work rate. These data suggest an increase in central command coincident with the onset of high-intensity exercise and the onset of hyperventilation (228). Even more convincing is the marked hyperventilation precipitated by experimentally induced muscle weakness (with curare) which provides additional evidence in support of a strong recruitment of central command influences on $\dot{V}_E$ during heavy intensity, fatiguing exercise (9, 10, 15, 133). Accumulation of muscle metabolites in heavy exercise may also promote enhanced feedback from locomotor muscles metaboreceptors. When this feedback was partially blocked at the spinal level (without effecting muscle strength) via intrathecal administration of an opioid receptor agonist, the hyperventilatory response to heavy exercise in humans was significantly reduced (9). However, this effect of afferent blockade was greater earlier in the exercise trial when lactic acid production was less versus later in the exercise trial when systemic metabolic acidosis and locomotor muscle fatigue had peaked. Also the relative hypoventilation and CO_2 retention caused by this blockade was significantly greater during low versus high-intensity exercise (7).

The hyperventilation of heavy exercise presents even more examples than the isocapnic hyperpnea of moderate exercise of feed-forward and feedback sensory inputs influences on $\dot{V}_E$. The major obvious difference is that in heavy intensity exercise we now have large changes in additional known carotid chemoreceptor stimuli in arterial blood which surely contribute to some extent to the hyperventilatory response. However, available indirect evidence also points to the additional (and likely interactive) strong descending influences of augmented central command which are heightened with the onset of muscle fatigue. Theoretically, this enhanced central command may also rely critically on stored information from past "memorable" experiences of high exercise intensities (321). Locomotor muscle fatigue onset is also likely to precipitate greater input from muscle metaboreceptors to drive hyperventilation. However, we know of no direct experimental support for this idea and the ventilatory reducing effects of muscle afferent blockade were greater at moderate versus heavy-exercise intensities (7). We believe the available evidence support a dominant contribution to heavy-exercise hyperventilation from feed-forward central command and muscle metaboreceptor feedback, with secondary influences from circulating muscle metabolite-induced stimulation of the CBD.

Finally, sustaining constant work-rate heavy exercise (>75% $\dot{V}_{O_2}$ maximum) beyond about 5 to 10 min also causes a time-dependent tachypneic hyperventilatory response. An important difference between short- and long-term high-intensity exercise is that arterial $[H^+]$ may actually be *falling* in the long-term as opposed to *rising* in short-term heavy exercise (150). This change occurs because the net release of lactic acid from the working muscle may actually fall over time at constant workloads, and the level of hypocapnia becomes the dominant determinant of arterial $[H^+]$. Nevertheless, carotid chemoreceptor stimuli in the form of time-dependent increases in circulating norepinenephrine and potassium continue to be present in long-term exercise. Additionally, there is potential for augmented central command and feedback influences associated with limb locomotor muscle fatigue (see above). An additional consideration here is the time-dependent rise in core, blood, and/or brain temperature (349), which has a unique effect among $\dot{V}_E$ stimuli in humans. This rise in temperature produces a predominant tachypnea rather than a tidal volume response. Furthermore, preventing a majority of this core body temperature increase via skin cooling was shown to prevent a significant portion of the time-dependent tachypneic hyperventilation in long-term exercise (221). At exactly what sites the increase in temperature might be acting to cause hyperventilation is uncertain. The CB are temperature sensitive. Furthermore, this tachypneic response may be stimulated by increased hypothalamic temperature, thereby serving as a thermoregulatory response for selective brain cooling (349), analogous to that commonly experienced in the fur-bearing, panting animal.

Mechanical constraints on ventilation during heavy intensity exercise

There are two types of mechanical constraints on the $\dot{V}_E$ response to heavy exercise that deserve consideration, even in health, namely: (a) the capacity of the inspiratory pump muscles to generate a negative pleural pressure, as required for both force output at any given muscle length and for generating the velocity of respiratory muscle shortening and (b) the capacity of the intrathoracic airways to maintain patency, thereby allowing increased flow rates during active expiration.

