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Exercise physiology: exercise hyperpnea

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The classical view of proportional chemoreceptor feed-back (central; carotid-body) and neural feed-forward (central command; muscle reflex) in controlling ventilation to regulate arterial PCO_2 during exercise still has currency. However, control-system redundancy has led to several innovative schemes being proposed (e.g. optimization; plasticity; precedence; autocracy) which, while creative, require identification of physiological substrates. Impediments to convincing resolution include technical and interpretational limitations to isolating putative control mechanisms in intact exercising humans and the provision of animal equivalents to allow more invasive interventions. The insights provided by this review contribute to the knowledge base of human investigation, and introduce some novel and potentially exciting chemogenetic approaches in small animals. These should not lose sight, however, of the logical imperative to discriminate between robust control schemes that (a) integrate processes within plausible physiological equivalents, and (b) account for both the dynamic and steady-state system response over the entire range of exercise intensities.

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Introduction

The 'state-of-the-art' regarding ventilatory ($\dot{V}E$) control during exercise in healthy normoxic, normothermic humans[1] at sea-level has been extensively reviewed in the last decade [1–5], together with its recent-historical evolution [6]. This article reviews significant advances in the field, typically since 2016 although earlier sources are cited when necessary context is warranted.

Evaluation of putative control processes has to take account of temporal-based and intensity-based system behavior. Thus, the primary operation in moderate-intensity exercise, that is for work rates (WRs) not eliciting a sustained metabolic acidosis (<lactate threshold (θ_L)) [7], is regulation of arterial PCO_2 ($PaCO_2$) through a matching of ($\dot{V}E$) to pulmonary CO_2 output ($\dot{V}CO_2$) (Figure 1, top panel). However, this shifts to arterial pH (pHa) regulation for supra-θ_L WRs characterized by a metabolic acidosis which may stabilize (heavy intensity; <critical power (CP)) or develop progressively to the limit of tolerance at the maximum O_2 uptake ($\dot{V}O_2$) (very-heavy intensity) [7].

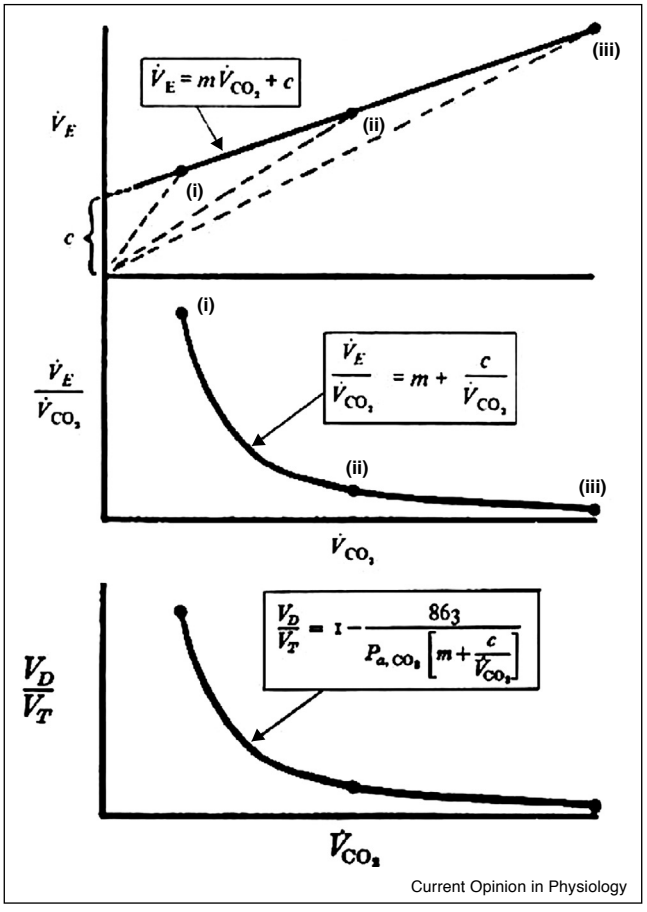
For constant-WR exercise <θ_L, $\dot{V}E$ control reflects an initial immediate and abrupt increase ($\phi 1$ component), followed by a more dominant exponential $\phi 2$ component leading to the steady-state ($\phi 3$ component) [5,7]. The underlying mechanistic bases remain debatable [1–5]. $\phi 1$ control is viewed to reflect neurogenesis (peripheral-muscle and/or central neural) [8,9] or cardio-circulatory mediation [10]. The close dynamic coupling of $\dot{V}E$ to $\dot{V}CO_2$ in $\phi 2$ ($\dot{V}E$ tracking slightly behind $\dot{V}CO_2$) may reflect CO_2-linked control whose origin remains tantalizingly elusive, not the least because of the absence of a significant sustained $PaCO_2$ error signal [2,4] that could stimulate the carotid body chemoreflex (CBCR) and central chemoreflex. $\phi 3$ control has been ascribed to addition of $\phi 1$ and $\phi 2$ control outcomes. Whether or not the $\phi 3$ response is influenced by factors such as 'plasticity' (a long-term adaptive control strategy whereby the augmenting effects of an imposed $\dot{V}E$ stimulus persist for a prolonged period following its removal) or 'optimization' (the minimization of a $\dot{V}E$ controller 'cost' function comprising both humoral and mechanical elements) [3,11] remains unresolved.

