Control of breathing during exercise: Who is the leader?

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Control of breathing during exercise. Follow the leader?

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TO THE EDITOR: Control of breathing during exercise has been discussed widely in the literature. Generally, it is accepted that feedforward central command signals provide the primary drive for increased breathing, or hyperpnoea, at the onset of exercise. It is also accepted that a variety of peripheral signals are capable of regulating breathing during exercise. However, the exact contributions of multiple concomitant mechanisms to exercise hyperpnoea is contested. This is evident in a recent *Exchange of Views* on feedback control of ventilation during exercise (Haouzi, 2020; White & Bruce, 2020). With this in mind, we thought it would be of interest to readers if we highlight another peripheral input, originating from pulmonary vascular baroreceptors, with potential to stimulate breathing during exercise.

Almost fifty years ago, Wasserman and colleagues (Wasserman *et al.*, 1974), suggested a feedforward, cardiodynamic component to exercise hyperpnoea. That is, the increase in breathing during exercise may be mechanistically linked to the increase in cardiac output for efficient ventilation-perfusion matching. However, no signal or receptor capable of coupling ventilation to cardiac output was identified.

The pulmonary circulation provides an ideal location for a receptor that couples right ventricular outflow and ventilation. Pulmonary arteries are more compliant than systemic counterparts and distend relatively easily to accommodate increases in right ventricular outflow. Furthermore, the main pulmonary artery and the left and right branches are richly innervated by myelinated afferents running within the vagus nerve. And, neurophysiological recordings demonstrate vagal afferent discharge related to pulsatile pressure in the pulmonary artery of conscious and anaesthetized animals.

Previously in this journal, Hainsworth (Hainsworth, 2014) reviewed evidence indicating that distension of the pulmonary artery in experimental animals elicits several reflex responses, including increases in phrenic nerve (inspiratory) activity. This suggests that input from pulmonary vascular baroreceptors is capable of stimulating breathing. Notably, the effect of augmented fluctuations in intrathoracic pressure on pulmonary artery

transmural and intra-arterial pressures during exercise has potential to increase the gain of this positive feedback loop.

The physiological role of baroreceptors in human pulmonary vasculature has been largely overlooked, potentially due to the technical difficulty of isolating pulmonary artery baroreflex responses from other closed-loop influences. Recently we utilized inhalation of vasodilator nitric oxide to elicit significant reduction in pulmonary artery systolic pressure (PASP), of around 6 mmHg, in healthy humans at high altitude; this was achieved without a change in cardiac output (Simpson *et al.*, 2020). Whilst the objective of that investigation was study of an effect on sympathetic neural activity, which was reduced when PASP was lowered, our work does provide an experimental approach that may enable examination of afferent input from pulmonary vascular baroreceptors to breathing control. Thus, finding a way to selectively induce pulmonary vasodilation during exercise may provide insight into the role of pulmonary vascular baroreceptors in exercise hyperpnoea.

It is clear from the aforementioned *Exchange of Views*, that the mechanisms subserving ventilatory control during exercise remain controversial. Furthermore, we acknowledge that our contribution to the debate is speculative, and the role of afferent input from pulmonary vascular baroreceptors in humans needs to be tested. However, physiological redundancy in integrated responses to exercise is recognized, and this may be another example of a mechanism whose potential is uncovered only when central command and other peripheral mechanisms are compromised.

AUTHOR CONTRIBUTIONS

LLS, ME and JPM contributed equally.

DISCLOSURES

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