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Control of breathing during exercise. Follow the leader?

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

12 Almost fifty years ago, Wasserman and colleagues (Wasserman *et al.*,
13 1974), suggested a feedforward, cardiodynamic component to exercise
14 hyperpnoea. That is, the increase in breathing during exercise may be
15 mechanistically linked to the increase in cardiac output for efficient ventilation-
16 perfusion matching. However, no signal or receptor capable of coupling
17 ventilation to cardiac output was identified.

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

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

1 transmur al and intra-arterial pressures during exercise has potential to
2 increase the gain of this positive feedback loop.

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

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

24 **AUTHOR CONTRIBUTIONS**

25 LLS, ME and JPM contributed equally.

26 **DISCLOSURES**

27 No conflicts of interest, financial or otherwise, are declared by the authors.

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