Additional drives related to metabolic acidemia are superimposed >θ_L. That is, $\dot{V}E$ is caused to increase out of its sub-θ_L proportion to $\dot{V}CO_2$, the consequent hypocapnia serving to constrain the falling pHa (respiratory compensation). However, the kinetics of the respiratory compensation are slow, which may reflect the existence of an amplitude-related or time-related threshold for CB $[H^+]$ detection, perhaps involving slow intracellular expression of the metabolic acidemia and/or slow signal transduction by H^+-sensitive voltage-sensitive tandem-P-domain K^+ channels) [reviewed in Ref. [5]]. Thus, in contrast to slow-incremental exercise for example, the onset of respiratory

[1] Reference will be made to other conditions and species, as appropriate.

Glossary
$[HCO_3^-]a$: Arterial bicarbonate concentration
$PaCO_2$: Arterial CO_2 partial pressure
pHa: Arterial pH
BCBR: Bilateral carotid-body resection
CHF: Chronic heart failure
CBCR: Carotid body chemoreflex
CNS: Central nervous system
$\dot{V}CO_2$: CO_2 output
PCO_2: CO_2 partial pressure
α: CO_2 solubility coefficient
CP: Critical power
DREADD: Designer receptors exclusively activated by designer drugs
$P_{ET}CO_2$: End-tidal CO_2 partial pressure
$\dot{V}E$: Expired ventilation
GD: Glycogen depletion
θ_L: Lactate threshold
Mmax: Maximal M-wave
MVCR: Mixed-venous chemoreflex
pK': Negative logarithm of ionization constant
PO_2: O_2 partial pressure
$\dot{V}O_2$: O_2 uptake
ϕ1: Phase 1
ϕ2: Phase 2
ϕ3: Phase 3
V_D/V_T: Physiological dead space fraction of the breath
RCP: Respiratory compensation point
RTN: Retrotrapezoid nucleus
$\Delta\dot{V}E/\Delta\dot{V}CO_2$: Slope of relationship between ventilation and CO_2 output
$\dot{V}E/\dot{V}CO_2$: Ventilatory equivalent for CO_2
WR: Work rate

Figure 1



Schematic depiction of the responses of ventilation ($\dot{V}E$), ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) and physiological dead space fraction of the breath (V_D/V_T) as a function of CO_2 output ($\dot{V}CO_2$)during progressive moderate exercise (i.e. assuming $PaCO_2$ stability). *m*, $\dot{V}E - \dot{V}CO_2$slope ; *c*, $\dot{V}E$-intercept.
Top and middle panels: Modified, with permission, from WhippBJ and Ward SA. **Cardiopulmonary coupling during exercise**. *J Exp Biol* 1982, **100**:175-193 (Figure 2).
Bottom panel: Modified, with permission, from Ward SA. **Ventilatory control in humans: constraints and limitations**. *Exp Physiol* 2007, **92**:357-366 (Figure 2).

