VIEWPOINT

Precedence and autocracy in breathing control

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THE MEANDERING PATHS FOLLOWED by the evolutionary pressure produced by chance and necessity (32) have shaped the structures and functions of the respiratory control system through the slow process of natural selection (7, 8, 35). The resulting complexity of the respiratory control system has made it difficult to decipher the intricate laws or properties behind the mechanisms controlling the rhythmic activity of the respiratory muscles in humans. This contention does not pertain so much to our understanding of the functions of the specific receptors (chemoreceptors, pulmonary, cardiac, muscle, laryngeal stimuli, etc.) or of the medullary or supramedullary structures involved in breathing. Rather what is still lacking is a comprehensive and meaningful frame of reference making intelligible the mechanisms producing various ventilatory outputs in keeping with the conditions imposed on an individual. For instance, to the question “what sustains breathing at a level that keeps arterial $PCO_2$ around 40 Torr at rest?” one could answer, following Dejours (10), that ~20% of the resting breathing activity depends on a tonic drive from the carotid bodies (CB) (41). However, not only do we have little clue about what controls the remaining 80%, but also the physiological meaning and relevance of this baseline CB tonic activity remain unclear. Indeed, individuals with a low, or no ventilator response to hypercapnia, can generate the same drive to breath resulting in eugonic breathing, just like in a “normal” individual (38, 39). Similarly, the behavior of $P_{aCO_2}$ during exercise, wherein metabolism can increase by more than 10 times within minutes (43) dragging along ventilation, continues to resist our sagacity, despite all the information accumulated on the putative receptors involved (16). In all of these conditions, the knowledge accumulated on the $CO_2$ or $O_2$ sensitivity of the respiratory control system, mediated by the central and peripheral chemoreception (25, 31), is of little help to account for the maintenance of eugenea. This is also true in COPD or obese patients who can display from a reduced to a virtually abolished $CO_2$ sensitivity (14, 18) but can still appropriately regulate their breathing, albeit at a higher $P_{aCO_2}$, at least when awake or exercising (4, 17).

Plasticity (15, 28, 36), optimization (37), short-term potentiation (11, 40), after discharge (12), reconfiguration (27), redundancy (33, 34), or degeneracy (21, 29) are some of the properties that have been proposed to render comprehensible the operational modalities of the respiratory control system (RCS). This paper presents the view that two fundamental properties of the RCS must be considered to account for the behavior of breathing control at rest, during exercise, as well as in some very unusual conditions, wherein circulation is altered.

The first property is the ability of the RCS to select among various inputs, some of them taking precedence over others, in elaborating the ventilatory outcome. This behavior cannot be anticipated or predicated from the behavior of individual receptors. This strategy is well illustrated by the effects of the temporal dissociation of various stimuli to breathe operating otherwise at the same time (19). For instance, the control (13) and the effects of moving limbs on muscle receptors (24) have very different kinetics from the change in gas exchange (42) (very rapid for the former, much slower for the latter). When imposing fast vs. slow up-and-down variations in work rate changes during exercise (3, 44), breathing appears to “follow” the slow change in metabolism/pulmonary gas exchange and to ignore the effects of the motor activity as well as corollary signals originating from the structures controlling muscle contractions or locomotion (19). Yet signals related to the control of muscle locomotion as well as those resulting from contractions (intensity or frequency) do stimulate ventilation (5, 9).

The respiratory control system, when engaged in exercise, appears, therefore, to select a strategy, which constrains ventilation to follow information that prevent $P_{aCO_2}$ from rising, disregarding in the process other powerful sources of breathing stimuli, even if they are much faster.

