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Reviews

Determinants and control of breathing during muscular exercise

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Introduction

Exercise hyperpnoea is considered to be one of the major remaining challenges to understanding the control of human systemic function. The topic is currently in an exciting phase, both with respect to novel perspectives on its control and the application of novel techniques to investigate previously proposed mechanisms. However, despite this, the integrative aspects of the control that so closely regulates arterial $P\mathrm{CO_2}$ ($P\mathrm{aCO_2}$) and pH (pHa) during moderate exercise, and which constrains the fall in pHa at higher work rates, seem no less elusive.

We attempt in this review to provide a current perspective on the mechanisms proposed to contribute to the exercise hyperpnoea in humans (typically under laboratory conditions) using, as a frame of reference, the different regulatory demands of the different temporal and intensity domains.

What is an "appropriate" ventilation?

It is often stated that ventilation during muscular exercise increases in proportion to metabolic rate. This is, in fact, not true! This is not simply because of the imprecision implicit in the failure to specify whether the metabolic rate is that for O_2 utilisation or CO_2 production, but that under conditions in which there are changes in body gas stores (especially for CO_2) ventilation changes not as a function of CO_2 produced in the exercising muscle, but rather as a function of CO_2 exchanged at the lungs. Regulation of pHa during moderate exercise, during which arterial bicarbonate concentration ($[HCO_3^-]a$) is typically unchanged, is achieved through regulation of $P\mathrm{aCO_2}$. This requires that ventilation changes not in proportion to metabolic CO_2 production, but in proportion to pulmonary CO_2 exchange, as shown in equations 1–4.

For CO_2 exchange, therefore:

$$P\mathrm{ACO_2} = \frac{863 \times \dot{V}\mathrm{CO_2}\ (\mathrm{STPD})}{\dot{V}\mathrm{A}\ (\mathrm{BTPS})} \qquad (1)$$

where the constant 863 corrects for the different conditions used standardly to report the ventilatory and gas exchange volumes—that is, body temperature, pressure, and saturation (BTPS) and standard temperature and pressure, dry (STPD) respectively—and the transformation of fractional concentration to partial pressure, $\dot{V}\mathrm{CO_2}$ is pulmonary CO_2 output, and $\dot{V}\mathrm{A}$ is alveolar ventilation.

Similar considerations apply to pulmonary O_2 exchange:

$$P\mathrm{AO_2} = P\mathrm{IO_2} - \frac{863 \times \dot{V}\mathrm{O_2}\ (\mathrm{STPD})}{\dot{V}\mathrm{A}\ (\mathrm{BTPS})} \qquad (2)$$

As is evident from equations 1 and 2, alveolar $P\mathrm{CO_2}$ and $P\mathrm{O_2}$ can only be maintained at constant levels during exercise if $\dot{V}\mathrm{A}$ changes in precise proportion to $\dot{V}\mathrm{CO_2}$ and $\dot{V}\mathrm{O_2}$. As $\dot{V}\mathrm{A}$ is common to both equations:

$$\frac{863 \times \dot{V}\mathrm{CO_2}}{P\mathrm{ACO_2}} \leftarrow \dot{V}\mathrm{A} \rightarrow \frac{863 \times \dot{V}\mathrm{O_2}}{P\mathrm{IO_2} - P\mathrm{AO_2}} \qquad (3)$$

Note that the effect on $P\mathrm{AO_2}$ of the slight difference between the inspiratory and expiratory ventilations that occurs when the respiratory exchange ratio (R) does not equal 1 is ignored, as the effect is small.

Under conditions in which $\dot{V}\mathrm{O_2}$ and $\dot{V}\mathrm{CO_2}$ differ, alveolar ventilation cannot meet the demands of both; hence $P\mathrm{AO_2}$ and $P\mathrm{ACO_2}$ cannot therefore both be regulated simultaneously. This situation is not unusual during exercise, changes in substrate utilisation profiles, and/or transient variations in body CO_2 stores. When this occurs, ventilation has been consistently shown to change in closer proportion to $\dot{V}\mathrm{CO_2}$ than to $\dot{V}\mathrm{O_2}$[1,2] (fig 1). Why and by what means remain important issues. The consequence, however, is that $P\mathrm{ACO_2}$ is the more tightly regulated variable. In normal individuals at sea level, the consequent changes in arterial $P\mathrm{O_2}$ ($P\mathrm{aO_2}$) remain on the relatively flat upper region of the O_2 dissociation curve; any effect on arterial O_2 content or saturation is therefore small. This is why the ventilatory demands of exercise are usually considered using CO_2 exchange rather than O_2 exchange as the frame of reference.

At any "set point" (or regulated) level of $P\mathrm{ACO_2}$, the demands for alveolar ventilation increase as a linear function of $\dot{V}\mathrm{CO_2}$ (equation 1): the greater the $\dot{V}\mathrm{CO_2}$, the greater is the ventilatory requirement. But if $P\mathrm{ACO_2}$ is regulated at (or reduced to) a lower value, $\dot{V}\mathrm{A}$ must be appropriately higher for any given level of $\dot{V}\mathrm{CO_2}$. A further consequence of this relation is that the increment in ventilation needed to reduce $P\mathrm{ACO_2}$ by a particular amount—for example, 10 mm Hg—is progressively greater the higher the $\dot{V}\mathrm{CO_2}$. In order to achieve the same degree of respiratory compensation for metabolic acidosis, a fit individual must there-

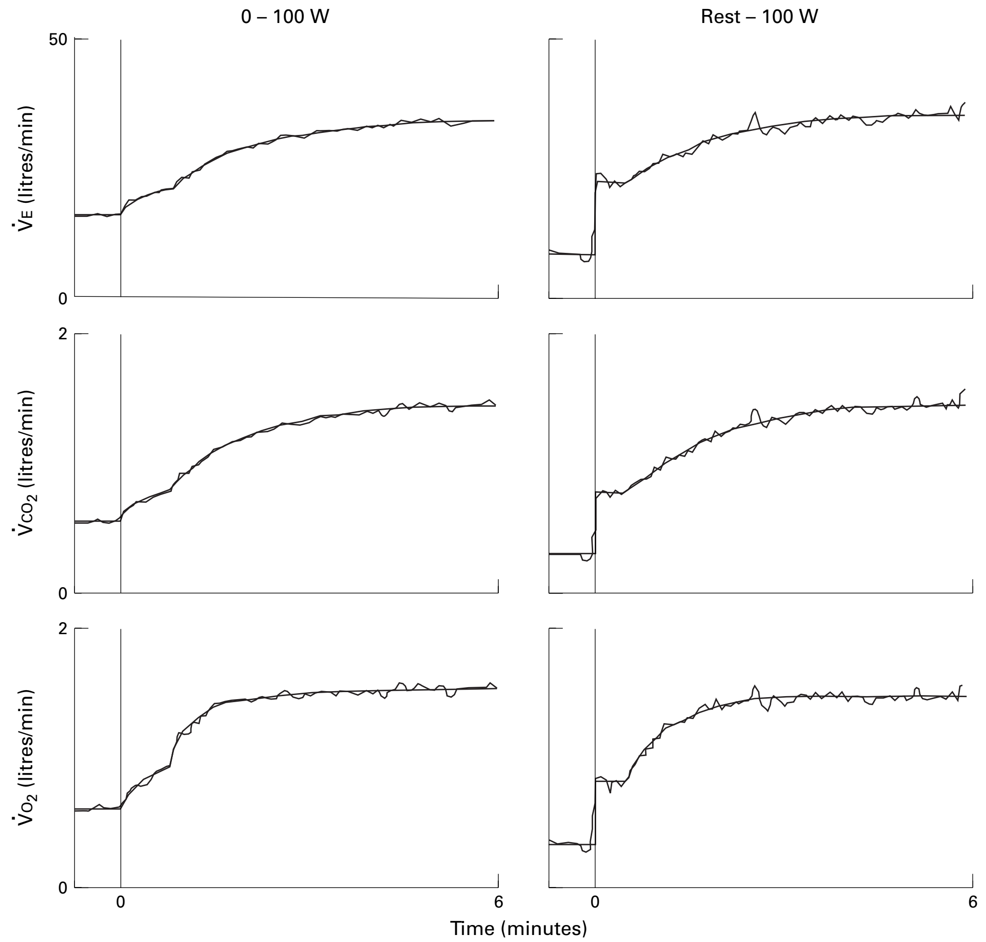

Figure 1 Ventilatory and gas exchange responses to moderate intensity constant load cycling (100 W) from either rest (right) or from unloaded pedalling—that is, 0 W—(left). Modified with permission from Whipp and Ward.[2]

fore increase $\dot{V}$A appreciably more than an unfit individual.