In health, the dynamic capacity of the inspiratory (or expiratory) muscles for force generation probably never limits the $\dot{V}_E$ response to exercise. In healthy young adults, only about one-half of this capacity is reached at peak exercise, at ventilations of 100 to 120 l/min; however, as much as 80% to 90% of inspiratory muscle dynamic capacity can be

required to generate the necessary intrapleural pressures in highly trained athletes working at about twice the metabolic requirement and $\dot{V}_E$ responses as in the untrained (187). A key factor in protecting against the need for relatively extreme levels of inspiratory muscle pressure production is the reduction in end-expiratory lung volume (achieved via expiratory muscle activation) which increases intra-abdominal pressure and lengthens the diaphragm, thereby preserving its high maximum force generating capacity. In prolonged high-intensity endurance exercise to exhaustion the diaphragm (and expiratory muscles) will experience significant fatigue (184). However, while this fatigue likely activates metaboreflexes originating in inspiratory and expiratory muscles, which in turn increases sympathetic vasoconstrictor outflow and influences blood flow redistribution (159, 160, 286), the hyperventilatory response is not compromised.

The maximum flow:volume loop usually exceeds the maximum tidal loop observed at maximum exercise; thus the airways usually do not present a mechanical constraint on $\dot{V}_E$. However, the airways occasionally do present a significant limitation to expiratory airflow resulting in dynamic hyperinflation, increased respiratory muscle work and $\dot{V}_E$ limitation during heavy-intensity exercise. Healthy subjects most susceptible to mechanical airway limitations to expiratory flow during heavy exercise include fit prepubescent children (251), fit aging adults with reduced lung elastic recoil (185) and highly fit young adult females (229, 230). In the latter group, it was shown that the $\dot{V}_E$ response to inhaled CO_2 (via rebreathing) decreased in slope at heavy-intensity exercise (vs. rest or mild exercise), coincident with evidence of expiratory flow limitation. Also inhaling reduced density gas mixtures ($He:O_2$), increased the maximum flow:volume envelope, abolished flow limitation during tidal breathing and increased exercise $\dot{V}_E$ and the $\dot{V}_E$ response to inspired CO_2 (229, 230). These subject groups tend to show a high prevalence of exercise induced expiratory flow limitation for two reasons: (i) their intrathoracic airways tend to be narrower for any given lung volume in older versus young adults (185, 186), children versus adults, and adult females versus males (146) and (ii) their relatively high $\dot{V}_{O_2}$ maximum means that they can achieve higher work rates (vs. the normal fit) which in turn require higher $\dot{V}_E$ responses thereby bringing them to the limits of their already compromised maximum flow:volume loop. Further, a minority of highly trained young male adults also show expiratory flow limitation at their extraordinarily high ventilations required in max exercise, resulting in a very limited level of compensatory hyperventilation (186). Eliminating the flow limitation (via $He:O_2$) allowed a greater hyperventilatory response in these subjects (89, 230).

There are also complex mechanical effects of intrathoracic and intra-abdominal pressures on stroke volume and cardiac output which are just beginning to be defined in the exercising animal and human. Expiratory flow limitation accompanied by high expiratory pressures which approach or even exceed the airway critical closing pressure during exercise has been shown to result in increased left ventricular afterload and reduced stroke volume (236, 237). Alternatively, subatmospheric pressures generated during inspiration contribute significantly to a rising stroke volume during moderate and heavy-intensity exercise (160, 238). If inspiration is achieved primarily via diaphragmatic contraction, then the accompanying increase in intra-abdominal pressure upon descent of the diaphragm impedes femoral venous return from the exercising limb. However, these deficits in flow are recovered during expiration, with little net effect on overall venous return (237).