The second feature can be described as an autocratic behavior of the respiratory control system: the respiratory neurons appear to be able to maintain their ongoing level of activity (whether low, high, or periodic) regardless of the signals or conditions that have triggered or maintained this activity. This property is best exemplified by the observation that the generation of normal breath cycles is maintained during the initial period of a cardiac arrest (CA) in the sheep, despite the absence of pulmonary or systemic blood flow (20). Similarly, breathing is maintained unchanged in humans, in conscious sedation, during and after a 10- to 15-s period of experimental fibrillation-induced CA and the ensuing phase of low blood pressure leading to blow flow restoration while testing implantable defibrillators (20). In addition, during ventricular fibrillation-induced CA at the cessation of muscle contractions in sheep (23), minute ventilation persists at the same level and with the same pattern as during the period of exercise (Fig. 1), notwithstanding the cessation of the contractions. Consequently, because breathing is higher during contractions than at rest, minute ventilation was therefore maintained at much higher levels (up to 50 l/min) during the recovery from exercise.
with no circulation than at rest (23), despite similar levels of PaCO₂ or blood pressure, before CA in both conditions. It is therefore difficult to reconcile the known effects of the main feedback systems affecting breathing control at rest or in exercise with the persistence of a breathing pattern proportional to V̇CO₂ and the circulatory status before CA (23), whereas the major peripheral and central inputs thought to be responsible for this effect have vanished. Indeed, the most relevant changes produced by a CA should have affected respiration within one breath as soon as blood pressure and cardiac output drop. For instance, the abrupt disappearance of arterial (6) or central pH oscillations (30), whether CA occurs at rest or after exercise, should depress breathing, whereas any dramatic drop in blood pressure should increase, with no delay, breathing via the stimulation of the arterial baroreceptors (22) and chemoreceptors (26). It is only after minutes that an apnea occurs, followed by the production of gasps, likely related to a progressive anoxia of the brain stem. The RCS behaves as if none of the initial chemical or circulatory consequences of a cardiac arrest were able to produce any significant effect on breathing. Even more intriguing is the observation obtained during and after a short period of CA in a patient with Cheynes-Stokes (CS) breathing (1), related to chronic cardiac failure. We found that neither the rhythmicity nor the amplitude of ventilatory oscillations of CS breathing were affected by an 8- to 9-s cardiac arrest, followed by a 12- to 15-s period of low blood flow, occurring during the ascending phase of one of the 45-s period ventilatory cycles (Fig. 1). This unaltered CS breathing was observed despite profound changes in cerebral blood flow and perfusion of the carotid bodies, which should be virtually abolished during the phase of circulatory arrest (1) and should slowly recover as a sinus rhythm is restored. Breathing control continued to operate as per the pre-CA metabolic and circulatory status, regardless of the disruption of important circulatory feedback information.

These two properties imply that the respiratory control system has a finite number of scenarios that can be used in response to rapid and dramatic changes in metabolism or circulation. When many, and often redundant, signals are present (exercise), the respiratory control system seems to

Fig. 1. A: ventricular fibrillation induced cardiac arrest after exercise in 1 sheep [reprinted from (23), with permission from Elsevier]. This example shows a long periods of "eupneic" breathing after cardiac arrest (CA). Breath-by-breath respired CO₂, respiratory flow (V̇), respiratory rate (f), minute ventilation (V̇i), and carotid blood pressure (ABP) are displayed. Horizontal arrow represents the end of the period of exercise, which lasted 4 min (not shown). Vertical arrow is the moment when the heart was fibrillated. Note that breathing averaged ~30-35 l/min by the end of the period of exercise; ventilation increases modestly thereafter, before stopping 2 min or so later. Breathing pattern and minute ventilation were unchanged at the onset of the cardiac arrest, and as a consequence, alveolar CO₂ dropped dramatically. Note the swings in ABP during CA caused by persistent breathing activity. B: trace showing the effects of an episode of CA by pulseless ventricular fibrillation (between the 2 arrows) and recovery occurring during the ascending phase of a periodic breathing (PB) cycle in a patient with cardiac failure [reproduced with permission from the American College of Chest Physicians (1)]. End-tidal CO₂ fraction, respiratory flow, continuous noninvasive blood pressure (BP), and ECG are shown. Note that the discharge of the implantable defibrillators caused a transient artifact on the airflow signal. C: end-tidal CO₂ and respiratory flow signals of the PB cycle during which PVF was produced are presented in black, whereas the subsequent PB cycle has been superimposed in red line. Despite the difference in CO₂ and the circulatory delay created by the period of pulseless ventricular fibrillation and recovery (circulation was altered for more than 20 s), the production of breaths with periodic changes in tidal volume amplitude was unaffected by the cardiac arrest and recovery, except for a transient artifact during defibrillation.
follow the most relevant signals and strategies to keep blood gas homeostasis; when contradictory inputs are present (CA), ventilation remains unchanged, although it is deprived of any role in blood gas homeostasis—whether at rest, immediately after exercise, or during periodic breathing. Incidentally, this latter situation results in the production of rudimentary but significant swings in blood pressure, produced by the changes in intrathoracic pressure. In other words, during a cardiac arrest, the thoraco-abdominal pump is playing the role, although imperfectly and very inefficiently, of a circulatory pump. This leads to an intriguing function of the respiratory system, wherein circulation and ventilation are under the sole influence of the respiratory control system (23).

How pieces of information are processed by the medullary and supramedullary structures involved in respiration is largely unknown. The neurophysiological basis and the meaning of these intriguing observations may well remain difficult to uncover because of the Rube Golberg machine-like features that the RCS has developed over millions of years. In contrast to the view that there is a form of wisdom of the body (2), the observation that breathing is not initially affected by a cardiac arrest, as well as the question of the role of CO₂ sensitivity per se in eupneic breathing, illustrates how evolution can sometimes render unintelligible a physiological function, in terms of its finality, when considered at the level of an organism.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: P.H. conception and design of research; P.H. performed experiments; P.H. analyzed data; P.H. interpreted results of experiments; P.H. prepared figures; P.H. drafted manuscript; P.H. edited and revised manuscript; P.H. approved final version of manuscript.

REFERENCES