Ventilation of the alveoli requires that the dead space be simultaneously ventilated. The actual ventilatory demand of muscular exercise, however, is manifested as the total (or minute) ventilation ($\dot{V}$E), rather than just that of the alveoli—that is,

$$\dot{V}_A = \dot{V}_E\,[1 - V_D/V_T] \tag{4}$$

Therefore

$$\dot{V}_E = \frac{863 \times \dot{V}CO_2}{PaCO_2\,[1-(V_D/V_T)]} \tag{5}$$

where VD and VT are the physiological dead space and tidal volumes respectively, VD/VT is the dead space fraction of the breath, and $PACO_2$ and $PaCO_2$ are assumed to be equal.

We may therefore consider the ventilatory demands of exercise with respect to the defining variables of equation 5:

(*a*) the pulmonary CO_2 clearance rate, $\dot{V}CO_2$ (note, not necessarily the metabolic rate);

(*b*) the set point at which $PaCO_2$ is regulated;

(*c*) the physiological dead space fraction of the breath (VD/VT), which represents an index of the "inefficiency" of pulmonary gas exchange.

PULMONARY CO_2 CLEARANCE

It is only in the steady state of exercise, when body CO_2 stores are not changing, that $\dot{V}CO_2$ equals the metabolic CO_2 production rate ($\dot{Q}CO_2$) and the respiratory exchange ratio (R) equals the metabolic respiratory quotient (RQ). The substrate mixture undergoing catabolism, reflected in the RQ, can markedly influence $\dot{V}CO_2$ and hence the ventilatory demands. As shown in table 1, a given rate of high energy phosphate formation requires a greater rate of O_2 utilisation when fatty acids are metabolised than when carbohydrate serves as the substrate. But as the CO_2 yield from carbohydrate metabolism is about 40% greater than from fatty acid oxidation, this results in a greater demand for CO_2 clearance and, by inference, for ventilation.

In the non-steady-state, however, $\dot{V}CO_2$ is dissociated from $\dot{Q}CO_2$ as a result of transient changes in the body CO_2 stores. For example, during the on-transient phase of constant load

Table 1 Substrate oxidation energetics

	RQ	*$\dot{V}O_2$ (litres/min)*	*$\dot{V}CO_2$ (litres/min)*	*˜P:O_2*	*˜P:CO_2*	*O_2:˜P*	*CO_2:˜P*
Glycogen	1.0	1.0	1.0	6.00	6.00	0.17	0.17
Palmitate	0.7	1.0	0.7	5.65	8.13	0.18	0.12
Glycogen/palmitate	1.43	1.0	1.43	1.06	0.74	0.94	1.42

Values are expressed relative to a $\dot{V}O_2$ of 1 litre/min.
RQ, Respiratory quotient; ˜P, high energy phosphate.

exercise, some of the metabolically produced CO_2 never reaches the lungs because of the appreciable capacitative storage of CO_2 in the exercising muscles and in their venous effluent. During this phase therefore $\dot{V}CO_2$ is less than $\dot{Q}CO_2$. In contrast, alterations in the muscle O_2 stores are trivially small; R therefore falls transiently to reach a nadir at the time when the *rate* of CO_2 storage is maximal. Subsequently, R rises again as muscle PCO_2 stabilises at its new higher exercise value, becoming equal to the RQ in the new metabolic steady state.

As the dynamics of ventilatory change during the on-transient phase of exercise are closely coupled to those of $\dot{V}CO_2$ (see Whip and Ward[2] for discussion), it follows that $\dot{V}E$ changes slowly with respect to $\dot{V}O_2$ which has more rapid response dynamics (fig 1). Consequently, PAO_2 and PaO_2 are temporarily reduced in the on-transient. After the cessation of exercise, the increased levels of the CO_2 stores induced during the exercise now discharge. This results in R being transiently greater than RQ, often increasing to values greater than 1.0. The symmetry between the on- and off-transient responses for $\dot{V}E$ with respect to $\dot{V}CO_2$ for moderate exercise (fig 1) seems to provide an important clue to the control.

The rate of pulmonary CO_2 exchange is increased further at work rates associated with metabolic (chiefly lactate) acidosis (fig 2). That is, additional CO_2 is produced by the HCO_3^- component of proton (H^+) buffering at these work rates. This results in a more rapid rate of change of $\dot{V}CO_2$ relative to $\dot{V}O_2$ during incremental exercise tests. This provides the core rationale for the non-invasive estimation of the lactate (or anaerobic) threshold. Note that it is strictly incorrect to consider that lactic acid is produced during exercise, which then dissociates into a lactate ion and an associated proton; the dissociation actually occurs higher in the glycolytic chain. Lactic acid has a high dissociation constant (pK ~3.5); this means that the ratio of [lactate] to [lactic acid] is about 1000:1. The main buffering component, at least in the arterial blood, is sodium bicarbonate ($NaHCO_3^-$):

$$\begin{gathered} CH_3 \cdot CHOH \cdot COO^- + H^+ + NaHCO_3 \rightarrow \\ CH_3 \cdot CHOH \cdot COONa + H_2CO_3 \rightarrow \\ CO_2 + H_2O \end{gathered} \quad (6)$$

The amount of additional CO_2 formed in these reactions is substantial. Consider the complete aerobic catabolism of one glucosyl unit of glycogen to CO_2 and H_2O. This yields 37 ATP molecules. However, its subsequent breakdown to two lactate ions (and two associated protons) yields only three ATP molecules. Glycolytic flux must therefore increase by 12.3-fold—that is, 37/3—if the same ATP production rate is to be sustained, resulting in the formation of 24.6 mEq of lactate—that is, 2 × 12.3 mEq. As HCO_3^- has been shown to account for some 90% of this buffering capacity (protein and phosphate buffers accounting for the remainder), the decrease in [HCO_3^-] will be ~22 mEq. However, of this additional ~22 mM CO_2 production, 6 mM replaces the CO_2 that would have been produced aerobically for this rate of ATP formation. Consequently, the net 16 mM CO_2 yield represents a ~2.5-fold increase in $\dot{V}CO_2$, for the proportion of the total energy transfer contributed by these "anaerobic" reactions.