compensation (respiratory compensation point, RCP) for rapid-incremental exercise does not occur at the θ_L but some way beyond [reviewed in Refs. [5,12,13]]. As a result, $\dot{V}E$ continues to increase with its sub-θ_L proportion to $\dot{V}CO_2$ between θ_L and RCP, such that $PaCO_2$ stability is maintained despite the metabolic acidosis (isocapnic buffering phase).

It should be emphasized that the RCP is a ventilatory-control not a metabolic construct, and therefore is not a proxy for CP. Thus, unlike θ_L and peak $\dot{V}O_2$, RCP occurs at a higher $\dot{V}O_2$ [7,12,13] and WR [14] (despite concerns regarding the influence of $\dot{V}O_2$ kinetics [15]) with more-rapid WR incrementation rates. In addition, RCP occurs sooner with enhanced hypoxia-induced CBCR drive [12,13]. Any similarity between RCP and CP is therefore likely to be fortuitous rather than causal.

$PaCO_2$ and pHa regulation requires proportional matching of normally hyperbolic $\dot{V}E/\dot{V}CO_2$ and V_D/V_T responses (Figure 1, middle and bottom panels) [5,16,17]:

$$PaCO_2 = 863/\left[\left(\dot{V}E/\dot{V}CO_2\right)\cdot\left(1 - V_D/V_T\right)\right] \quad (1)$$

$$pHa = pK' + \left[\log\left(\left[HCO_3^-\right]a/25.9\right)\right] \cdot \left[\dot{V}E/\dot{V}CO_2\right]\cdot\left[1 - V_D/V_T\right] \quad (2)$$

where 863 is a constant correcting for the different conditions of reporting gas volumes (standard temperature and pressure, dry; body temperature and pressure, saturated) and transformation of fractional concentration to partial pressure; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2; V_D/V_T, physiological dead-space fraction of breath; pK', negative logarithm of carbonic acid ionization constant; $[HCO_3^-]a$, arterial [bicarbonate]; α, CO_2 solubility coefficient). If V_D/V_T were not to decline hyperbolically,

then nonlinearities would obtain in the $\dot{V}E$–$\dot{V}CO_2$ relationship or $PaCO_2$ would not be regulated, or both [16]. Exactly how such apparent matching might occur has yet to be resolved, but "the system seems to 'know' that when V_D/V_T is reduced (making $\dot{V}E$ more efficient with respect to alveolar ventilation) $\dot{V}E$ 'needs' to increase less per unit $\dot{V}CO_2$ to effect its regulatory function, with the necessary logical assumption, of course, that there is such regulation. But unless one is badly confusing subsequence and consequence, it is hard to believe, in the light of the evidence cited above, that there is not." [2].

