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Invited Commentary

Evolving paradigms in H^+ control of breathing: From homeostatic regulation to homeostatic competition

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In his classic treatise "The Wisdom of the Body" Walter B. Cannon (Cannon, 1929, 1932) marveled at the exquisite stability of some vital physiologic variables—body temperature, blood chemistry, water content, etc.—which are normally maintained within narrow limits in the face of wide environmental and physiological disturbances. He termed this apparent near-static equilibrium state of the body's *milieu intérieur* (Bernard, 1878–1879) 'homeostasis', a notion that has prevailed as a basic tenet of physiology and medicine for the past eight decades. An everyday example of homeostasis is found in human subjects going from rest to muscular work. In this instance the sudden metabolic and thermal challenges are met by proportionate, concerted increases in respiration, circulation and eccrine activity, keeping in check any resultant changes in arterial blood gas and pH levels and in systemic blood pressure and core temperature. In a recent issue of RPNB Wasserman et al. (2011) provide a detailed account of the absolute bounds of the homeostasis of H^+ concentration in arterial plasma ($[H^+]a$) during aerobic and anaerobic exercise. Specifically, these authors show that in normal subjects performing incremental exercise below the lactic acidosis threshold (*LAT*), $[H^+]a$ is maintained closely at its resting value of ~40 nmol/L, increasing only slightly even when the equivalent amount of H^+ being produced, transported and eliminated (in the form of CO_2) per minute stands in the order of tens of mmol, or ~1,000,000 times the amount of H^+ in 1 L of blood plasma. At work rates above *LAT*, $[H^+]a$ rises more rapidly relative to the increases in total ventilation ($\dot{V}E$) due to lactic acidosis but the changes are still relatively small. Whereas arterial pH in humans is well-known to decrease only slightly from rest to exercise (Barr et al., 1964; Stringer et al., 1992), it is the ultimate conversion from pH to $[H^+]a$ units in a sizable group of subjects ($n = 16$) that reveals the steep, monotonic and piecewise-linear underlying relationship between $\dot{V}E$ and $[H^+]a$ over a wide range of work rates, delineating for the first time the fine margins of $[H^+]a$ homeostasis below and above *LAT*.

1. The dilemma of $[H^+]a$ homeostasis during exercise

In contrast to $[H^+]a$, the exercise $\dot{V}E$–Pa_{CO_2} relationship is typically non-monotonic, with Pa_{CO_2} (arterial PCO_2) increasing and decreasing slightly at work rates below and above the *LAT*, respectively (Stringer et al., 1992; Wasserman et al., 2011). The authors argue that it is $[H^+]a$, rather than Pa_{CO_2} *per se*, that is being regulated over the full range of exercise, presumably via peripheral and central chemoreceptors that are thought to be sensitive to H^+ [reviewed in Jiang et al. (2005), Lahiri and Forster (2003); but see Harada et al. (1985a,b), Huckstepp et al. (2010)]. This renewed emphasis on the importance of $[H^+]a$ homeostasis over Pa_{CO_2} homeostasis in ventilatory control during exercise brings a new perspective to the preeminent role of arterial acid–base balance that is increasingly recognized in recent models of the chemical control of breathing at rest (Duffin, 2005). It also brings a new twist to an age-old dilemma: whereas $\dot{V}E$ is stimulated by increases in Pa_{CO_2} during CO_2 breathing, it rises in proportion to metabolic CO_2 output without similar increases in Pa_{CO_2} during exercise. This dilemma, which applies equally to $[H^+]a$ (actual stimulus) as with Pa_{CO_2} (commonly measured or estimated stimulus) especially below the *LAT* (Fig. 1), raises two fundamental questions regarding respiratory control that lie at the heart of respiratory physiology and neurobiology: (Q1) Why are $[H^+]a/Pa_{CO_2}$ regulated so tightly during exercise but not during CO_2 breathing? (Q2) What then is the mechanism of exercise hyperpnea, if it is just to maintain $[H^+]a/Pa_{CO_2}$ homeostasis?

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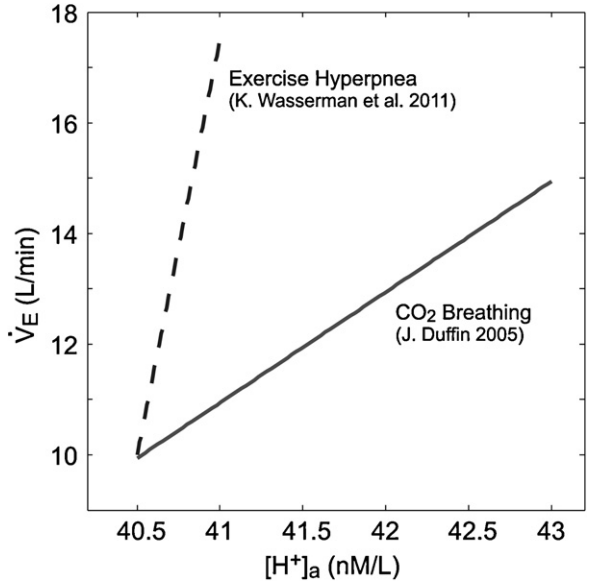

Fig. 1. The exercise hyperpnea dilemma for $[H^+]a$ regulation. See: Swanson (1978). Data for aerobic exercise are from Wasserman et al. (2011). Data for CO_2 breathing are from Duffin (2005).

