The Journal of Physiology

JOURNAL CLUB

Abnormal muscle metaboreflex control of ventilation in patients with chronic obstructive pulmonary disease: what mechanisms should be blamed?

Liliane Cunha Aranda[1], **Jeann L. C. Sabino-Carvalho**[2], **Talita Miranda-Silva**[1] **and Marcelle Paula-Ribeiro**[1,3]

[1] *Pulmonary Function and Clinical Exercise Physiology Unit, Division of Respiratory Diseases, Department of Medicine, Federal University of São Paulo, São Paulo, Brazil*

[2] *Faculty of Physical Education, University of Brasília, Brasília, Brazil*

[3] *Translational Medicine, Department of Physiology, Federal University of São Paulo, São Paulo, Brazil*

Email: lilianearanda@yahoo.com.br

One of the main complaints of patients with chronic obstructive pulmonary disease (COPD) is dyspnoea, which substantially contributes to exercise intolerance and physical inactivity. Dyspnoea has been mainly attributed to a phenomenon known as neuromechanical uncoupling. This consists of high efferent neural activity to effector organs, mainly to respiratory muscles, which paradoxically produces cardiorespiratory responses that are unable to maintain homeostasis of blood gases, or maintain the homeostasis of blood gases at high cost (e.g. high ventilation and energy expenditure of breathing). The uncoupling has been predominantly credited to changes in effector organs of the cardiorespiratory system that generate inefficient gas exchange (e.g. increased dead space, lung hyperinflation, etc.). However, it is possible that dysfunction of skeletal muscle reflexes also contributes to the COPD exercise pathophysiology. The reason for this is that COPD generally evolves with morphological and functional abnormalities in skeletal muscles, which may increase the stimuli to terminal endings of muscle afferents sensitive to mechanical (mostly type III afferents) and metabolic (mostly type IV afferents) stimuli. Alternatively, neural components of the reflex response to mechanical and metabolic stimuli may *per se* be altered by COPD.

In 2012, an important study published by Dr Maltais's group from the Université Laval in Canada confirmed the hypothesis that skeletal muscle afferents contribute to the COPD exercise pathophysiology. Intrathecal infusion of phentanyl at the lumbar region was used to blunt afferent feedback from both type III and IV muscle afferents of the lower limbs during cycling exercise in patients with COPD. This approach prolonged the time to exhaustion, and reduced the ventilatory response and dyspnoea during exercise. Nevertheless, patients with COPD were not compared to healthy controls. Moreover, the intrathecal infusion of phentanyl does not allow discrimination of the role specifically played by each type of muscle afferent.

In this context, a recent study published in *The Journal of Physiology* by Bruce *et al.* (2016) sought to shed light on cardiorespiratory responses, with particular focus on the ventilatory response, in the face of isolated metaboreflex activation in patients with COPD. Patients with COPD with and without chronic hypercapnia and healthy controls were asked to perform a rhythmic handgrip task, which consisted of 1 s contraction at 50% of maximum voluntary contraction and 1 s relaxation, for 2 min. The authors then trapped the metabolites produced during exercise in skeletal muscles via circulatory occlusion to interpret the effect of metaboreceptor activation on ventilation without the presence of cortex (i.e. central command) and mechanoreceptor activation. The main finding was that activation of the metaboreflex maintained ventilation significantly above baseline in patients with COPD, which was not observed in healthy subjects. In contrast, no differences in ventilation, heart rate and mean blood pressure were observed between patients with and without hypercapnia.

The results reported by Bruce *et al.* (2016) certainly enlarge the knowledge about the contribution of muscle afferents sensitive to metabolites to the control of ventilation in patients with COPD. However, the data from Bruce *et al.* (2016) differ from data reported by previous studies that also investigated patients with COPD. For example, Nakamoto *et al.* (2007) reported that the metaboreflex effect on ventilation was similar between patients with COPD and healthy controls. Noteworthy, the inconsistency regarding the metaboreflex is not restricted to studies that assessed patients with COPD, but has also occurred in studies conducted in patients with other diseases, such as chronic heart failure. The reason for that is multifactorial, and some of the possible factors involved are discussed next.

Cardiorespiratory responses to the activation of metabosensitive muscle afferents function as a negative feedback loop. The neural arc is composed of receptors, afferent fibres, integration at the central nervous system, efferent fibres and effector organs. Thus, the net cardiorespiratory response to activation of metaboreceptors is the tip of the iceberg, and the overall reflex response may be reduced, preserved, or augmented due to a complex interaction between the levels of the initial stimuli and the functioning of the elements that compose the neural arc.

Patients with COPD have a reduction in the proportion of type I fibres and an increase in the proportion of type II fibres, along with a reduction in oxidative enzyme activity (Allaire *et al.* 2004), which, altogether, may result in earlier onset muscle acidosis. Therefore, for a given level of absolute exercise intensity, the stimuli for metaboreceptors are certainly greater in patients than controls. And the stimuli for metaboreceptors may still be greater, even when exercise intensity is set at a relative proportion of the maximal aerobic capacity or maximal voluntary contraction. For example, time to exhaustion during isometric contraction of the knee extensors at 60% of the maximal voluntary contraction in patients with COPD was reported to be approximately half the time to exhaustion of healthy controls (Allaire *et al.* 2004). Thus, a fixed time of relative intensity exercise may more stressful for metaboreceptors in patients with COPD. The stimuli disparity may be greater when submaximal dynamic exercise is used to activate metaboreceptors, particularly when large muscle groups are engaged, compared with isometric exercise, recruiting small muscle mass, since the former represents a bigger challenge for integrative cardiorespiratory and muscular responses than the latter, and so, probably widens stimuli differences between patients

 DOI: 10.1113/JP273462

and controls. In contrast, differences in stimuli between patients and controls may be reduced when exercise is conducted until exhaustion (Amann & Dempsey, 2008).

