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Cardiac autonomic regulation during hypoxic exercise

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Autonomic nervous system regulation of the heart and vasculature plays a key role in enabling the tight coupling between the oxygen consumption of exercising skeletal muscles and oxygen delivery. The withdrawal of cardiac parasympathetic nerve activity and elevation in cardiac sympathetic nerve activity facilitate the exercise intensity dependent increase in heart rate, ventricular contractility, stroke volume and cardiac output (5). Robinson et al., (10) laid the foundations for present understanding of cardiac autonomic regulation in exercising humans with the demonstration that administration of atropine (to block cholinergic muscarinic receptors) markedly diminishes elevations in heart rate only during low-to-moderate intensity dynamic exercise, whereas administration of propranolol (to block β-adrenergic receptors) principally attenuates the cardiac acceleration during strenuous dynamic exercise. In the current issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Siebenmann et al., (12) utilize a similar methodological approach to provide new insights into cardiac autonomic regulation during hypoxic exercise in humans.

Hypoxia elevates heart rate at rest and during submaximal exercise (2). This serves to enhance oxygen delivery by increasing cardiac output in an attempt to protect against the reduction in arterial oxygen content. The heightened activation of the sympathetic nervous system has historically been the prime candidate for this cardiac acceleration, partly because catecholamine release and muscle sympathetic nerve activity are increased during hypoxic exercise (7, 9), however, the withdrawal of cardiac parasympathetic activity has also been implicated (8). Hopkins et al., (6) observed that during exercise, the additional elevation in heart rate and cardiac output caused by hypoxia persisted with either cholinergic or β-adrenergic receptor blockade. This raised the intriguing possibility that an important alternative mechanism is involved. However, the existence of complex pre- and post-synaptic interactions between the cardiac parasympathetic and sympathetic fibres mean that a compensatory action by the non-blocked portion of the autonomic nervous system cannot be ruled out.

The laudable study by Siebenmann et al (12) addresses this issue by comparing the heart rate and cardiac output responses to an exhaustive incremental exercise protocol in normoxia and hypoxia (F_iO_2 = 12%) under control (no drug) conditions, separate β-adrenergic blockade (propranolol) and cholinergic blockade (glycopyrrolate), and critically, combined β-adrenergic and cholinergic blockade.

Interestingly, the hypoxia-induced increase in heart rate under control conditions (averaged across all exercise workloads) was similar to that with β-adrenergic blockade, but reduced by ≈50% with cholinergic blockade and by ≈60% with combined β-adrenergic and cholinergic blockade. There are a number of implications to these findings, with two of the most significant being that: the withdrawal of cardiac parasympathetic activity is an important component of the additional increase in heart rate during exercise in hypoxia, and the explanation for a significant proportion of the heart rate response to hypoxic exercise remains obscure. The former may be explained by the activation of metabolically sensitive group III and IV skeletal muscle afferents, which are better known for their sympatho-excitatory properties but may also inhibit cardiac parasympathetic activity (4). Although not an inconsiderable undertaking, future studies in which the activity of group III and IV skeletal muscle afferents is experimentally attenuated during hypoxic exercise (e.g., using intrathecal fentanyl (1)) with the concomitant blockade of β-adrenergic and cholinergic receptors might provide further insight into their role.

Siebenmann et al., (12) discount several possible explanations for the hypoxia-induced increase in heart rate during exercise that occurs independently of β-adrenergic and cholinergic receptor stimulation, including incomplete cardiac autonomic blockade (although not directly tested) and the Bainbridge reflex, and instead propose the involvement of an α-adrenergic mechanism. The chronotropic responses to α-adrenergic stimulation are not widely recognised, and ordinarily administration of an α-adrenoreceptor agonist evokes a pressor response that decreases heart rate via a baroreflex mechanism. However, α_1-adrenoreceptor stimulation (phenylephrine) will evoke an increase in heart rate in young humans when administered with complete β-adrenergic and cholinergic blockade (11). It is tempting to speculate whether the addition of an α-adrenoreceptor antagonist (e.g., prazosin, phentolamine) administered during exercise along with combined β-adrenergic and cholinergic blockade, would abolish the cardiac acceleration evoked by hypoxia. Aside from classical adrenergic or cholinergic transmission, the contribution of peptidic neurotransmission to the hypoxia-induced heart rate responses described can not be ruled out (3).

The experiments undertaken by Siebenmann and colleagues (12) provide an important advance in our understanding of cardiac autonomic regulation via β-adrenergic and cholinergic receptors during hypoxic exercise. Careful studies are now

needed to reveal the mechanism accounting for the unexplained portion of the increase in heart rate occurring in hypoxic exercise.

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