COMMENTARIES ON VIEWPOINT: 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). For instance, Himalayan highlanders demonstrate reduced central chemoreflex sensitivity to CO2 compared with lowlanders; however, the nonchemoreflex drives remain similar in both groups (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
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$_2$ response curve awaits revision of its logic and relevance.

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Andrew Huszczuk

PRECEDECE AND AUTOCRACY EVINCE OPTIMIZATION AND DECISION-MAKING IN BREATHING CONTROL

TO THE EDITOR: Haouzi is to be commended for acknowledging that breathing control may involve higher order strategies such as precedence and autocracy (1). Yet as such, he has unwittingly subscribed to the optimization model of respiratory control (2), which he and many followers of the Sherringtonian school have strived to eschew. As with the latter case, a fundamental flaw in Haouzi’s reasoning is the assumption that breathing control necessarily amounts to a combination of simple reflexes such that any physiological perturbations—such as during a cardiac arrest—must affect respiration “within one breath” and “with no delay.” Recognizing the irreconcilable fallacy of this model, Haouzi then rightly concludes that breathing control may be influenced by other strategies instead but fails to explain how so. Specifically, any precedence and autocracy-based “selection” between competing “redundant” and “contradictory” inputs is not arbitrary but is likely optimized toward some overriding objectives [e.g., fitness of survival (2)], a process which has been dubbed “homeostatic competition” (4). In a catastrophic event such as cardiac arrest, continuing to breathe gives the best—albeit slim hope of prolonging survival never mind the indulgence of homeostasis. Indeed, selecting between competing options is tantamount to decision making, a form of plasticity-based cognition/perception that has been suggested to underlie the optimization of breathing (3, 5). Haouzi’s interesting cardiac arrest data therefore add to the 10 open questions posed in (3, 5) delineating respiratory control under varying physiologic/pathophysiologic disturbances in health, heart failure, and COPD, for which the model in (2) may offer a unifying framework.

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HAOUZI’S RAZOR

What a gem this brainy stem
In truth turns out to be.
Huff and puff and all that stuff
And now autocracy.
Surely not, you’ll scare the lot.
Nervous science will be seething.
Integration; but consolidation?
Yes—the patient is still breathing.
Haouzi’s razor is sharp—no doubt.
I’m still trying to work it out!

A poem by Ken D. O’Halloran

COMMENT ON “PRECEDECE AND AUTOCRACY IN BREATHING CONTROL”

TO THE EDITOR: In his recent Viewpoint, Haouzi (4) referred to the complexity in understanding how respiration is maintained during the acute phase of cardiac arrest (CA) and how irregular breathing patterns like Cheyne-Stokes (CS) breathing remained unaltered in a patient with chronic heart failure (CHF) during a brief episode of CA. Haouzi mentioned that both peripheral and central control of breathing are completely vanished during CA due to the absence/reduction of blood flow and the lack of central pH oscillations. However, the carotid bodies (CB) contribute to the regulation of ventilation by monitoring changes of several stimuli in the arterial bloodstream (3), including fluctuations in blood flow (2, 3). Indeed, blood flow restriction to the CB results in an enhanced CB-mediated chemoreflex drive (2). Therefore, during CA the CB afferent discharge should increase, leading to an enhanced reflex respiratory drive. In CHF, the generation of irregular breathing patterns is strongly associated with the potentiation of the CB chemoreceptors (1). Importantly, the mechanism underlying the augmented CB discharge in CHF depends on the reduction of blood flow (5). Thus the maintenance of CS breathing during momentary CA in CHF could be related to increases in CB activity even after the blood flow restriction. In summary, it is plausible that during CA the augmented afferent activity that rises from the CBs continues to influence the respiratory control center to affect respiration.

REFERENCES
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 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 fast sources of breathing signals like the corollary discharge of).

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