2. Reflexogenic stimuli interaction hypothesis of exercise hyperpnea

An instinctive reaction to these critical questions is to surmise that a distinct feedback or feedforward stimulus may be activated by exercise to augment $\dot{V}E$ independently of the $[H^+]a/Pa_{CO_2}$ stimulus. This would have been a silver bullet except that such an 'exercise stimulus' has so far remained elusive. These open questions, while seemingly cut-and-dried at first blush, have continued to bedevil respiratory physiologists and exercise physiologists for the past one-and-a-half centuries. Comroe (1974) once reflected on this dilemma:

> *The respiratory response to muscular exercise is the easiest to study experimentally; particularly every respiratory physiologist of the last 100 years has done so and has contributed either new methods, data, equations, theories or models. It is startling, therefore, to learn that we still do not know the cause or causes of the increased ventilation associated with muscular exercise. . .This means either that this seemingly simple, uncomplicated problem is an exceedingly difficult one or that respiratory physiologists have not been very perceptive or both. One of the difficulties is that most physiologists have been – and still are – searching for a simple measurable stimulus and mechanism that will explain all the data. Another is that good respiratory physiologists are not necessarily good neurobiologists or good control-system engineers, and maybe they must be to solve the problem.*

According to Comroe, some of the well-searched/well-researched and open-ended exercise stimulus candidates of all times included: CO_2, low O_2, H^+, humoral chemicals, increased temperature, impulses from motor cortex, mechano/ergoreceptors or pain receptors in the muscles or joints, conditioned reflexes, etc. Many of these and other reputed stimuli continue to be fervently pursued and debated to this day [see for example Waldrop et al., 2006]. The inability to find a single feedback or feedforward mechanism that can unequivocally explain exercise hyperpnea led Comroe to conjecture that "*multiple factors is involved and that it is the interplay, potentiation or algebraic sum of these that determine the final exercise ventilatory response.*" In a similar vein, Dempsey (2006) recently remarked that "*a key to truly understanding the control of exercise hyperpnea will be to quantify the interactive effects of these combined stimuli.*"

Can multiple feedback/feedforward stimuli conspire to maintain $[H^+]a/Pa_{CO_2}$ homeostasis during exercise instead? Unfortunately, having multiple putative exercise stimuli superimposed to the $[H^+]a/Pa_{CO_2}$ stimulus in an algebraic sum does not really solve the problem as this faces a similar dilemma as with a single exercise stimulus, just more of the same. The fact that many factors may influence exercise $\dot{V}E$ does not necessarily mean that any of them—singly, redundantly or compositely—are obligatory to the attendant $[H^+]a/Pa_{CO_2}$ homeostasis.

Alternatively, exercise may interact with the $[H^+]a/Pa_{CO_2}$ stimulus to augment $\dot{V}E$ in a multiplicative instead of additive fashion. Indeed, it has been shown that holding Pa_{CO_2} constant at an elevated level during CO_2 breathing potentiates the exercise $\dot{V}E$ response with a multiplicative effect in addition to an additive effect (Poon and Greene, 1985; Poon, 1989c). However, because such a potentiation of exercise $\dot{V}E$ occurs only under hypercapnia, it cannot explain the hyperpnea at normal $[H^+]a/Pa_{CO_2}$ levels during eucapnic exercise either.

Another type of interactive effect for respiratory stimuli involves a learned component presumably as a conditioned reflex from prior experiences. Somjen (1992) conjectured that a major part of error-free physiological regulation might be learned through trial-and-error at an early age and re-learned throughout life whenever errors occur due to stress or overload, acclimatization, aging and disease, etc. It has been shown that repeated pairing of airway CO_2 load and exercise augments subsequent exercise $\dot{V}E$ (Wood et al., 2003), such that the potentiation effect of hypercapnia on exercise $\dot{V}E$ (Poon and Greene, 1985; Poon, 1989c) is "remembered" after repeated pairings. However, as with other putative exercise stimuli it remains unclear if such an experience-dependent learning component is obligatory to the $[H^+]a/Pa_{CO_2}$ homeostasis during exercise.

3. Optimization hypothesis of exercise hyperpnea

Implicit in the reflexogenic stimuli interaction hypothesis of exercise hyperpnea is the assumption that the respiratory controller may employ distinct control strategies depending on the occasion: homeostatic regulation of $[H^+]a/Pa_{CO_2}$ during exercise and chemoreflex with increased $[H^+]a/Pa_{CO_2}$ during CO_2 breathing. To a physiologist, the adoption of differing control schemes under different physiological challenges (exercise vs. CO_2 breathing) seems perfectly logical, even teleologically plausible. After all, $[H^+]a/Pa_{CO_2}$ homeostasis and chemoreflex are both time-honored and generally accepted first principles of respiratory physiology, aren't they? True, but to a neurologist, the unwavering adherence to two incongruous control tactics for the same cause (elimination of CO_2, whether metabolically produced or inhaled) spells schizophrenia! If the job of the respiratory controller is indeed to regulate $[H^+]a/Pa_{CO_2}$ during exercise around some presumed "set point", as the data of Wasserman et al. (2011) now reaffirm, why then is such homeostasis not upheld during CO_2 breathing (question Q1)?

To this intriguing question, Comroe (1974) has offered a simple yet insightful answer: "*The lung is designed to eliminate CO_2 in a CO_2-free medium, air. When CO_2 is added to the inspired air, it clogs the mechanism for CO_2 elimination, and arterial CO_2 must rise.*" Indeed, once the inhaled CO_2 level exceeds ~5%, it is practically impossible to maintain the resting $[H^+]a/Pa_{CO_2}$ levels no matter how hard one tries to breathe. It would be pointless to try and restore an $[H^+]a/Pa_{CO_2}$ homeostatic state that is now out of reach. Rather than keep fighting an uphill and losing battle against a steep metabolic hyperbola, the controller is "smart" enough to loosen up in this case