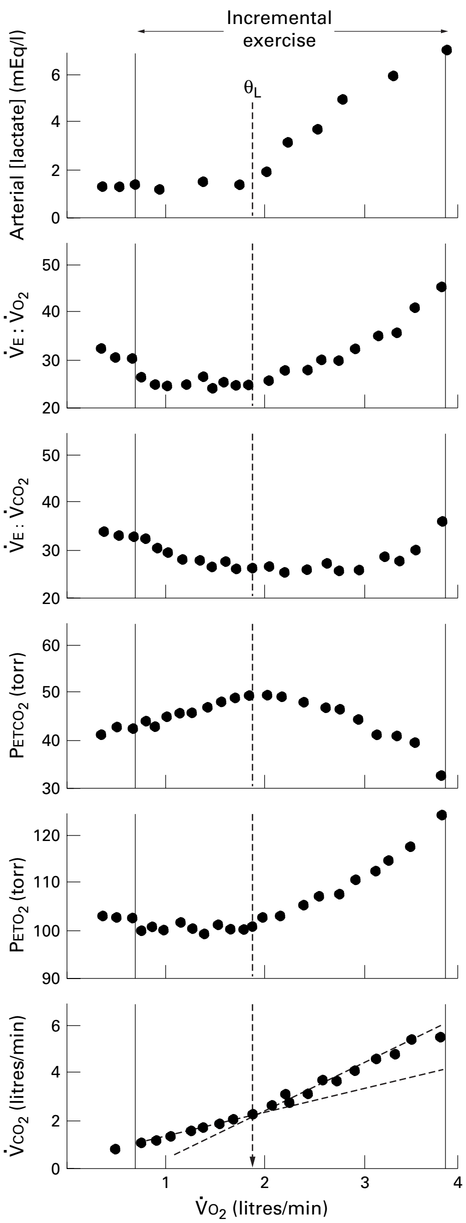

Fig 2 Ventilatory, gas exchange, and metabolic responses to an incremental exercise test (15 W/min) to the limit of tolerance, preceded by 0 W cycling. $\dot{V}O_2$ and $\dot{V}CO_2$ are pulmonary O_2 uptake and CO_2 output respectively, $\dot{V}E$:$\dot{V}O_2$ and $\dot{V}E$:$\dot{V}CO_2$, the ventilatory equivalents for O_2 and CO_2 respectively, and $PETO_2$ and $PETCO_2$, the end tidal PO_2 and PCO_2 respectively. Solid vertical line, exercise onset; dashed vertical line, lactate threshold (θ_L). Modified with permission from Whipp.[3]

Non-bicarbonate buffering mechanisms (such as protein and phosphate), although important for [H^+] regulation, do not produce extra CO_2. It is also important to recognise that the extra amount of CO_2 produced under these conditions is a function of the amount of [HCO_3^-] decrease in the muscle and blood compartments. However, as emphasised by Douglas[4] as early as 1927, it is the *rate* at which the HCO_3^- levels fall that determines the *rate* at which extra CO_2 is produced from these reactions, not the *amount* of the $[HCO_3^-]$ decrease.

Consequently, the more rapid the rate of increase in [lactate] and the rate of decrease in $[HCO_3^-]$, the greater is the increase in $\dot{V}CO_2$, which accounts for both $\dot{V}CO_2$ and R being considerably higher in the period of increasing blood [lactate] during rapidly increasing exercise and at maximum exercise, compared with tests in which the incrementation rate is relatively low.[2]

REGULATION OF ARTERIAL PCO_2

In the steady state of moderate intensity exercise, $PaCO_2$ is normally regulated at, or close to, the resting level at sea level. This stability is slightly less "tight" in the non-steady-state phase of the response. As the time constant of the $\dot{V}E$ response ($\tau\dot{V}E$) is slightly longer (~55–60 seconds) than that of $\dot{V}CO_2$ (~50–55 seconds), there is a consequent transient, but small, increase in both mean $PACO_2$ and $PaCO_2$.[2] This is most strikingly demonstrated with exercise formats that engender continuous non-steady states, such as sinusoidally varying work rate.[2] End tidal PCO_2 ($PETCO_2$), of course, does not show such stability, even during moderate exercise. This is because the CO_2 flux across the alveolar-capillary interface increases, predominantly as a result of the increased mixed venous PCO_2, making the alveolar phase of the expired PCO_2 profile steeper. End tidal PCO_2 therefore reflects the peak of the intrabreath alveolar (and arterial) PCO_2 oscillation, whereas arterial PCO_2 (as conventionally measured) reflects its mean value. $PETCO_2$ can exceed arterial PCO_2 by some 6–8 mm Hg, depending on the pattern of breathing.[5]

At work rates that induce metabolic acidosis, compensatory hyperventilation—that is, lowering of $PaCO_2$—is required to constrain the fall in pHa:

$$pHa = pK' + \log \frac{[HCO_3^-]a}{\alpha\, PaCO_2} \qquad (7)$$

where α is the solubility coefficient for CO_2. This results in a further depletion of the body CO_2 stores and provides an additional source of extra CO_2 output at high work rates.

Substituting for $PaCO_2$ in equation 7 from equation 5 yields an alternative means of considering the determinants of pHa regulation during exercise, in terms of what may be considered metabolic "set point", "control", and ventilatory "efficiency" terms respectively:

$$pHa = pK' + \log \left\{ \underset{\substack{\downarrow \\ \text{Set point}}}{\left[\frac{[HCO_3^-]a}{25.8} \right]} \underset{\substack{\downarrow \\ \text{Control}}}{\left[\frac{\dot{V}E}{\dot{V}CO_2} \right]} \underset{\substack{\downarrow \\ \text{Efficiency}}}{\left[1-(V_D/V_T) \right]} \right\} \qquad (8)$$

VENTILATORY EFFICIENCY

In all but the ideal lung, total dead space ventilation includes contributions from both the anatomical and the alveolar dead space volumes. The alveolar dead space is small in healthy individuals at rest in the upright posture, and is largely a reflection of the relative underperfusion of apical alveoli.

During exercise, however, the increased pulmonary artery pressure leads to a more even topographical distribution of perfusion throughout the lung; this reduces the alveolar component of the dead space. In addition, despite the volume of the dead space actually increasing because of the end inspiratory expansion of the conducting airways and the penetration of the stationary interface toward the alveoli during exercise, the V_D increase is small compared with the total V_T increase; consequently, V_D/V_T decreases. As a result, the ventilation needed to "clear" a litre of CO_2 is proportionally reduced. This accounts for both the magnitude and the pattern of decrease in the ventilatory equivalent for CO_2 ($\dot{V}E$:$\dot{V}CO_2$) with increasing work rate in individuals who regulate their $PaCO_2$ (fig 2).

System limitations

The difference between maximum voluntary ventilation and the maximum $\dot{V}E$ actually attained during exercise has been termed the "breathing reserve".[6] Moderately fit individuals have a considerable breathing reserve even at maximum levels of exercise.[6] In addition, the spontaneously generated expiratory flow-volume curve does not normally encroach upon the boundaries of the maximum expiratory flow-volume curve.[7] This is not the case for elite athletes, however. The high air flow demands of the high levels of ventilation required by the supranormal metabolic rates can lead to air flow limitation. For example, in such individuals the spontaneous expiratory flow-volume curve during exercise can impact upon the outer envelope of the maximum expiratory flow-volume curve.[8 9] Also, maximum $\dot{V}E$ values of some 90% of the maximum voluntary ventilation have been achieved in highly trained athletes.[10] In older athletic individuals, in whom lung recoil is reduced because of aging, this can occur at appreciably lower metabolic rates[9] (fig 3). Consequently the genetic make up of the athlete, in terms of airway dimensions and lung recoil, can play a decisive role in whether the air flow demands can be met without flow limitation over a portion of the expiration. Further complications arise from the reduction in vital capacity and in respiratory muscle strength and endurance that have been observed after prolonged exercise—for example, during the ultra-marathon.

Impaired pulmonary performance can also result from the high pulmonary vascular pressures associated with the high levels of cardiac output and pulmonary blood flow during high intensity exercise in elite athletes. Pulmonary artery pressures in excess of 40 mm Hg and pulmonary wedge pressures of 25–30 mm Hg have been reported in healthy young individuals.[11] Similarly high pulmonary vascular pressures were observed at appreciably lower levels of cardiac output in older but healthy individuals.[11] These elevated pulmonary vascular pressures can predispose to pulmonary-interstitial oedema and also increase the potential for structural damage to the delicate alveolar-capillary membrane.[12]

Whether pulmonary oedema actually develops during severe exercise in highly trained athletes is at present not clear, although case reports are suggestive of it. Were oedema to occur, it could result in exacerbation of arterial hypoxaemia, greater tachypnoea consequent to stimulation of pulmonary J receptors, more intense exertional dyspnoea, and even, it has been suggested, reflex inhibition of spinal motor neurons.[13]

Evidence suggestive of mechanical stress failure of the fine structured pulmonary capillaries in the presence of the high pulmonary capillary pressures that can occur during high intensity exercise has been reported for elite cyclists undergoing exhausting high intensity exercise.[14] These individuals had higher levels of erythrocytes, total plasma protein, and leukotriene B_4 in bronchoalveolar lavage fluid than sedentary individuals. This appeared not to be a primary inflammatory response, as indicated by the similar levels of markers such as tumour necrosis factor bioactivity, lipopolysaccharide, and interleukin 8 in the two groups. Stress related failure of the pulmonary blood-gas interface in elite human athletes (when it occurs) may only result from supramaximal efforts, however, as the effect could not be shown even for prolonged exercise of a somewhat lower intensity (one hour at 80% of $\dot{V}O_2$ MAX).