The theoretical minimum or asymptotic value of $\dot{V}E/\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$ min; typically occurring close to or soon after θ_L, but before RCP) and the slope of the sub-RCP $\dot{V}E$–$\dot{V}CO_2$ relationship ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) (Figure 1, middle and top panels) are widely used as 'ventilatory efficiency' indices, especially prognostically [e.g. 17,18]. Equality between these two indices is based on $\dot{V}E/\dot{V}CO_2$ min approximating $\Delta\dot{V}E/\Delta\dot{V}CO_2$ at very high $\dot{V}CO_2$s (Figure 1, top and middle panels), but this may not be so for poorly fit individuals in whom θ_L and RCP can occur on the still-falling $\dot{V}E/\dot{V}CO_2$ trajectory [13,19]. Under such circumstances, an increase in $\dot{V}E/\dot{V}CO_2$ is not necessarily a prerequisite for RCP identification; that is respiratory compensation could be achieved with $\dot{V}E/\dot{V}CO_2$ still declining, but a lesser rate than isocapnia would require [5,12]. A brief comment on the normally small and positive $\dot{V}E$-intercept of the $\dot{V}E$–$\dot{V}CO_2$ relationship is warranted (Figure 1, top panel). The $\dot{V}E$-intercept can usefully be viewed as a 'positional' construct that anchors the $\dot{V}E$–$\dot{V}CO_2$ relationship on the resting $\dot{V}E, \dot{V}CO_2$ locus, and whose value – obtaining at a $\dot{V}CO_2$ of zero – expresses the notion of a dead space ventilation at that hypothetical $\dot{V}CO_2$ value [16]. Whether it reflects the direct outcome of an underlying control mechanism or whether it is simply the 'algebraic' consequence of how $PaCO_2$ and V_D/V_T interact to determine $\dot{V}E$ remains to be established. Some have suggested that the $\dot{V}E$-intercept may have clinical significance, as it has been reported to increase progressively with disease severity in chronic obstructive pulmonary disease while $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was less variant [17]. Finally, an often-overlooked but essential caveat is that an increased $\dot{V}E/\dot{V}CO_2$ min or $\Delta\dot{V}E/\Delta\dot{V}CO_2$ necessarily reflects only pulmonary gas-exchange dysfunction, which is arguably not the case if a greater-than-normal $\dot{V}E/\dot{V}CO_2$ min were to be required to maintain $PaCO_2$ lower-than-normal because of competing drives related to, for example, acute or chronic arterial hypoxemia or metabolic acidosis [13,17].

Central chemoreceptors

Animal studies suggest that the, retrotrapezoid nucleus (RTN) a ventrolateral medullary site of central chemosensitivity and integration, may influence $\phi 3$ $\dot{V}E$ control [20•]. Thus, acutely and reversibly silencing neurons in the rostral ventrolateral medullary parafacial region of rat which includes the RTN and also the cardiovascular-related C1 area (via adeno-associated viral vector transduction of muscarinic-receptor M_4-based G_i-coupled DREADD[2] expression *in vivo*) during electrically induced hind-limb exercise (sciatic or femoral nerve stimulation) in anesthetized rats had no effect on heart rate or blood pressure responses or the initial $\dot{V}E$ response relative to control, but was associated with a reduced $\phi 3$ $\dot{V}E$. Intriguingly, in awake rats running on a treadmill, the reversible neuronal block was also associated with a reduced exercise capacity. Although not commented on, closer inspection of the $\dot{V}E$ response profile shows that as baseline $\dot{V}E$ was also reduced, the $\Delta\dot{V}E$ appeared less affected (Ref 20•, Figure 4B); reminiscent of individuals with impaired central chemosensitivity consequent to a 'congenital central hypoventilation syndrome' [21]. Although a not-insignificant technical challenge, were temporal discrimination to be improved with (a) multiple exercise-test repetitions that is now standard for human investigations and (b) breath-by-breath or multiple-breath measurement not only of $\dot{V}E$ but also gas exchange [7,22], it would be of interest to see whether judgements could be drawn regarding the influence of the RTN on dynamic $\dot{V}E$–$\dot{V}CO_2$ coupling and $PaCO_2$ regulation (see Eq. (1)) [2,5,12].

Carotid chemoreceptors

The potential for gaining insight into CBCR modulation of the exercise hyperpnea [4,5,23] has been boosted by the recent re-visiting of bilateral carotid-body resection (BCBR) [24], for example, in chronic heart failure (CHF) and its associated sympathetic nervous system hyperactivity in which the CBs have been proposed to be involved [25,26]. Thus, an exaggerated hypoxic $\dot{V}E$ responsiveness (transient nitrogen inhalation) has been demonstrated to be an independent predictor of poor long-term prognosis in CHF [27]. Furthermore, $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was decreased post-BCBR (2 mo), with $PaCO_2$ being increased; exercise tolerance time was also increased, consequent possibly to CBCR-mediated attenuation of sympathetic muscle vasoconstrictor constraint and/or exertional dyspnea [28]. How these findings impact on normal $\dot{V}E$ control in exercise is less clear, given the obvious ethical constraints.