Finally, during heavy sustained exercise, another important type of respiratory:circulatory interaction occurs between respiratory muscle fatigue, sympathetic vasoconstriction, and blood flow distribution. Just as in limb muscles, there are type III-IV metaboreceptors in the diaphragm which are activated during fatiguing contractions (165). This activation causes sustained sympathetic activation presumably acting via phrenic afferent supraspinal reflex pathways (306). Phrenic arterioles also have the special property (vs. arterioles in limb muscle) of showing a markedly blunted vasoconstriction in response to norepinephrine (1). Accordingly, during heavy sustained exercise, respiratory muscle blood flow may command 8% to 10% of the total $\dot{V}_{O_2}$ and cardiac output in the untrained and as much as 14% to 16% in the highly trained (160, 222). Thus, when respiratory muscle work is reduced during heavy (using a mechanical ventilator), limb vascular conductance and blood flow are increased significantly (159) presumably because of reduced energy and blood flow requirements of the inspiratory and expiratory muscles. Alternatively, resistive loading of the respiratory muscles during heavy exercise reduces limb locomotor muscle conductance and blood flow (159).

Modeling the Control of Breathing During Exercise

As summarized by Swanson (317), two types of models have been used to study the control of breathing in exercise (318). The first type, usually referred as *empirical models,* attempts to answer the question, "how does a system behave?" These models are nondescriptive in terms of structure but they intend to provide the most accurate parameters that would describe the behavior of the $\dot{V}_E$ response to exercise. These responses have been described using step, ramp, sinusoidal, or impulse exercise (37, 64, 65, 131, 132, 346, 347). For instance, the time constant of $\dot{V}_E$ during phase II exercise does not necessarily have a structural meaning but it is a reliable way to describe the onset of exercise. Electrical or mechanical analogues have been used for didactic purposes as a way to simplify the $\dot{V}_E$ response to exercise both in the time and the frequency domain.

In contrast, *structural models* try to answer the question, "what is the most appropriate mechanistic structure of the system?" Grodins et al. (144) applied tools used in engineering to describe complex regulatory systems and to propose the first

structural models of respiratory control in exercise. Structural models assume there is a fundamental strategy followed by the respiratory control system in exercise. The tenet of this strategy relies on the "principle" of optimality sometimes referred as economy or minimization hypothesis (138,364,365). In structural models, it is proposed that the mechanical and metabolic cost of breathing is minimized using feedback or feed-forward inputs. The general theory is that the only possible outcome resulting from this optimization principle is an isocapnic exercise hyperpnea despite a several fold increase in CO_2 production. For example, a recent model proposed by Poon et al. (279) is that through associative learning, "an emergent controller signal encoding the projected metabolic level is predicted by the principle as an exercise-induced "mental precept" or "internal model," which "achieves optimality through continuous identification of, and adaptation to, the causal relationship between respiratory motor output and resultant chemical-mechanical afferent feedbacks." This postulated mechanism achieves optimality balancing all the physiologic demands during exercise through: (a) an internal model neural network, (b) chemical and mechanical feedback, (c) an efferent process whereby the respiratory output sends efference copies to the brainstem controller, and (d) by neural adaptation to specific inputs. Supposedly, this proposed mechanism will achieve near homeostasis of arterial blood gases throughout submaximal exercise without the need for any feed-forward stimulus or signal. However, this model is based on several premises that need to be substantiated by experimental evidence. The notion of internal model remains to be defined in terms of structures. The very notion of optimization which appears to most of us rather self evident, may not be the used by the respiratory control system as a universal law.

As summarized by Grodins et al., models must be testable and given an experimental dimension and validation:

> *"if we were to find that pulmonary ventilation and cardiac output behaved in such a way that the total metabolic cost of pumping air and blood at any given level of exercise were minimized, the physiologist's response would likely be, 'So what!' That does not tell me what neural and/or humoral mechanisms are responsible for this nice behavior!' (*144*). And of course he would be right."*

A challenge is to create a testable model that explains the immediate increase in $\dot{V}_E$ after a step change in work rate which is followed, without a further change in motor activity, by an exponential $\dot{V}_E$ increase over 3 min temporally linked to changes in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Such a model would also address how the $\dot{V}_E$ kinetics are similar during the exercise on and off transient and how the $\dot{V}_E$ responses to sinusoidal and impulse exercise forcing can be dissociated from the motor activity. Thus what could be the role of the central command which parallels locomotion and breathing? What is the actual contribution of muscle information strictly related to the mechanical effects of contractions? These questions do not imply that information related to motor or locomotor activity are not involved in the exercise hyperpnea, but they do suggest that some characteristics of the $\dot{V}_E$ response to exercise can be produced without such types of information.