Whereas arterial oxygenation levels are well maintained throughout the entire tolerable range in most "normal" subjects, highly trained endurance athletes are prone to developing arterial hypoxaemia at high work rates.[11,15,16] Various factors are thought to contribute to this hypoxaemic response: (*a*) post-pulmonary shunt; (*b*) increased dispersion of ventilation: perfusion ratios; and (*c*) diffusion limitation resulting from pulmonary capillary vascular transit times that are too short to allow equilibration of capillary PO_2 with alveolar PO_2.

Control of the exercise hyperpnoea

The major challenge for investigators studying the control of the exercise hyperpnoea is not simply to provide a cluster of mechanisms capable of stimulating breathing, each often considered in isolation and, not uncommonly, under conditions remote from actual dynamic exercise. Rather, it is to incorporate them into a defensible control scheme that accounts for the actual exercise response, both in its steady state and non-steady-state phases. And as we believe the "steady state" to be largely a contrivance of investigative convenience with respect to spontaneous activity, the elucidation of the mechanisms of the dynamic features of the ventilatory and related gas exchange responses may be seen as the predominant challenge.

It is these features that not only provide the clues to the control but also set the important questions to be resolved. For example, after exercise onset, there is an initial short period in which ventilation increases, despite pulmonary gas exchange being effectively isolated from the demands of increased muscle metabolic rate (fig 1), except, of course, that the mechanisms that increase muscle blood flow also lead to increased pulmonary blood flow. This period has been termed phase 1. When mixed venous composition begins to change as a result of the increased ratios of muscle $\dot{Q}O_2$ and $\dot{Q}CO_2$ to muscle blood flow, this triggers a subsequent and distinct phase of the hyperpnoea (phase 2), with the new steady state being phase 3.[2]

The phase 1 to phase 2 transition raises the following important and rarely examined questions. What is the trigger(s)? If it is

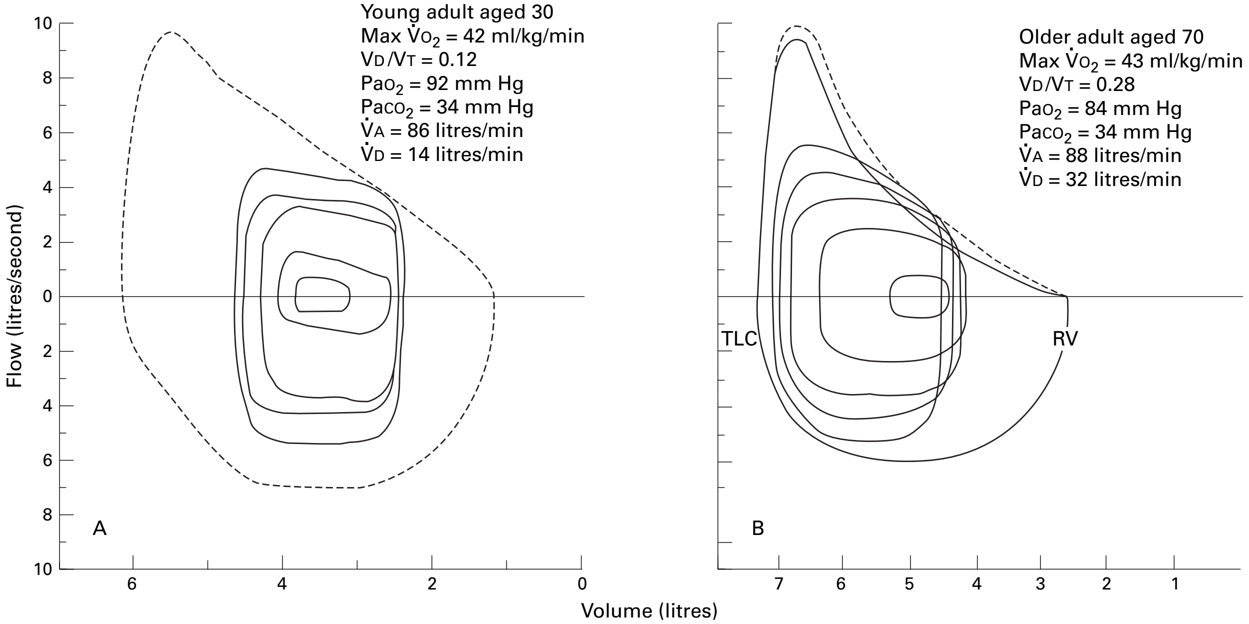

Figure 3 Spontaneous respiratory flow-volume loops generated at rest (inner solid loop) and at progressively higher work rates up to maximal exercise (outer solid loop) in a healthy moderately fit young adult (A) and an elderly subject of similar fitness (B), relative to their resting "forced" (or maximum) flow-volume loops (outer dashed loop). Note that in the elderly subject the expiratory loop impacted on the forced loop for all but the lightest of the work rates; this was not the case for the young subject, however. TLC = total lung capacity; RV = residual volume. Modified with permission from Johnson and Dempsey.[9]

neurogenically mediated, why is it not manifested until then? If it is humoral, what are the precise temporal correlates of the accelerated ventilatory and pulmonary gas exchange responses? What is the stimulus (or stimuli), and on which receptor(s) do they act?

NEURAL MECHANISMS

The immediacy of the ventilatory (and cardiovascular) responses to dynamic muscular exercise is seen by proponents of "neurogenic" control of exercise hyperpnoea to be of fundamental importance. Both central neural feedforward ("central command") and peripheral feedback from the exercising muscles have been proposed as mediators.

Central command

Zuntz and Geppert[17] were possibly the earliest proponents of feedforward, or what has become termed central command,[18] control of exercise hyperpnoea. In this control scheme, also termed "cortical irradiation" by Krogh and Lindhard,[19] mechanisms related to the cortical somatomotor command to locomotion are proposed to influence brainstem respiratory (and cardiovascular) control regions in parallel. Proponents of central command argue that the resulting hyperpnoeic and locomotory responses are sufficiently proportional that only a modest degree of feedback control or "fine tuning" (mediated humorally or by peripheral neurogenic mechanisms) is needed to ensure that the ventilatory response is appropriate for the metabolic demands of the exercise.[20 21]

There are several regions in the brainstem and higher regions of the central nervous system that have been shown to project into both the medullary cardiorespiratory integrating regions and the locomotor "pattern generator" in the spinal cord[20–22]: (*a*) cerebral cortical motor regions; (*b*) the subthalamic locomotor region (also termed the hypothalamic locomotor region) which extends into the "defence area" and includes dorsal and posterior areas of the hypothalamus and the fields of Forel; (*c*) locomotor regions in the mesencephalon; (*d*) the amygdala.

Several techniques have been used in anaesthetised or decerebrate animal preparations to selectively explore the contribution of putative central command sites to the control of the exercise hyperpnoea (see Eldridge and Waldrop[20] and Waldrop *et al*[21] for discussion). These include selective electrical stimulation, localised pharmacological stimulation by microinjection of γ-aminobutyric acid (GABA) antagonists and subsequent reversal by GABA agonists, focal lesioning, and antidromic activation techniques. In humans (and also awake animals), techniques that have attempted to dissociate the magnitude of central command from its subsequent motor outcome have been undertaken, as have indirect techniques for assessing regional central neuronal activation such as positron emission tomography (PET); this technique utilises isotopic tracer distribution to monitor the associated changes in regional cerebral blood flow that accompany local changes in neuronal O_2 consumption.

For example, the combination of PET with nuclear magnetic spectroscopy undertaken by Fink *et al*[23] during volitional rhythmic knee extension exercise has provided evidence of increased activity within the superomedial primary motor cortical areas corresponding to the motor cortical projection for the legs and also within superolateral primary cortical areas shown previously to be associated with volitional activation of the respiratory muscles. During the subsequent resting recovery phase, activity in the the cortical "locomotor" areas ceased, but that in the "respiratory" areas remained elevated. However, although this impressive study supports a role for cortical neurogenesis in the exercise hyperpnoea, its proportional contribution is less clear.

