Title	Sympathetic vasomotor activity during dynamic exercise with resistive breathing: Sex differences and the nerve to show it!
Author(s)	O'Halloran, Ken D.
Publication date	2018-02-05
Original citation	O'Halloran, K. D. (2018) 'Sympathetic vasomotor activity during dynamic exercise with resistive breathing: Sex differences and the nerve to show it!'. Experimental Physiology, In Press, doi: 10.1113/EP086904
Type of publication	Article (peer-reviewed)
Link to publisher's version	http://dx.doi.org/10.1113/EP086904 Access to the full text of the published version may require a subscription.
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Embargo information	Access to this article is restricted until 12 months after publication by request of the publisher.
Embargo lift date	2019-02-05
Item downloaded from	http://hdl.handle.net/10468/5447

Sympathetic vasomotor activity during dynamic exercise with resistive breathing: sex differences and the nerve to show it!

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Respiratory muscle metaboreflexes exert substantial influence over cardiorespiratory and autonomic control, exemplified during heavy dynamic exercise in health, and in obstructive airways disease even at rest. Intense activation of the respiratory muscles, particularly under loaded conditions, manifests an altered metabolic milieu enhancing sensory traffic from the working muscles, with resultant effects on the distribution of cardiac output, increasing respiratory muscle blood flow (Dominelli et al. 2017) at the expense of working ambulatory muscles, thereby limiting exercise capacity. The phenomenon is considered a competitive raid by the ventilatory muscles replenishing the oxygen cost of respiratory work, often framed as frustrating to the performance athlete although one wonders how well s/he would exercise with a discontented diaphragm! Increased work of breathing can be a scourge to the ailing respiratory patient driving dyspnoea and profoundly curbing exercise tolerance.

Sex–dependent cardiovascular responses to inspiratory muscle metaboreflexes are evident such that increased blood pressure and limb vascular resistance responses to respiratory loading are diminished in women compared with men. Whereas sex differences in the sympathetic vasomotor response to static handgrip exercise have been reported (Jarvis et al. 2011), it has not hitherto been demonstrated during dynamic exercise. In this issue of Experimental Physiology, Katayama et al. (2018) describe the outcome of their ambitious study, which set out to determine if there is evidence for relatively restrained sympathetic nerve activation in women compared with men during dynamic exercise with resistive breathing, which might account for blunted blood pressure responses. In young healthy male and female volunteers, cardiorespiratory and metabolic parameters were measured during rest and dynamic leg cycling exercise at 40% VO_{2peak} during periods of spontaneous breathing, and controlled breathing with and without fixed added resistance (30% peak inspiratory pressure) to load the respiratory muscles. Microneurography was employed to record multiunit muscle sympathetic nerve activity from the median nerve. Beat-to-beat blood

This is an Accepted Article that has been peer-reviewed and approved for publication in the Experimental Physiology, but has yet to undergo copy-editing and proof correction. Please cite this article as an Accepted Article; doi: 10.1113/EP086904.

pressure was estimated using finger photoplethysmography. Absolute changes in measured parameters were compared to account for baseline differences between the two sexes, notably lower sympathetic nerve activity and blood pressure in female subjects.

Vasomotor and cardiovascular responses were equivalent in men and women during dynamic exercise under all conditions without added resistance. Exercise with added inspiratory resistance evoked further significant elevations in muscle sympathetic nerve activity and blood pressure compared with exercise without resistance in both sexes. Heart rate responses and Borg scores for self-rated exertional dyspnoea were likewise elevated and equivalent between men and women, yet absolute changes in sympathetic nerve activity and blood pressure during exercise with resistive breathing were significantly less in women compared with men. Thus, comparing baseline with exercise during resistive breathing, mean arterial blood pressure increased from 91 to 123mmHg in men compared with 81 to 103mmHg in women. Muscle sympathetic nerve burst frequency increased from 30 to 44 per minute in men compared with 24 to 34 per minute in women. The findings appear to support the authors' hypothesis that the blunted cardiovascular response to increased inspiratory muscle work in women compared with men relates to diminished sympathetic outflow.

A challenge for studies such as this, beyond the technical prowess required to obtain the data, is the difficulty in conducting 'like-with-like' comparisons to reveal putative integrated sex differences against the backdrop of other sex differences, which clearly exist. In such circumstances, identifying the basis and locus of the sex difference can prove difficult. Intrinsic sex differences are such that like-with-like assessments of integrated responsiveness may not be an easy task. To that point, known differences between sexes exist in respiratory mechanics, the work of breathing, the respiratory muscle oxygen cost of exercise, the muscle metabolic signature of resistive breathing, and perhaps in respiratory muscle biochemistry and physiology such that, notwithstanding normalized experimental conditions in the study by Katayama et al. (2018), the nature of the stimulus carried by muscle thin afferents to the brainstem network governing autonomic responses could be quite different. In other words, it is plausible that the efferent vasomotor outflow (response) differs between sexes because the afferent input (stimulus) differs. Indeed, that is in effect the principal conclusion of recent studies (Jarvis et al. 2011; Katayama et al. 2018), namely that the afferent arm of the metaboreflex differs between sexes. However, reported sex differences in sympathetic vasomotor response to different and varied afferent cues might also indicate a fundamental difference between sexes, beyond myogenic matters of the metaboreflex, suggestive of sex differences in the central integration of afferent inputs and/or neurotransmission via efferent pathways. Of note, centrally-administered oestrogen attenuates sympathetic nerve activity in experimental animals. Sex differences in reflex sympathoexcitation might be expected to provide female protection or advantage in afferent nerve mediated hypertension, but interestingly this does not appear to be the case in chronic intermittent hypoxia carotid body-mediated hypertension, although sex differences in respiratory-sympathetic coupling are apparent (Souza et al. 2016). Arguing against sex differences in central integration or efferent neurotransmission is the observation that sympathetic activation during the cold pressor response is equivalent in men and women (Jarvis et al. 2011).

Interestingly, in the study by Katayama et al (2018), heart rate responses to leg cycling exercise with inspiratory resistive breathing were equivalent in men and women. This hints that the locus of the sex difference might reside on the efferent arm of the control loop at the level of sympathetic control of the vasculature. It is possible that the sex difference relates to a blunted vasoreactivity in women in response to enhanced sympathetic efferent traffic, a point acknowledged by the authors. Poor correlation between muscle sympathetic nerve activity and total peripheral resistance is established in women, unlike men, and sex differences in adrenergic tone may be primarily important in determining blood pressure differences and responsiveness between men and women (Hart et al. 2012). And all that before one considers the matter in the context of ageing and disease.

Such complexities are the fabric of integrative physiology, the delight and despair of experimental adventure, with sobering implications for patients. How curious it is that men and women utilize different integrated mechanisms to maintain cardiovascular constancy. Or perhaps not. Different and at times opposing strategies to various stressors between the sexes are the very fabric of a balanced life. One might reason that agreement between the sexes ensuring harmony pays dividends too, but that’s a different story for another day!

Conflicts of Interest

None.

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