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LETTER TO THE EDITOR

Control of the depth and rate of breathing: metabolic *vs.* non-metabolic inputs

We read with great interest the review paper by Tipton *et al.* (2017). The authors examined the ventilatory response to a wide range of stressors, with a special interest in the differential regulation of respiratory frequency (f_R) and tidal volume (V_T). Despite a clear differential control of f_R and V_T emerging from the reviewed studies, the authors highlight how their regulation was typically neglected. An exception to this is our recent work on the differential control of f_R and V_T during high-intensity exercise (Nicolò *et al.* 2017), which was inspired by previous observations (Nicolò *et al.* 2015, 2016). Our findings fit nicely with some of the evidence reviewed by Tipton *et al.* (2017) despite the very different conditions explored. Therefore, the integration of information from both contributions has allowed us to expand on the breathing control perspective proposed by Tipton *et al.* (2017). We present here a deliberately simple viewpoint on the differential control of f_R and V_T which, despite the complexity underlying breathing control, applies in a wide range of conditions.

By manipulating recovery intensity and exercise duration during high-intensity interval training, we found that f_R, unlike V_T, responded rapidly and in proportion to variations in workload, and was dissociated from some markers of metabolic stimuli in response to both experimental manipulations (Nicolò *et al.* 2017). We concluded that fast inputs (including central command) appear to contribute more than metabolic stimuli to f_R regulation. We also supported our conclusions by presenting evidence that V_T, unlike f_R, is regulated by metabolic stimuli in various non-exercise conditions. This notion is even more convincing in the light of a number of findings reviewed by Tipton *et al.* (2017).

The authors report that the prototypic human response to stress (fight or flight) includes a fast increase in ventilation, mediated preferentially by f_R. This response is common to various stressors including cold, panic and pain. For instance, immersion in cold water produces the 'cold shock response', which includes a fast increase in minute ventilation ($\dot{V}_E$) primarily determined by an increase in f_R, with V_T not increasing until f_R begins to fall back towards pre-immersion levels (Tipton *et al.* 1991). This f_R response is possibly driven by the dynamic response of the peripheral cold thermoreceptors determining the 'cold shock response', which attenuates within the first 2 min of immersion. Thereafter, the respiratory response to cold water immersion is mainly driven by the metabolic demands of shivering, which is an involuntary form of skeletal muscle contraction (Tipton *et al.* 2017). This alteration in the inputs driving ventilation determines a diminution of the contribution of f_R to $\dot{V}_E$ and an increasing contribution of V_T, which becomes the predominant component of $\dot{V}_E$ with shivering (Tipton *et al.* 2017).

Panic is a sudden sensation of fear or anxiety which affects ventilation through central mechanisms rather than metabolic stimuli. The evidence collected by Tipton *et al.* (2017) suggests that panic increases f_R, but not V_T, when it is evoked by non-metabolic interventions. Conversely, panic increases V_T more than it does f_R when it is induced by hypercapnia, which is also a potent metabolic stimulus (Tipton *et al.* 2017).

Pain is an unpleasant sensory experience which affects ventilation through a mixture of behavioural response and a direct effect on medullary respiratory centres (Tipton *et al.* 2017). When a behavioural $\dot{V}_E$ response is induced by warning the subjects of an incoming painful stimulus, anticipation of pain causes an increase in f_R (Willer, 1975). On the other hand, when the hormonal stress response induced by pain is reproduced by intravenous infusion of cortisol, adrenaline and glucagon, an increase in $\dot{V}_E$ mediated by V_T – but not f_R – is observed (Weissman *et al.* 1986).

Collectively, the reported findings point to a non-metabolic regulation of f_R, while V_T appears to be strongly regulated by metabolic stimuli. This is further supported by remarkable findings on animals (Borison *et al.* 1977) and humans (Guz *et al.* 1966) showing that some metabolic stimuli, including hypercapnia, have no direct effect on f_R. Instead, the increase in f_R observed with severe levels of hypercapnia may be evoked by volume feedback, panic and other behavioural responses induced by hypercapnia (Tipton *et al.* 2017). Therefore, for those conditions where f_R seems to partly respond to metabolic stimuli, potential alternative explanations should be considered. On the other hand, f_R seems to be primarily regulated by fast inputs, some of which may not contribute substantially to regulating V_T. In this context, fast inputs are central command and other brain inputs (e.g. from brain areas involved in emotional processing), muscle and other non-chemical afferent inputs driving ventilation. Temperature is another non-metabolic stimulus which has a strong effect on f_R, but the underlying mechanisms need further clarification (Tipton *et al.* 2017). For a series of additional aspects that can affect the ventilatory pattern (e.g. mechanical aspects), the reader is referred to Tipton *et al.* (2017).

The fact that f_R and V_T are regulated by different inputs may also help explain why they differ in the timing of their responses. With the onset of a variety of stressors (Tipton *et al.* 2017) including exercise (Nicolò *et al.* 2017), a fast increase in f_R and a delayed response of V_T is often observed. Among respiratory physiologists, it is commonly proposed that fast inputs drive the rapid increase in ventilation in such conditions, while metabolic stimuli fine-tune the control of ventilation in order to meet the metabolic requirements. We propose that the fast increase in $\dot{V}_E$ is guaranteed by a preferential regulation of f_R, while the fine-tuning role is played by V_T. Therefore, f_R and V_T can be respectively regarded as the behavioural and metabolic components of $\dot{V}_E$. This differential control of f_R and V_T is particularly favourable if we consider how they affect alveolar ventilation (Tipton *et al.* 2017).

While we acknowledge that our interpretation of the control of f_R and V_T is a simplification of the complex regulation of breathing, it has important implications for teaching and future research in different disciplines.

Andrea Nicolò, Michele Girardi and Massimo Sacchetti

Department of Movement, Human and Health Sciences, University of Rome 'Foro Italico', Piazza Lauro De Bosis 6, Rome 00135, Italy

Email: andrea.nicolo@yahoo.com

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.