In 1991, the group led by Dr Sinoway from Pennsylvania State University in the USA used magnetic resonance spectroscopy to characterize the metabolic response to handgrip exercise in patients with chronic heart failure and healthy controls. Under comparable metabolic stress, the metaboreflex effect on muscle sympathetic nerve activity was reduced in patients with chronic heart failure. Another method was recently advanced in humans in an attempt to standardize the stimuli level and remove the influence of confounding factors. It consists of the assessment of sensations evoked by intramuscular infusion of a 'metabolites soup' with a known concentration of key metabolites. These approaches and others could be helpful to elucidate the metaboreflex sensitivity in patients with COPD, dissecting whether the reflex is altered due to higher stimuli or any abnormality in the neural arc.

Animal models have been used to investigate the metaboreflex sensitivity, particularly after induction of chronic heart failure. Using intricate recordings of type III and IV afferent discharge, under standardized metabolic and mechanical stimulation, it has been postulated that type III fibre sensitivity is augmented, whereas type IV fibre sensitivity is reduced in rats with chronic heart failure (Wang *et al.* 2010). The aetiology of this dysfunction is under investigation, but possibly involves, for example, alteration in the number and function of acid-sensing ion channel 3 (ASIC3) channels, purinergic receptors subtype 2X (P2X) and prostaglandin E2 receptors subtype 4 (EP4) in the terminal endings of muscle afferents. In addition, purinergic receptor subtype 2X3 (P2X3) has been reported to be upregulated, and transient receptor potential vanilloid 1 (TRPV1) downregulated, in dorsal root ganglion of rats with chronic heart failure (Wang *et al.* 2010). It is possible that the aforementioned alterations reported in animals with chronic heart failure may also occur in the presence of COPD. However, experiments in animal models of COPD are still warranted.

The capacity of effector organs to respond to efferent neural signals is an important factor that should likewise be taken into consideration to interpret the sensitivity of the metaboreflex. Patients with COPD, for instance, pursue several alterations in the respiratory system, which lead to static and dynamic lung hyperinflation. The hyperinflation, in turn, may restrain the tidal volume increase during exercise. Dr O'Donnell's group from Queen's University in Canada has confirmed that patients with moderate to severe COPD present higher ventilation at rest and low exercise intensity compared to controls. But as exercise intensity increases, the ventilation increase is blunted, which is associated with the level of dynamic hyperinflation and dyspnoea qualified as 'hunger of air'. Thus, even if the skeletal muscle afferents are more activated by a higher level of stimuli in patients with COPD, their activation may not result in an enhanced ventilatory response due to a ceiling effect under some circumstances.

In summary, the complex physiology of the metaboreflex for the regulation of ventilation in patients with COPD is just starting to be revealed. Bruce *et al.* (2016) showed that patients with COPD presented higher ventilation during metaboreflex activation, but it is not clear whether this was attributed to enhanced stimuli at the terminal endings on muscle afferents and/or alteration in the sensitivity of the neural arc *per se*. It is noteworthy, however, that ventilation was higher in patients with COPD as a result of exercise paired by relative intensity and duration. Moreover, peak force was lower in patients with COPD, so they exercised at a lower absolute workload. In spite of that, they presented an enhanced ventilatory response. As the absolute load may be more important for daily life activities than the relative load, the metaboreflex may be important for the dyspnoea during everyday life in patients with COPD, and so, may have important clinical implications.

References

Allaire J, Maltais F, Doyon JF, Noel M, LeBlanc P, Carrier G, Simard C & Jobin J (2004). Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* **59**, 673–678.

Amann M & Dempsey JA (2008). Locomotor muscle fatigue modifies central motor drive in healthy humans and imposes a limitation to exercise performance. *J Physiol* **586**, 161–173.

Bruce RM, Turner A & White MJ (2016). Ventilatory responses to muscle metaboreflex activation in chronic obstructive pulmonary disease. *J Physiol* **594**, 6025–6035.

Nakamoto FP, Neder JA, Maia J, Andrade MS & Silva AC (2007). Skeletal muscle ergoreflex overactivity is not related to exercise ventilatory inefficiency in non-hypoxaemic patients with COPD. *Eur J Appl Physiol* **101**, 705–712.

Wang HJ, Li YL, Gao L, Zucker IH & Wang W (2010). Alteration in skeletal muscle afferents in rats with chronic heart failure. *J Physiol* **588**, 5033–5047.

Additional information

Competing interests

None declared.

Funding

T. Miranda-Silva (grant: 16/01155-6) and M. Paula-Ribeiro (15/22198-2) received scholarships from the São Paulo Research Foundation (FAPESP).

Acknowledgements

The authors thank Dr Bruno M. Silva for mentoring the literature discussion and reviewing this manuscript. We apologize for not citing all relevant articles due to reference limitations.