Nonetheless, several issues remain unresolved, such as (a) why the sensitivity of the $\phi 2$ $\dot{V}E$ response (amplitude and kinetics) to imposed hypoxia and hyperoxia is more prominent than for $\phi 3$, (b) why the O_2-induced slowing of $\phi 2$ $\dot{V}E$ kinetics may not be entirely explicable by CBCR silencing, and (c) what is the origin of the slow metabolic-acidemic compensatory $\dot{V}E$ response $>\theta_L$ that persists with sustained hyperoxia [29]? One observation that might relate to issue (a) is the proposed potentiation of exercising-muscle mechanoreflex drive with CBCR

[2] Designer receptors exclusively activated by designer drugs.

$\dot{V}E$ responsiveness, demonstrated in well-familiarized individuals using passive (confirmed electromyographically) knee-extension (isokinetic dynamometry; 30 s; 4 repetitions) to provide muscle reflex activation (presumed not to affect metaboreceptors) and isocapnic hypoxia (12% O_2) to provide CBCR stimulation [30]. When imposed concomitantly, $\dot{V}E$ was increased to a greater degree than the sum of the $\dot{V}E$ increases resulting from each condition imposed separately. It was tentatively speculated that this potentiating effect was more likely to be mediated downstream of the CBCRs within the central nervous system.

Mixed-venous chemoreceptors

The historical evidence base relating to putative mixed-venous chemoreflex (MVCR) involvement in $\dot{V}E$ control during exercise was meticulously reviewed recently with regard to the longstanding debate about whether such receptors exist in humans and, if so, how might they contribute to the control process [31]. What could constitute an 'ideal' stimulus to MVCRs in terms of its temporal profile and site of imposition was speculated on. Is it sufficient to assume that putative MVCRs, sensitive to PO_2 and PCO_2, are best located within or close to the right heart and/or pulmonary artery? Or might they be distributed more diffusely at multiple locations along the venous axis between the exercising muscles and the right heart, such that 'the CNS would derive metabolic rate by adding or multiplying these many chemoreceptor signals with appropriate weighting.' [31].

The logical dilemma of how a MVCR could transduce mixed-venous PCO_2 and PO_2 into a metabolic-rate construct requires greater scrutiny, as $\dot{V}E$ during moderate exercise does not respond to metabolic rate but rather closely 'follows' $\dot{V}CO_2$ in a range of experimental conditions that includes exercise non-steady states [e.g. 2,5,12]. On kinetic grounds, therefore, $\dot{V}E$ cannot track exercising-muscle O_2 consumption, exercising-muscle CO_2 production or pulmonary O_2 uptake—all of which have faster kinetics than $\dot{V}CO_2$. Also, knowledge of the blood flow in which mixed-venous PCO_2 and PO_2 are expressed would be required, as recognized in the 'CO_2 Flux' hypothesis [32], with the necessary consequence that 'any such control link will depend not on the rate at which CO_2 is brought to the lung per unit time but that *minus* the rate at which CO_2 leaves the lung in the pulmonary arterial blood.' [2]. Nonetheless, an imperative for further investigation is highlighted, especially with regard to the temporal profile of $\dot{V}E$ response to post-exercise cuff-occlusion release that would benefit from revisiting post-BCBR [31].