Finally, the major challenge is to create a testable model to explain the hyperpnea of exercise that occurs during submaximal exercise without a change or even a decrease in stimulus level at known receptors for the variables that are regulated (Pao_2, $PaCO_2$, and arterial pH).

Coordination of Multiple Responses to Meet Demands of Exercise

Multiple respiratory-related efferent and afferent systems change activity during exercise. It seems intuitive that there is a site(s) within the brain for integration or coordination of this information. Potential sites include but are not limited to the cerebellum (fastigial nucleus (CFN) and/or the anterior lobe) and the periaqueductal gray (PAG).

Role of the cerebellum

During exercise, the cerebellum receives an "efference copy" of motor commands from higher CNS structures as well as muscle and joint afferents from the periphery (95, 100, 260). The classic concept of the cerebellar role is to utilize these sources of information to match the efferent locomotor command with the peripheral locomotor activity. Anatomical studies also established reciprocal neural pathways between the cerebellum and brainstem nuclei including the nucleus tractus solatarii (NTS), vestibular nucleus, and pre-Bötzinger complex (11, 95, 162, 366). These data indicate the cerebellar nuclei receives information regarding baroreflex and chemoreflex mechanisms and that the CFN projects to brainstem respiratory nuclei.

In anesthetized mammals, stimulation of the anterior lobe of the cerebellum inhibits breathing (81, 249) while ablation of this region stimulates breathing (75, 309). In addition, ablation of the anterior cerebellum decreases the increase in $\dot{V}_E$ induced by pressure application or stretch of the gastrocnemius muscle (268). Also in anesthetized mammals, electrical or chemical stimulation of the CFN increases breathing (30, 218, 219, 352, 357, 358). Moreover ablation of the CFN attenuates the respiratory responses to hypercapnia and hypoxia (360, 361). Finally, the CFN contains respiratory-modulated neurons responding to hypercapnia and hypoxia (145, 219, 359).

A role in cardiorespiratory control for the CFN has also been demonstrated in awake mammals. For example, Dormer (94) found in dogs that lesioning the CFN attenuated the cardiovascular responses to dynamic exercise. In addition, in awake goats focal acidosis in the CFN stimulates breathing (226), lesioning this nucleus attenuates the $\dot{V}_E$ response to hypercapnia (225) and reduces by 2 mmHg, the normal hypocapnia of goats during exercise (224). These CFN lesions

may underestimate the contribution to the exercise hyperpnea as only 55% of the CFN was destroyed and the post lesion studies were delayed at least a week until the goats were capable of again walking on the treadmill; thus, compensation may have occurred for the CFN deficit.

To our knowledge it has not been postulated nor is there rationale or evidence to suggest that cerebellar nuclei are the primary source of the stimulus for the exercise hyperpnea. However, it appears the cerebellum contributes to cardiorespiratory control during exercise. We speculate this role is in coordination/integration of multiple physiologic systems to meet the demands of exercise.

Role of the PAG

The PAG is a mesencephalic heterogeneous structure divided into five columns with each area eliciting different autonomic responses involved in the integration of cardiovascular changes associated with emotional behaviours (25, 59). Neurons activated in the ventrolateral columns in awake animals result in decreases of mean arterial blood pressure (MAP) and HR along with immobility behaviors (24, 25, 59). Activation of neurons in the lateral/dorsolateral columns also increase MAP and HR but result in the flight/fight response (24, 25, 59, 79). In humans, activation of the former columns decreases MAP and HR while activation of the latter columns elicits the opposite cardiovascular responses (60). These cardiovascular changes are mediated through descending signals from the PAG (influenced by the dorsomedial hypothalamus (23, 41, 211) to brain stem autonomic centers such as the subretrofacial and paragigantocellularis nuclei (61, 62, 216).

