COMMENTARIES ON "PRECEDENCE AND AUTOCRACY IN BREATHING CONTROL"

TO THE EDITOR: I read the Viewpoint article by Haouzi (1) entitled “Precedence and autocracy in breathing control” with great interest. The author makes a strong and informative case for the complexity of the mechanisms involved in the control of breathing. But he makes conventional error of assuming that “it evolved by chance and necessity . . . shaping the structures and functions of the respiratory control system through the slow process of natural selection.” First, Natural Selection is a metaphor, not a mechanism. On the other hand, we have successfully deconvoluted the evolution of the mammalian lung from the fish swim bladder by tracing cellular-molecular changes determined by cell-cell interactions across developmental and phylogenetic space and time (4). We now know that the swim bladder of physostomous fish such as the Zebra fish is the functional and molecular homolog of the lung (5). Focusing on the vertebrate water-land transition (WLT) that forced the evolution of amphibians, reptiles, mammals, and birds from fish (3), documented gene duplications occurred within specific physiologic contexts during this transition (3). It is known that the deflation of the swim bladder is controlled by sympathetic adrenergic neurons (2) and that the β-adrenergic receptor is one of the genes that duplicated during the WLT; this cascade offers the opportunity to systematically deconvolute the origins and evolution of breathing control phylogenetically and ontogenetically through comparative developmental and phylogenetic functional genomics. By using this rational approach, the evolutionary complexity of control of breathing and that of all complex physiology is now comprehensible.

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BREATHING CONTROL IN HIGH ALTITUDE: MODIFICATION OF CHEMOREFLEX RESPONSES

TO THE EDITOR: Haouzi (3) presents an interesting perspective on the natural design of the respiratory control system (RCS) including two essential elements in breathing behaviors, precedence and autocracy. Although the mechanisms of breathing remain elucidated (3), breathing control can be attributed to chemoreflex and nonchemoreflex drives (4, 5).

Because of the lack of evidence, it is not convincing that RCS can choose a strategy to follow necessary steps to prevent the increase of P CO2 level in the absence of other breathing stimuli. Haouzi stated that RCS maintains the activities for minutes after insults such as cardiac arrest, before apnea or gasps; however, the transition mechanisms from eupneic to gasps also have not been clearly understood. We agree that the regulation of ventilation does not merely depend on the interaction of specific chemoreceptors. Miyamoto et al. (4) observed no changes in minute ventilation despite altered central blood volume (CBV) and end-tidal P CO2. Their finding suggested that CBV shifts can modify respiratory operating point (ROP), as ROP is more noticeable in high altitude along with acclimatization (1, 2, 4, 5).

Therefore, in our view, a more comprehensive understanding is paramount in explaining the complexity of RCS. As the example implies, chemoreflex feedback is crucial for respiratory regulation in altitude. Nevertheless, a further investigation based on these aspects above will add values to the study.

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TO THE EDITOR: This is an interesting attempt to “rock the boat” a little, as most of us tend to project the observed respiratory responses through prevailing standard rules of respiration physiology—rules amassed, in large part, by means of experimental studies in anesthetized animals. Naturally, anesthesia limits the scope of potential concomitant effects that may influence breathing. When we speak, sing, or eat, the act of breathing, its rhythmicity and depth, are temporarily subordinate to the mechanisms controlling these functions despite disturbance of the respiratory gas exchange. By the same token, severe, life-threatening impediments of circulation demonstrated in all three panels of Fig. 1 (see Ref. 1) can be

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regarded as the “survival” mode type of breathing. It is plausible to assume that the process of evolution imprinted in the living creatures, especially the highly complex ones, the automatic pattern of action aiming at sustaining the cardiorespiratory functions, thus life. Figure 1A prompts the question: would the respiration persist equally long into the period of cardiac arrest (CA) in sheep if the CA was preceded by the eupneic breathing at rest, instead of the exercise-induced hyperpnea? In other words: does the respiration in this experiment demonstrate the flywheel-like behavior? Similarly, would the periodic pattern of breathing of patients (Fig. 1, B and C) remain unaltered if the ventricular fibrillation were initiated during periods of apnea instead of the evolving volleys of augmentation. The tendency to associate control of respiration with the classical CO\textsubscript{2} response curve awaits revision of its logic and relevance.

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ARE RESPIRATORY FREQUENCY AND TIDAL VOLUME REGULATED BY DIFFERENT INPUTS DURING EXERCISE?

To the Editor: We recently found a strong link between respiratory frequency and rating of perceived exertion (RPE) during high-intensity exercise (4). This link is of great importance from a breathing regulation perspective, because RPE is an indirect measure of central command (2). When isolating the effect of central command on cardiorespiratory responses by imagining exercise under hypnosis, Thornton et al. (5) found that respiratory frequency, but not tidal volume, responds to central command. Furthermore, Bell and Duffin (1) reported an immediate response of respiratory frequency, but not of tidal volume, in the transition from rest to exercise (and vice versa) and in the transition from passive to active exercise. Together, these findings suggest the intriguing hypothesis that central command regulates respiratory frequency, but not tidal volume.

Haouzi (3) proposes that during exercise the most relevant signals to keep blood gas homeostasis take precedence over fast sources of breathing signals (like the corollary discharge of central command) in the regulation of breathing. However, gas homeostasis is not maintained during high-intensity exercise, where central command is very high. Furthermore, evidence that ventilation follows the slow change in metabolism and not central command is mainly based on the assumption that sinusoidal changes in workload accurately reflect changes in central command (3). However, central command increases not only with workload but also with time-on-task, an often forgotten variable (2). Investigating whether central command and metabolic stimuli differently regulate respiratory frequency and tidal volume may help shed some light into the complex regulation of breathing during exercise.

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To the Editor: Whereas “precedence” or “redundancy” has historically been posited as an element in the ventilatory (Ve) control system (VCS) operative during exercise, the capacity for “autocracy” in the VCS appears novel in concept and intriguing in application (1). The author’s ventricular-fibrillation (VF) model is one of the more innovative employed to investigate ventilatory control, the detailing of temporal response profiles providing invaluable insight into events immediately after the onset of cardiac arrest (1). The demonstration that, for a short period (~10–15 s), Ve appears impervious to the sequence of experimentally induced VF at rest in anesthetized sheep and consciously sedated humans and at exercise offset in anesthetized sheep—with consequently profound hypocapnia—(reviewed in Ref. 1), contrasts starkly with the prompt and essentially isocapnic hypopnea that results from partial cardiopulmonary bypass in resting and exercising anesthetized dogs (3). It is “as if” the VCS effects an over-riding behavioral state-change when such circumstances become extreme, triggered possibly by the attainment of a sufficiently-low PCO2 threshold (although not so low as to precipitate anoxic apnea), in an attempt to protect cerebral oxygen delivery (2). As the maintained stability of Ve appears crucial to the author’s hypothesis, it would be of interest to them to ascertain the effects of (considerably more-demanding) multiple VF repetitions to improve response signal-to-noise characteristics (Fig. 1B in Ref. 2) and rule out a fortuitous offsetting of the excitatory consequence of arterial hypertension on Ve (reviewed in Ref. 1) with inhibitory actions of hypoperfusion and its consequences for vascular venous return of CO2 (4).

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