Central neurogenesis

The potential for motor corticospinal excitability of exercising muscle to influence $\dot{V}E$ during high-intensity ($>\theta_L$) constant-WR cycling has been demonstrated, utilizing a submaximal-exercise, glycogen-depletion (GD) paradigm (45 min at θ_L) [33•]. Despite no difference in $\dot{V}O_2$ relative to control, GD was associated with a lower arterialized [glucose] at rest (measurement of muscle glycogen not being feasible) and a less marked pH decrease and [lactate] increase during supra-θ_L exercise with an increased sense of leg effort (as had been shown previously). $\Delta\dot{V}E$–$\Delta\dot{V}CO_2$ was increased with a decreased $PaCO_2$ (estimated from end-tidal PCO_2 ($P_{ET}CO_2$)). Vastus lateralis corticospinal excitability during exercise (assessed as mean motor evoked potential amplitude, normalized to the maximal M-wave (Mmax) obtained by femoral nerve magnetic stimulation, induced by motor-cortex transcranial magnetic stimulation) was less in GD than control. It was argued that the hyperventilatory response following GD could not be attributed to an enhanced CBCR but was more likely to reflect an increased central nervous system (CNS) feedforward drive related to the increased sense of leg effort required because of the decreased corticospinal excitability of exercising muscle. Exactly how corticospinal excitability was affected in the GD condition was speculated on, with possibilities including low muscle [glycogen] reflexly imposing a degree of supra-spinal CNS inhibition [34,35] and/or brain glycogen depletion [36]; a lack of change in Mmax was taken to rule out altered sarcolemmal excitability.

Exercising-muscle neurogenesis

The influence of limb-movement frequency on $\dot{V}E$ control was recently explored, by comparing responses to sinusoidally imposed pedaling-speed profiles to those for sinusoidally imposed pedal-load profiles (with matched sinusoidal and mean $\dot{V}O_2$ amplitudes); the sinusoidal profile being chosen to minimize the possibility of respiratory-locomotor entrainment [37•]. The sinusoidal pedaling-speed paradigm evoked larger and more rapid sinusoidal $\dot{V}E$ responses than the sinusoidal pedaling-load paradigm. The departure of these results from an earlier study in which $\dot{V}E$ was dynamically coupled with $\dot{V}CO_2$ [38] was ascribed to control of $\dot{V}O_2$ between tests. Thus, it was concluded that limb cadence may be a significant factor in $\dot{V}E$ control during exercise, possibly involving muscle reflex drives from type III and IV afferents. An unexplained observation was attenuation of the sinusoidal pedaling-speed $\dot{V}E$ response in endurance-trained athletes.

As type III and IV afferents are known to be stimulated by venular distension in animals which may in turn stimulate $\dot{V}E$ during exercise [10], the influence of graded subsystolic venous occlusion of the bilateral proximal quadriceps muscles (randomized cuff inflation/deflation, 2 min on/2 min off; 20, 40, 60, 80, 100 mmHg) in order to induce limb congestion during moderate-intensity cycling (30% peak WR) has been investigated in humans [39]. This resulted in a proportional hyperventilation (i.e. increased

$\dot{V}E/\dot{V}CO_2$ and decreased $P_{ET}CO_2$) achieved largely through breathing frequency, with increased 'ventilatory drive' (i.e. tidal volume/inspiratory duration), perceived exertion (RPE) and dyspnea. It was argued, therefore, that venous distention during moderate exercise activates skeletal muscle afferents with consequent $\dot{V}E$ stimulation which likely led to the increased dyspnea, and exacerbation of effort perception. However, it was also noted that muscle ischemia consequent to the higher cuff pressures potentially could have activated metaboreceptors and/or nociceptors.