Hypnotic suggestion of exercise in resting individuals has also been shown to increase ventilation.[24 25] Recent studies by Wuyam *et al*[26] showed that mental imagery of previously performed dynamic exercise can also induce hyperventilation, which was apparent in some "athletic" subjects but not so in "non-athletic" subjects.

These observations are taken by some investigators as support for a motor-cortical feedforward component of the exercise hyperpnoea in humans. The results of studies on awake animals does not support the motor cortex as being the sole site of this mediation. For example, unanaesthetised decorticate cats show spontaneous locomotion in association with prompt respiratory and cardiovascular responses.[20 21]

Proponents of hypothalamic mediation of central command derive their experimental support from animal studies that show locomotor activity and simultaneous hyperpnoea (and cardiovascular activation) in response to focal electrical and pharmacological stimulation.[20 21] These evoked responses have been shown to be abolished by hypothalamic lesioning. Furthermore, as they are unaffected by muscle paralysis, they appear to be independent of increased metabolic rate and muscle contraction.

Other evidence from awake animals and humans does not support this view of hypothalamic mediation. For example, awake animals with hypothalamic lesions have been reported to have an essentially normal hyperpnoeic response to exercise.[27 28] Furthermore, PET disclosed no evidence of increased neuronal activity in the hypothalamic locomotor area during exercise in humans, despite evidence of increased cortical respiratory motor activity (see above).[23] In addition, it should be pointed out that the hyperpnoea induced by hypothalamic stimulation is typically accompanied by rapid and usually marked hypocapnia[20] rather than the isocapnia that is characteristic of the normal response to moderate exercise in humans and some animal species such as the awake calf[29] and, under certain conditions, the awake goat[30]; other species—for example, pony and cat—do show hypocapnia, however.[31] Although the extent of hypothalamic involvement in the normal ventilatory responses to

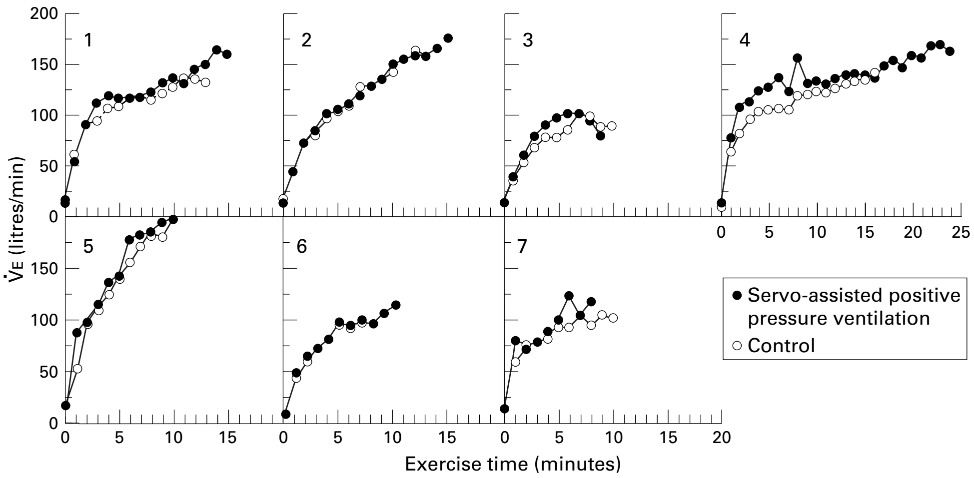

Figure 4 Ventilatory ($\dot V_E$) response to heavy intensity constant load cycling exercise in seven healthy subjects (a) during servo-assisted positive pressure ventilation to provide a proportional (about one third) "assist" to ventilation, and (b) under normal control conditions—that is, no "assist". See the text for details. Modified with permission from Krishnan et al.[41]

exercise in humans therefore remains conjectural, its generation of slow and exponential ventilatory dynamics is consonant with the phase 2 hyperpnoea.

Regardless of the site of the putative central command mechanism, several lines of evidence have been cited in support of its involvement in the exercise hyperpnoea in humans. For example, the "tonic vibration reflex" can be activated through selective stimulation of muscle spindles by the application of high frequency vibration to a contracting muscle; the resulting reflex facilitation of motor neurons to the exercised muscle "takes over" a component of force generation from central command sources. This has been reported to be accompanied by a smaller hyperpnoeic response in humans performing isometric contractions of the biceps muscles.[18] Conversely, when vibration was applied to the antagonist triceps muscle, producing the requirement for a greater involvement of central command to overcome the resulting reflex inhibition, the ventilatory increase was accentuated. Furthermore, subjects with complete pharmacologically induced motor paralysis (and who were therefore artificially ventilated) reported a sense of increased ventilation when attempting to perform contractions of the forearm.[32] These observations are consistent with a component of the exercise hyperpnoea being mediated through central command, under these conditions, at least.

A second line of evidence that supports an involvement of central command in mediating exercise hyperpnoea is the accentuation of the hyperpnoeic response to isometric exercise that has been shown in the presence of partial neuromuscular blockade of the involved muscles.[33 34] In addition, subjects with unilateral leg weakness have been reported to have a larger ventilatory response to a given task when performed with the weak leg, compared with the control leg, despite $\dot V O_2$ being similar.[35]

These observations have, however, to be considered in the light of studies in which the magnitude of the ventilatory drive during exercise has been dissociated from that of the presumed central command. These argue against a dominant obligatory influence of central command in the control of the exercise hyperpnoea in humans.

(1) The magnitude and dynamics of the hyperpnoeic response to direct electrically induced exercise of the quadriceps muscles (which therefore obviates the need to induce a central command) have been shown to be essentially normal with respect to those of pulmonary CO_2 output in individuals with clinically complete spinal cord transection.[2 36–39] It should be noted, however, that this exercise modality limits the range of achievable metabolic response.

(2) Evidence has been derived from studies with servo-assisted positive pressure ventilation, whereby the applied positive pressure is synchronised with the continuing respiratory cycle, as a means of subserving a proportion of the normal respiratory flow. In exercising humans, this results in a proportional compensatory reduction in the intrinsic ventilatory drive, despite central command presumably remaining unaltered, such that overall ventilation is essentially unchanged[40 41] (fig 4). The central command hypothesis would presumably require that the centrally mediated ventilatory drive remain unchanged, regardless of the ventilatory assistance: the overall ventilation would therefore be expected to increase and sustained hypocapnia to ensue. This was not the case.

(3) For cycle ergometer exercise, the magnitude of the phase 1 hyperpnoeic response is relatively constant, regardless of the imposed work rate and therefore the magnitude of the required central command and also the number of motor units recruited.[2]

(4) For the same work rate (and therefore the same central command), the phase 1 hyperpnoea for cycle ergometry (fig 1) is both smaller and slower in onset when the exercise is initiated from a background of unloaded cycling.[2] This is also the case when the exercise is initiated from rest, but in the supine posture.[2]

(5) The amplitude of the sinusoidal ventilatory response to the sinusoidal forcing of work rate over a range of increasing input frequen-

cies has been shown to decrease in proportion to the decrease in the amplitude of the corresponding $\dot{V}CO_2$ fluctuation. Importantly, the relation could be extrapolated to (or close to) the origin at high frequencies.[42] Such behaviour is not consistent with that expected of a rapid central command mechanism (or, for that matter, a rapid peripheral neurogenic mechanism), a component of the response dynamics of which should be sufficiently fast to drive ventilation with negligible response attenuation in this frequency range.

