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Commentary

Arterial blood acidity and control of breathing during exercise

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The recent paper by Wasserman et al. (2011) on "arterial H^+ regulation during exercise in humans" is to be regarded as part of the long tradition in respiratory physiology to decipher why and how ventilation rises by tens of liters per minute during exercise with no increase in $Pa_{CO_2}/[H]^+a$ (Comroe and Schmidt, 1943; Kao, 1956; Dejours, 1959; Whipp and Ward, 1980, 1991; Whipp et al., 1983; Wasserman et al., 1986; Eldridge and Waldrop, 1991; Dempsey et al., 1997).

"Invasive" human data during ramp like exercise are very precious, because they are rare. Following similar studies from the same group (Stringer et al., 1992; Sun et al., 2001), these data (Wasserman et al., 2011) confirm that there is virtually no change in $Pa_{CO_2}/[H^+]a$ below the "lactate threshold" in humans, despite the enormous amount of CO_2 produced. The fact that some of the subjects seem to start their exercise test with a moderate "alkalosis" is not essential to the point developed by the authors: several liters of CO_2 are produced every minute during moderate exercise, while the Pa_{CO_2} remains at its resting level. This observation was expressed in an even more impressive form in this paper: $[H^+]a$ remains constant in the nanomolar range (40 nmol/) in the arterial blood despite the increased production of the equivalent of millimoles of protons every minute.

The obvious question prompted by this description has been asked for decades by many physiologists including the founder of this journal, Pierre Dejours (1959): how could breathing increase so rapidly and by more than ten folds during moderate exercise without any "chemical error signal". In contrast to what Wasserman et al. (2011) are stating in their manuscript, the "neuro-humoral" theory of Dejours did not assume that the "humoral" phase has to be mediated through a change in the blood acidity (Dejours et al., 1956). This issue was actually tackled much earlier by Harrison and his group in the 30th (Calhoun et al., 1931; Harrison et al., 1932), whose outstanding work on exercise hyperpnea remains largely ignored. Harrison was not the first to formalize the apparent dilemma on the lack of blood acidity during moderate exercise-induced hyperpnea in humans, but he did not accept the dogma of his time, that the change in "automatic" breathing during exercise must be chemically mediated. His solution to this apparent contradiction was very logical and simple: as there is no acidity in the blood of a subject breathing at 50 l/min or more when exercising, $Pa_{CO_2}/[H^+]a$ cannot be the stimulus to breathe during exercise. If we assume that the "chemical" control of breathing is not essential to the control of exercise hyperpnea, the dilemma disappears. After all, the response to inhaled CO_2 is highly variable among humans and is certainly not isocapnic (Fordyce and Grodins, 1980a,b; Bennett et al., 1984), while the isocapnic ventilatory response to exercise is predictable (see below) regardless of the level of respiratory sensitivity to CO_2. Such a precision in keeping $Pa_{CO_2}/[H^+]a$ constant may well be the fundamental characteristic of the response to exercise but it is not observed during inhaled CO_2 (2–3% of inhaled CO_2 should not impede ventilation to keep Pa_{CO_2} constant). Perhaps more importantly, breathing is controlled by many non-chemical factors, which can result in P_{CO_2} homeostasis regardless of the level of CO_2/H^+ sensitivity (Haouzi and Chenuel, 2005; Haouzi, 2006).

As acknowledged by the authors, the study of Wasserman et al. (2011) does not provide any new clues on this "old" question. There is no doubt that models can be elaborated to reconcile an isocapnic response to exercise with a P_{CO_2}/pH which mean levels do not change in the arterial blood (Poon, 2011). This is how the system works! Providing the proof that the chemoreception can achieve such a regulation is a different question, we have evidence of the contrary (Whipp and Ward, 1991). Incidentally the same effects could also be achieved by such models (Poon, 2011), if sources of information unrelated to pH were used.

The anthropic nature of the assumption that the lack of change in arterial pH in exercising humans would be the reflection of some form of ultimate wisdom of "the body" can also be challenged on evolutionary grounds. First, blood acidity develops during heavy exercise, and very low pH (similar to those observed in patients dying from septic shock) along with severe hyperkalemia are present and harmless during very heavy exercise (conditions which

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would have certainly exerted evolutionary pressure). On the other hand, various animal species are found to be hypocapnic during running (Dempsey et al., 1997). One could therefore argue that keeping pH homeostasis so tightly is not that essential for "the body" since as soon as exercise level increases it would become an impediment to O_2 delivery to the exercising muscles. If we consider all the spectrum of pH changes in various human "models" – and not restricting our observation to fit individuals as an achievement of the natural selection – many normal subjects, presenting with chronic hyperventilation syndrome do hyperventilate during exercise and can still exercise. In real life conditions, outside the laboratory, where we expect our subjects to breathe very quietly and regularly to get nice data, exercise may consist in abrupt changes in work rate and is probably not isocapnic (see response to impulse exercise; Whipp and Ward, 1991). Patients with a pure metabolic acidosis do exercise pretty well. On the contrary as long ago demonstrated by Harrison et al. (1932), patients with cardiac failure are unable to exercise, hyperventilating without being acidotic. In other words, the fact that pH remains unchanged during moderate exercise in young healthy fit individuals is only the characteristics of how this system has evolved in humans (not all), it may not possess any intrinsic value or evolutionary advantages.

Similarly, the idea that a learning process, akin to the view developed by Somjen (1992), must take place to allow such a regulation remains to be established. Learning is essential for living systems to adjust to their environment, but the long evolution of the respiratory control system in vertebrate does not necessarily require any individual to "re-invent" the mechanisms that selection has allowed to emerge. It is far from being established that infant humans do experience repetitive hypercapnia at any point during their growth and maturation, besides breathing during locomotion appears to increase in infants as fast as it does in adults (Noah et al., 2008). This suggests that the systems controlling exercise hyperpnea are built in and fully operative from a very young age.

The lack of consensus on the mechanisms of exercise hyperpnea does not necessarily mean that the proper mechanisms have not been found yet; as mentioned in the previous paragraph, feedbacks of non-chemical nature do prevent Pa_{CO_2} and H^+ to rise, and can achieve CO_2 homeostasis when CO_2 production increases (see Haouzi and Chenuel, 2005; Haouzi, 2006 for discussion).

The new, and may be "fatal", obstacle that may prevent us to come up with a model accepted by everyone does not reside in the confrontation of different points of view (Whipp, 1981), but in the idea that studying breathing control in exercise is outdated. In keeping with this view, even if the "chemical" mechanisms defended by Wasserman et al. (2011) to account for pH homeostasis can be challenged, this study is very important, as we must clarify the terms of the debate and pursue the research on one of the most fundamental questions in respiratory physiology: how does breathing increase during exercise?

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