A more direct approach to the role of type III and IV muscle afferents in $\dot{V}E$ control has been provided by lumbar intrathecal injection of the selective μ-opioid agonist fentanyl (50 μg) to effect partial blockade of synaptic transmission between lower-limb muscle afferents and dorsal-horn cell μ-opioid-sensitive receptors without affecting muscle force-generating capacity [40,41]. Secondary effects of fentanyl on $\dot{V}E$ were argued to be unlikely, given (a) the absence of fentanyl in the systemic venous circulation and (b) the lack of effect on resting hypercapnic ventilatory response and the cardioventilatory responses to upper-body (arm) exercise that appears to rule out fentanyl having migrated within cerebrospinal fluid up to the medulla [40]. ϕ3 $\dot{V}E$ for graded cycling (3 min at each of 50, 100 and 150 W) was reduced relative to control, despite $\dot{V}O_2$ being unaffected, leading to the conclusion that type III–IV muscle afferents are an obligatory control element of ϕ3 $\dot{V}E$ control in moderate exercise. These observations appeared to contrast with those from a similar study, in which subjects cycled at a single WR (65% peak WR; 5 min) and for which end-exercise $\dot{V}E$ was not decreased [42]. It was subsequently asserted [43] that these differences could be reconciled with the recognition that 3 min is unlikely to be sufficient for acquisition of a steady-state $\dot{V}E$ (5–6 min being more appropriate [2,5,12]); indeed, hypoventilation was evident in both studies at ~3 min. These studies were taken to suggest that type III–IV muscle afferents exerted their influence on ϕ2 $\dot{V}E$ control, rather than ϕ3 [43]. Exactly how this conclusion accommodates the close dynamic coupling of $\dot{V}E$ to $\dot{V}CO_2$ in ϕ2 remains to be established.

Summary

It is telling that, in 2019, sentiments expressed a decade or so earlier regarding the dilemma of $\dot{V}E$ control in exercise still resonate. That is, how can $PaCO_2$ be so robustly defended during moderate exercise transients and steady states in the absence of sustained humoral error signals in arterial blood and cerebral fluids, and in the face of selective inactivation of putative control pathways? Despite comprehensive human and animal investigations, a satisfying resolution of how the exercise hyperpnea is controlled remains elusive. Simply identifying a cluster of mechanisms capable of stimulating $\dot{V}E$ under some particular experimental conditions should not, *a priori*, constitute sufficiency. The demonstrable $\dot{V}E$ control-system redundancy is particularly challenging [3,5,44•] and has contributed, in part, to the formulation of creative control schemes, such as optimization [e.g. 43], plasticity [e.g. 3] and, more recently, precedence and autocracy [45,46]; however, these carry the weight of establishing convincing physiological equivalence. Further, the logical imperatives that accrue from the integrated ventilatory, muscle-metabolic and pulmonary gas exchange response dynamics during exercise demand recognition: " . . . although many mechanisms have been demonstrated which can increase ventilation during exercise, the essential challenge which remains is why, for moderate exercise, does ventilation only increase to levels commensurate with the level of pulmonary CO_2 exchange?" [23].

"This is clearly an issue for a multitalented team of visionaries, preferably those who are willing to start with the belief that CO_2 exchange is truly the underpinning to ventilatory control and that 'somewhere out there' exist the appropriate receptor sites, specific stimuli, and the neural pathways" [47]. Such visionaries are as likely to emerge from novel small-animal exercise investigations that are amenable to genetic, molecular and cellular interventions (e.g. chemogenetics, optogenetics) targeted to discrete neural foci as they are from more traditional human integrative physiology, which nonetheless can be informed by translational 'accidents of nature' such as spinal-cord injury as well as the renewed interest in CBCR. In conclusion, therefore, how $PaCO_2$ regulation is effected during moderate exercise " . . . remains the unanswered question. Not providing *the* answer to the *entire* exercise hyperpnea but perhaps the crucial core or fundamental feature upon which factors such as volition, emotion, short-term, and/or long-term potentiation, mechanical constraint and limitation, among others, provide modulating influences." [2].

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Conflict of interest statement

Nothing declared.

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Despite some design shortcomings related to response discrimination, this innovative study in anesthetized rats demonstrated that the rostral ventrolateral medullary parafacial region which includes the chemoreceptive retrotrapezoid nucleus (RTN) can influence the ϕ3 but not the initial$\dot{V}E$ response to electrically induced hind-limb exercise, and can impair exercise capacity. RTN neurons were acutely and reversibly silenced using adeno-associated viral vector transduction of muscarinic-receptor M4-based Gi-coupled DREADD expression.

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