Short term potentiation

A central neurogenic mechanism has been proposed, however, with relatively slow response dynamics. This phenomenon, previously termed "reverberation"[43] is widely referred to as "short term potentiation" (STP).[21] It is manifested as a slowly decaying exponential ventilatory response after the abrupt cessation of sustained afferent stimulation from sources such as limb muscle afferents, vagal afferents, the carotid bodies, and the ventral medullary surface in the cat[20 21 44] and also after the abrupt cessation of volitional hyperpnoea in humans,[45] even when hypocapnia was prevented by controlled administration of CO_2.[46] The similarity between this STP response and that at the off-transient of volitional exercise—that is, they both have slow time courses—has led some investigators to propose that STP plays an important role in phase 2 $\dot{V}E$ control.[21]

However, there are two features of the exercise hyperpnoea in humans that this hypothesis fails to take account of.

(1) The phase 2 $\dot{V}E$ responses at the onset and cessation of moderate exercise in humans are clearly monoexponential and symmetrical, even in the face of altered peripheral chemoreflex sensitivity that can change the $\dot{V}E$ time constant as much as fourfold.[2] However, available evidence on the time course of STP in paralysed animal preparations, utilising "alternate breath" stimulation[20 21] suggests that it is symmetrical, the symmetry of this component being masked by a direct component at the on-transient that renders the overall response asymmetrical. This dynamic asymmetry is clearly at odds with the symmetry of the exercise hyperpnoea in humans.

(2) Apart from their symmetry, the dynamics of the phase 2 component of the exercise hyperpnoea bear a close relation to those of pulmonary CO_2 clearance (fig 1).[2] The STP scheme of control, as currently formulated, appears not to incorporate this feature.

Long term potentiation

Further complexities have been introduced by the recent proposal that the neural mechanisms controlling the exercise hyperpnoea show plasticity[30]—that is, repeated exposure to exercise has been argued to introduce a component of long term modulation or potentiation (LTP) of the exercise hyperpnoea, possibly through monoaminergic modulatory pathways.[47] This assertion is derived, for example, from evidence of consistent hyperventilation in goats performing a standard treadmill task after a two day training period in which the animals completed the same task repeatedly while breathing through an imposed external dead space (to provide an additional ventilatory stimulus from, for example, the resulting hypercapnia). The hyperpnoea in post-training trials without the added dead space was found to be augmented for a period of some six hours, an effect that was ascribed to the hyperpnoeic "history".[30] More recently, similar observations have been made in humans performing cycle ergometer exercise.[47 48]

Also, the marked depression of the ventilatory response to exercise (and consequent hypercapnia) in the goat that followed thoracic dorsal rhizotomy (presumably the result of interference with sensory traffic to the brainstem) was subsequently diminished after a series of repeated exercise trials. Interestingly, however, evidence of LTP of the exercise hyperpnoea was not observed when a hypoxic conditioning stimulus was employed.

Muscle reflexes

The anatomical loci for peripheral neurogenic control of the exercise hyperpnoea have been proposed to reside in the wide range of free nerve endings and receptors that have been identified in skeletal muscle. A substantial body of evidence can be assembled in support of peripheral neurogenesis.[20 31] For example, in animals, the cardiorespiratory stimulation that accompanies muscle contraction induced by stimulation of the muscles themselves or of the appropriate ventral spinal roots or motor nerves is abolished after dorsal spinal root section. This is consistent with peripheral mediation.[20 31 49] On the basis of the results of differential stimulation and blockade, an involvement of small diameter group III and IV muscle afferents has been proposed. Both metaboreception (by local "distortion" and increased intramuscular pressure) and chemoreception (possibly by changes in the local concentrations of mediators such as lactic acid, potassium, bradykinin, and prostaglandins) are candidates.[31 49]

Interestingly, however, in humans at the end of cycle ergometer exercise, inflation of pneumatic cuffs around the thighs to pressures greater than systolic results in a more rapid decline in $\dot{V}E$ than normal.[50] This observation is not consistent with the sustained activation of chemosensitive muscle afferents during the recovery period consequent to "trapping" of exercise induced metabolites in the muscle tissue; this might be expected to delay rather than hasten the recovery of $\dot{V}E$.

There are several other lines of evidence that do not cohere with a simple reflex neurogenic drive to ventilation during exercise in humans.[2 21] For example, in subjects with low spinal cord transection, the hyperpnoeic response to electrically induced dynamic leg exercise has been reported to be normal with respect to pulmonary CO_2 exchange.[2 36–39] This is also the case for normal individuals with muscle sensory blockade induced by epidural anaesthesia.[51]

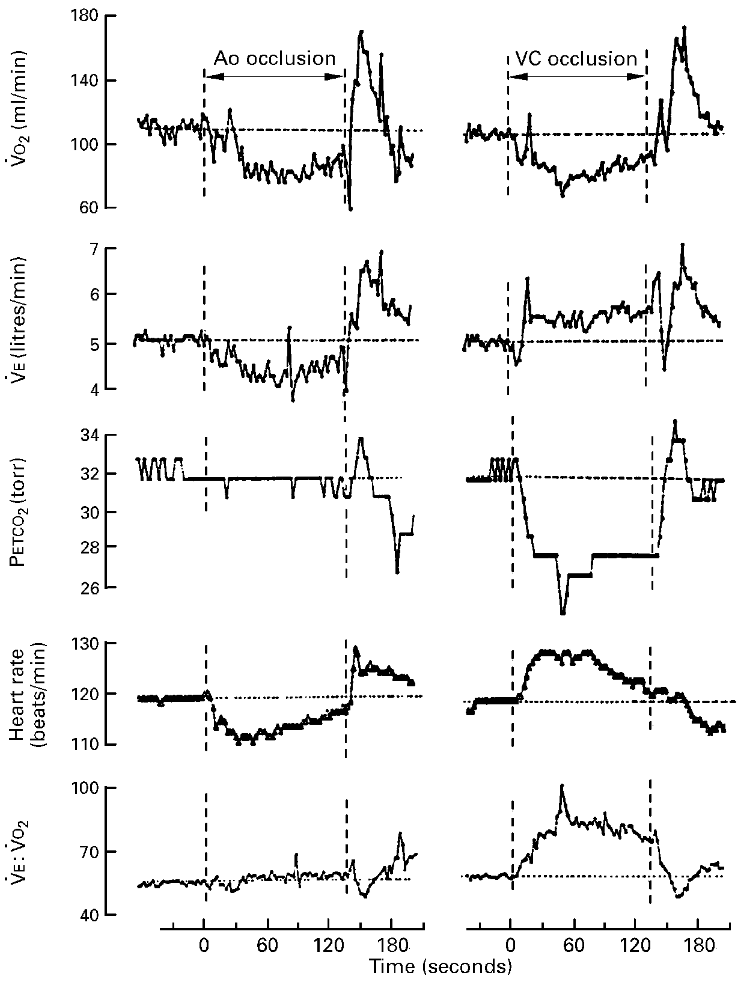

Figure 5 Ventilatory and gas exchange responses in a sheep to aortic (Ao) occlusion and release (left panel) and vena caval (VC) occlusion and release (right panel). See the text for details. Modified with permission from Haouzi et al.[61]

In addition, as stated above, $\dot{V}$E during exercise is not significantly affected when a respiratory "assist" is imposed (using a servo-controlled ventilator).[40,41] That is, the intrinsic ventilatory drive was proportionally reduced, despite there presumably being no change in mechanical feedback from the exercising muscles (or in central command).

Taken together, these various observations indicate that, although it is known that there are intramuscular mechanisms with the potential to influence $\dot{V}$E, it is less certain whether these represent a necessary component of ventilatory control during exercise in humans.