Even though the PAG is best known and most frequently studied for cardiovascular effects, activation of the PAG has also been shown to elicit increases in $\dot{V}_E$. For example, Brack et al. (52) found that injection of a panicogenic agonist into the PAG of anesthetized rats elicited a hyperpnea, and a hyperpnea is a common feature of a panic attack (12, 256, 257).

Exercise has been shown to increase PAG activity. For example, c-Fos expression increases in the PAG during hypertension induced by isometric exercise (210). Moreover, electrical stimulation of ventral roots innervating the hindlimbs of cats increases PAG activity (201), and lesion in the PAG prevent the hypertension induced by muscle contractions (351).

In human patients with movement disorders, electrodes have been chronically placed into the PAG or the periventricular gray (PVG) which is continuous with the PAG. Electrical stimulation in the dorsal PVG causes hypertension while stimulation in the ventral PVG causes hypotension (140). During recording of electrical activity in the PAG, a consistent finding has been increased neural activity during anticipation of exercise, during different low levels of exercise, and after exercise when venous blood was trapped in the previously exercising muscles. The increased PAG activity was associated with a hyperpnea, tachycardia, and hypertension (29, 139, 141).

Since activity of the PAG can be increased by electrical stimulation of hindlimb muscles, by stimulation of the hypothalamus, and by exercise, the PAG has been proposed as a site "linking the central and peripheral systems during exercise" and being a "major integrating site" of multiple stimuli for the exercise hyperpnea (Fig. 11) (29).

Concluding Statements

The three authors have investigated the exercise hyperpnea each from different backgrounds and perspectives, and each with different experimental models that are cumulatively representative of a majority of investigations over the past century. The authors have extensively discussed ideas related to the exercise hyperpnea specifically deliberating in an attempt to resolve existing controversies.

We believe the evidence critically reviewed warrants the following conclusions. First and foremost, we have not identified a single stimulus or a combination of stimuli that convincingly and entirely explains the exercise hyperpnea. Second, the long-recognized coupling between $\dot{V}_E$ and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ is not causal but is due to each resulting from a common factor which somehow links the circulatory and $\dot{V}_E$ responses to metabolic rate. Third, the so-called humoral stimuli postulated to act at pulmonary or cardiac receptors or carotid and intracranial chemoreceptors are not primary mediators of the exercise hyperpnea. Fourth, a stimulus originating in exercising limbs and conveyed to the brain by spinal afferents is a contributor to the exercise hyperpnea. Fifth, the hyperventilation during heavy exercise is not primarily due to lactacidosis stimulation of CB. Finally, since volitional exercise requires activation of the CNS, neural feed-forward (central command) mediation of the exercise hyperpnea seems intuitive and is supportive by data from several studies, but there is no compelling evidence to accept this concept as an indisputable fact.

Our overall assessment is that even though the mechanism for the exercise hyperpnea has not been established, there has been considerable progress since the major reviews of Dejours (84) and Wasserman et al. (335). It seems evident certain studies would help resolve some controversies. For example, it is important to elucidate the explanation for the apparent conflict between sinusoidal exercise, which suggests that motor activity/central command do not contribute to the hyperpnea, and multiple other studies that strongly suggest a contribution by central command. Indeed, a major challenge is to complete studies to determine whether central command contributes to the hyperpnea in a "neurally intact" animal or human with a normal control system. In addition, studies are needed to establish whether indeed venule blood flow in exercising muscle is a major contributor to the hyperpnea during *in vivo* spontaneous exercise. Also, with the multiple physiologic systems changing during exercise, it seems integration must occur somewhere in the brain, but heretofore this issue has not been adequately addressed.

The need for a better understanding of the mechanisms controlling the exercise hyperpnea has implications well beyond the natural curiosity of respiratory physiologists.

As many patients with respiratory and cardiac diseases are suffering from dyspnea and are hyperventilating during exercise, it remains difficult to address the mechanisms of such limitation (central vs. peripheral origin) as we are still unable to provide a simple description of how this system functions in a normal, healthy human.

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