Cardiocirculatory mechanisms

Influences originating in the heart and central circulation have been shown to affect ventilation. For example, local mechanical distension of the heart and adjacent vasculature can lead to reflex hyperpnoea.[52-55] This discovery led to speculation that a "cardiodynamic" component of ventilatory control during exercise in humans may be derived from the increased venous return. Part of the evidence cited in support of this proposal[56] was the proportional increase in $\dot{V}$E and cardiac output that occurred in phase 1 of moderate exercise resulting in relative stability of end tidal $P\text{CO}_2$ and $P\text{O}_2$ and R.[2]

More recent observations do not cohere with this proposal, however. An essentially normal hyperpnoeic response to exercise has been reported in patients who have undergone heart transplantation.[57,58] This was also the case for calves with an implanted pneumatically driven artificial heart.[29] In addition, $\dot{V}$E was shown not to respond rapidly to an abrupt increase in resting heart rate (and therefore cardiac output) induced in patients with permanent demand-type pacemakers.[59]

Evidence is emerging, interestingly, of a peripheral circulatory focus for ventilatory control during exercise. It has been suggested that influences related to changes in vascular conductance and/or tissue pressure within the exercising muscles may drive $\dot{V}$E reflexly during exercise.[50,60] The results of vascular occlusion experiments by Haouzi *et al*[61] are consistent with such a mechanism. They showed in sheep (fig 5) that, for the same reduction in $\dot{V}\text{O}_2$ (resulting from reduced limb blood flow), vena caval occlusion resulted in stimulation of $\dot{V}$E, whereas aortic occlusion actually resulted in a reduction in $\dot{V}$E. Indeed, there is evidence that group III and IV muscle afferents can be stimulated not only by agents such as papaverine and isoprenaline, but also by vascular distension.[62,63] Williamson *et al*[64] have also shown that the application of lower body positive pressure, at a level previously shown to reduce limb blood flow, resulted in hyperventilation during constant load exercise of heavy, but not moderate, intensity in humans (fig 6).

CENTRAL CHEMOSENSORY MEDIATION

The contribution of the central chemoreceptors to the control of the exercise hyperpnoea in humans is difficult to assess because of their inaccessibility. Indirect approaches have therefore been used that rely on the use of hyperoxic inspirates to "silence" the peripheral chemoreceptors, dynamic discrimination techniques, or the use of particular patient populations.[65]

Regardless of the approach, there is no consistent body of evidence that central chemosensitivity is increased significantly with exercise or that central chemoreflex integrity is required for a normal hyperpnoeic response to moderate exercise. For example, there is no discernible humoral stimulus, as cerebrospinal fluid (CSF) pH remains relatively stable during the steady state of moderate exercise.[66] Neither is there evidence of a change in CSF [K$^+$], despite arterial [K$^+$] increasing.[67] Furthermore, subjects with congenital central hypoventilation syndromes, who have little or no ventilatory response in inhaled CO_2, show a ventilatory response to exercise that is essentially normal, both with respect to its magnitude and its kinetics. Consequently, $P\text{CO}_2$ is regulated close to resting levels.[68,69]

At higher work rates associated with metabolic acidosis—that is, above the lactate threshold—however, there does seem to be a role for central chemoreflex modulation of ventilation, but one of potential constraint: respiratory alkalosis results in the CSF because of the ventilatory compensation induced in response to the lactic acidosis.[66] The high CSF pH may be expected to (*a*) reduce central chemoreceptor discharge and (*b*) stimulate efferent projections to the carotid bodies that have been shown to be inhibitory to carotid afferent chemosensory activity.

A second source of influence could be slow leakage of H^+ from the acidaemic blood across the blood-brain barrier into the CSF.[70] This would serve to provide a slowly developing additional source of respiratory compensation for the acidaemia (see following section). For example, during prolonged high intensity constant load exercise, a slow recovery of pHa was evident after the initial transient decrease, despite peripheral chemosensitivity being suppressed by hyperoxia.[71] However, an alternative explanation could be that the transiently elevated PaCO_2 that was evident in these tests also provided an H^+-related drive to the central chemoreceptors independently of any direct H^+ flux.

PERIPHERAL CHEMOSENSORY MEDIATION

In humans, carotid chemosensory influences seem to have little or no effect on the early phase 1 component of the exercise hyperpnoea. Not only are alterations in the inspired O_2 fraction typically without effect,[72 73] but individuals whose carotid bodies have been surgically resected (CBR) show relatively normal $\dot{V}$E responses at exercise onset.[74]

In contrast, the subsequent phase 2 component of the exercise hyperpnoea does appear to be modulated by the carotid bodies in humans.[2] Factors, such as acute hypoxia or the chronic metabolic acidaemia resulting from ammonium chloride ingestion, that increase carotid chemosensitivity also accelerate the kinetics of the phase 2 hyperpnoea. This was the case both in absolute terms and relative to CO_2 output. Consequently, the degree of transient hypoxaemia and CO_2 retention in phase 2 is minimised, as a result of the lower ratio of $\tau\dot{V}$E to $\tau\dot{V}O_2$ and of $\tau\dot{V}$E to $\tau\dot{V}CO_2$; conversely, the transient hypercapnic condition is exacerbated when the carotid bodies are suppressed.[2] Furthermore, these ventilatory kinetics are slowed down by interventions that reduce or even suppress carotid body responsiveness. These include hyperoxia, $NaHCO_3$ ingestion, intravenous infusion of dopamine and CBR. As a result, the current evidence from analysis of the transients supports the contention that, in humans, the carotid bodies are important in establishing the precision with which PaO_2, PaCO_2, and pHa are regulated in this non-steady-state phase of dynamic exercise.

The role of carotid chemosensory drive in the steady state of moderate exercise in humans is generally acknowledged to be that of "fine tuning".[21 75 76] On the basis of the Dejours O_2 test (in which high inspired O_2 fractions are abruptly applied surreptitiously to suppress abruptly any carotid chemosensory contribu-

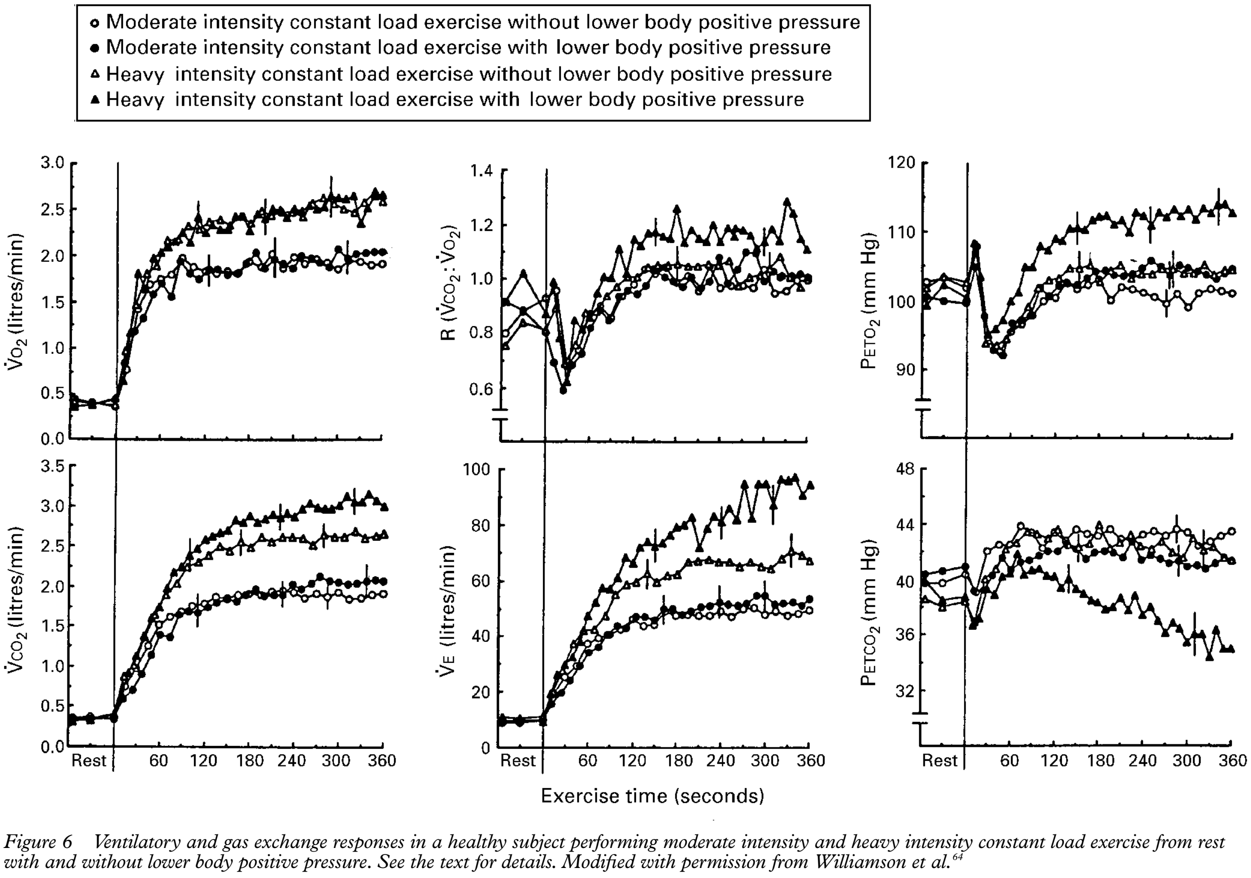

Figure 6 Ventilatory and gas exchange responses in a healthy subject performing moderate intensity and heavy intensity constant load exercise from rest with and without lower body positive pressure. See the text for details. Modified with permission from Williamson et al.[64]

tion to ventilatory drive),[73] this contribution appears to amount to ~20% of the phase 3 $\dot{V}$E response at best[76]; however, there is some concern that the Dejours test may underestimate the carotid body component of the exercise hyperpnoea.[76 77]

The identities of the stimuli underlying this carotid body component remain conjectural, however.[2] Known carotid body stimuli, such as increases in arterial [H$^+$] and [K$^+$], the rate of change in the respiratory related Pco$_2$-H$^+$ oscillation, adenosine, osmolarity, catecholamines, and temperature, all increase during exercise.

In particular, the carotid bodies in animals have been shown to be capable of transducing the oscillating CO$_2$-H$^+$ signal into respiratory stimulation.[78] Whether aspects of this signal, such as its amplitude, rate of change, or the perfusion related temporal density of the oscillation, actually influence $\dot{V}$E to any appreciable extent in phase 3 remains a source of debate. Similarly, the arterial hyperkalaemia of dynamic exercise resulting from increased K$^+$ flux from exercising muscles has been shown to stimulate $\dot{V}$E through the carotid bodies.[79–81] This source of ventilatory drive, and others that arise from the carotid bodies, can presumably contribute only to the ~20% of the exercise hyperpnoea that has been ascribed to carotid body mediation.

Those who question whether, in humans, the carotid bodies play any role in ventilatory control during moderate exercise (no-one seriously contends that they account for the entire hyperpnoea[31]) need to look at the issue that, after abrupt administration of 100% O$_2$ during moderate exercise: (*a*) $\dot{V}$E decreases with a delay equivalent to the lung-carotid body vascular transit delay[73]; (*b*) the magnitude of the transient ventilatory decrease is directly proportional to the prevailing degree of carotid chemosensitivity—indeed, under hypoxic conditions, this can account for 50% or more of the continuing hyperpnoea[74]; (*c*) this ventilatory response is entirely absent in subjects who do not have carotid bodies.[74]

The respiratory compensation for the metabolic acidosis of heavy exercise has been proposed to be mediated largely by the carotid bodies.[74] During heavy constant load exercise, pHa fell more for a given degree of metabolic acidosis in CBR subjects than in normal controls. This was a result of the absence of compensatory hyperventilation in the CBR subjects. It has been suggested, in contrast, that this marked attenuation of compensatory hyperventilation for the metabolic acidosis in these individuals may be a consequence of their asthmatic history rather than the absence of carotid bodies.[31] However, previous studies did not show any evidence of altered ventilatory responses to exercise in asthmatic control subjects, compared with normal controls.[82]

This issue of respiratory compensation was examined further by inducing a more prolonged metabolic acidosis in normal subjects during constant load exercise (change in standard [HCO$_3^-$] of 5 mEq/l) with altered inspired O$_2$ fractions.[71] As shown in fig 7, there was a significant O$_2$ labile component of the exercise hyperpnoea that was presumably attributable to carotid chemosensory mediation, although such marked changes in Pao$_2$ naturally would also have other influences on the exercise response. The effect, however, was that in hypoxia the magnitude of the transient decrease in pHa was constrained, whereas in hyperoxia it was amplified. It appears that the carotid bodies can be considered to play a significant, and even, dominant role in constraining variations of pHa in response to the acute metabolic acidaemia of exercise in humans. However, even when carotid body chemosensitivity was suppressed by inhalation of 80% O$_2$, a slow compensatory hyperpnoea was still discernible. This slower compensatory component may be of central chemosensory origin.[71] (see under "Central chemosensory mediation"). However, as it has been shown that $\dot{V}$E still has an upward concavity at high work rates during hyperoxic incremental exercise,[83] it is conceivable that hyperoxia does not abolish peripheral chemosensitivity. It is also interesting that infusions of dopamine at concentrations sufficient to virtually abolish hypoxic ventilatory responsiveness, and previously shown to slow the phase 2 ventilatory kinetics during moderate constant load exercise,[76] had

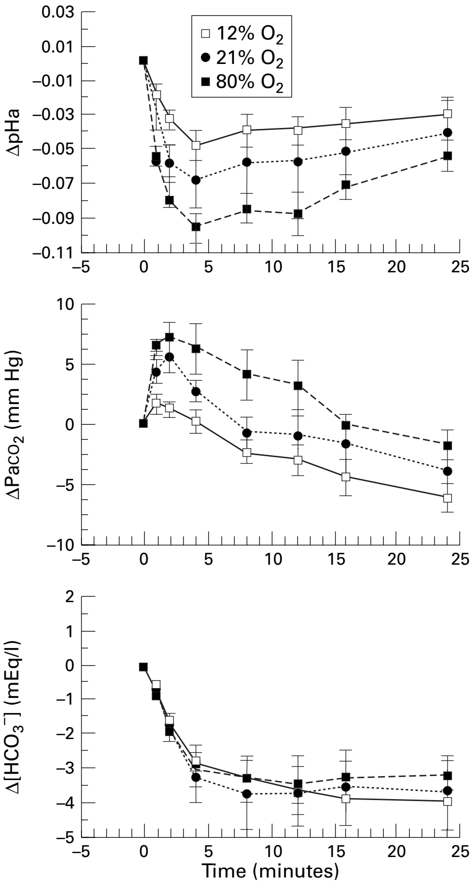

Figure 7 Arterial blood gas and acid-base responses to heavy intensity constant load cycling for three inspired O$_2$ concentrations (12, 21, and 80%), expressed as changes (Δ) from 0 W (unloaded) pedalling. See the text for details. Modified with permission from Rausch et al.[71]

no discernible effect on the ventilatory response to incremental exercise at high work rates.[84]

Further complicating our understanding of the role of the carotid bodies in mediating the compensatory hyperventilation of heavy exercise is the phenomenon of "isocapnic buffering".[2,6] That is, during rapidly increasing exercise, there is no compensatory hyperventilation for a range of work rates above the lactate threshold, the range being larger the more rapid the ramp rate. This suggests a compensatory mechanism with a significant response threshold and/or one with slow response kinetics, a scenario that seems to be incompatible with the response characteristics of the carotid bodies to other stimuli, such as hypoxia. The reasons for this difference between the results of constant load and rapid incremental exercise are at present obscure; further experiments are needed for their resolution.

It has been suggested that athletes may have low carotid chemosensitivity to hypoxia (as do their non-athletic relatives).[75] As both hypoxia and H^+ are sensed by the carotid bodies, it is tempting to speculate that they are also insensitive to the exercise induced metabolic acidaemia. Whether such a reduced peripheral chemosensitivity also ameliorates the sensation of shortness of breath in the athlete remains to be determined.

Conclusion

The fact that ventilation during muscular exercise varies so markedly as a function of (*a*) changes in the substrate mixture undergoing oxidation, (*b*) shifts of metabolic CO_2 into and out of the muscle CO_2 stores, and (*c*) reductions in blood lactate levels as a result of endurance training, coupled with the fact that it does not when an external pump contributes to the continuing inspiration, suggests that a component (at least) of the exercise hyperpnoea is geared to provide arterial blood gas and acid-base homoeostasis. Although numerous mechanisms have been proposed for the mediation, their proportional contributions and interactions are at present uncertain. The challenge remains one of integration.

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