POINT:COUNTERPOINT

Counterpoint: Exercise training-induced bradycardia: the case for enhanced parasympathetic regulation

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Training bradycardia is a well-established consequence of endurance exercise training and is, in fact, often used to demonstrate that an exercise training program had been effective (3). Despite decades of research, the mechanisms responsible for this reduction in baseline heart rate (HR) remain controversial (7, 9, 10, 13). Exercise training-induced changes in HR could result from either shifts in the autonomic neural balance toward dominant parasympathetic regulation of cardiac pacemaker cells (increased parasympathetic and/or reduced sympathetic neural regulation, the autonomic neural hypothesis), changes in spontaneous sinoatrial nodal (SAN) cell depolarization rates (changes in the inherent cardiac pacemaker rate, the intrinsic rate hypothesis), or some combination of the two mechanisms. Because of space limitations, the present article will provide only a selective and limited summary of the evidence in support of the autonomic neural hypothesis.

Three main lines of evidence support the autonomic neural hypothesis: 1) studies that indirectly evaluated cardiac autonomic regulation using changes in various indices of the beat-to-beat variation in HR, heart rate variability (HRV); 2) studies that used pharmacologic interventions to evaluate cardiac autonomic neural regulation; and 3) studies that directly evaluated the cardiac autonomic regulation using surgical approaches (selective cardiac denervation). Finally, the effects exercise training on atrial electrophysiology will also be described briefly.

Heart Rate Variability Studies

It is widely accepted that beat-to-beat variations in HR results from changes in the cardiac autonomic neural regulation (for reviews, see Refs. 5, 6, 15, 27). At the risk of oversimplification, HRV is considered to be directly related to cardiac parasympathetic activity and, to a lesser extent, inversely related to cardiac sympathetic regulation (5, 6, 15, 27). However, the exact contribution of each division of the autonomic nervous system (ANS) to HRV remains the subject of active investigation and continuing debate (5, 6).

Both cross sectional and longitudinal studies demonstrate that exercise training increases various indices of HRV (1, 7, 12, 14, 18, 19, 21, 23–25, 29, 32). In particular, the high frequency (HF) component of R-R interval variability, an index believed to correspond almost exclusively to cardiac parasympathetic regulation (5, 6, 15, 27), is elevated in trained compared with untrained individuals (1, 7, 18, 19, 21, 24, 25, 32). For example, we (7) found using a canine model that a 10- to 12-wk endurance exercise program elicited large increases in HF variability HRV (pretraining 7.1 ± 0.2 vs. postraining 8.2 ± 0.2 ln ms², P < 0.01), whereas this variable was unchanged in a sedentary time control group (presedentary 7.4 ± 0.5 vs. postsedentary 7.0 ± 0.6 ln ms², NS). The muscarinic antagonist, atropine, eliminated these differences.

Similar results have been obtained with human subjects (1, 3, 13, 17, 18, 22–24, 27, 28, 31). To cite one example, Levy and coworkers (23) found that aerobic exercise training elicited significant decreases in baseline HR in both younger (24–32 yr) and older (60–82 yr) men that were accompanied by large increases in HRV (older men 68% increase, younger men 17% increase). Similar results have been reported for women (24).

A meta-analysis of 13 studies (28) and a second analysis of 29 studies (3) further demonstrated that exercise training increased both R-R interval (i.e., decreased HR) and increased HF variability.

Autonomic Neural Blockade Studies

Combined muscarinic and beta-adrenergic receptor blockade provides a pharmacologic “denervation” of the heart, thereby unmasking the intrinsic or inherent SAN pacemaker rate. A number of studies report that intrinsic HR, as revealed by ANS blockade, was similar before and after the completion of exercise training programs (7, 12, 30, 31, 33). For example, we (7) found, in a canine model, that although endurance exercise training elicited significant reductions in baseline HR, HR after complete ANS blockade was similar in exercise-trained and sedentary groups both before and after the completion of the study (Fig. 1). Furthermore, these exercise training-induced changes in HR were accompanied by corresponding increases in both time and frequency domain markers of HRV (7), changes that could be eliminated by autonomic blockade (7). Indeed, the muscarinic antagonist atropine elicited larger reductions in HRV in exercise trained compared with sedentary animals, whereas beta-adrenoceptor blockade (propranolol) elicited similar HR and HRV changes both before and after the completion of an exercise training protocol (7).

Cardiac Denervation Studies

The preceding sections presented evidence either that indirectly evaluated cardiac autonomic neural regulation (HRV
sinoatrial node function studies) or employed techniques there were not cardioselective (pharmacologic interventions) and, thus, could have off target actions that complicate the data interpretation. If the autonomic neural hypothesis is correct, then the selective surgical disruption of cardiac autonomic innervation should prevent exercise-induced bradycardia. Indeed, using a canine model, Ordway and coworkers (26) found that exercise training failed to induce reductions in baseline HR in dogs with complete cardiac denervation (pretraining 95 ± 3.5 vs. posttraining 96 ± 5.3 beats/min, NS), whereas training elicited significant reductions in HR in sham-operated dogs (pretraining 64 ± 4.8 vs. posttraining 51 ± 3.2 beats/min, P < 0.05). Similar findings have been reported in cardiac transplant patients (4, 22). Furthermore, Danson and coworkers (11) found that the lower basal HR noted in atria isolated from exercise-trained mice compared with atria from sedentary animals resulted from an enhanced vagal responsiveness that was mediated via the activation of NOS-1 pathways. These data demonstrate that an intact cardiac autonomic innervation is required for the induction/maintenance of training bradycardia and provide the strongest confirmation of the autonomic hypothesis.

**Sinoatrial Node Function**

Exercise can also alter cardiac electrophysiological properties (8) that could contribute to changes in resting HR. However, we (7) recently demonstrated that SAN function was not altered by an endurance exercise program; exercise training failed to alter P wave duration, PR interval, atrial conduction time or SAN function (as measured by SAN recovery time after rapid atrial pacing) or the HR response to the potent negative chronotropic agent adenosine (20). These data suggest that exercise training did not induce an upregulation of either adenosine A1 receptors or adenosine-dependent potassium currents. Furthermore, HCN4 expression [the channel protein responsible for the important pacemaker current, I_{f}] increased rather than decreased in exercise-trained compared with sedentary animals. An increase in HCN4 expression would tend to increase rather than decrease the spontaneous pacemaker rate as drugs that selectively inhibit I_{f} reduce basal HR (2) as well as the HR response to exercise (17). As HCN4 channels are significantly regulated by cAMP level (2), HCN4 upregulation in the SAN may represent a positive adaptation to exercise and may also explain faster HR recovery after exercise observed in trained vs. sedentary dogs (7).

**Summary and Conclusion**

To summarize, a number of lines of evidence support the autonomic neural hypothesis for training bradycardia: 1) exercise training increases HRV, an indirect and noninvasive marker of cardiac parasympathetic regulation; 2) intrinsic rate, as unmasked by pharmacologic blockade of the ANS, was not altered by exercise training and was similar in both exercise trained and sedentary subjects; 3) selective cardiac denervation prevented the induction of training bradycardia in both animal studies and cardiac transplant patients; and 4) in canine studies, a model that faithfully replicates human atrial properties (16), exercise training did not alter either atrial electrophysiology or SAN nodal function. In fact, exercise training increased rather decreased HCN4 expression (a decrease would be expected if the intrinsic rate hypothesis were to be correct). When these data are considered together, one may conclude that the autonomic neural hypothesis provides the best explanation for training bradycardia; that is, exercise induced reductions in resting HR result from an augmentation of cardiac parasympathetic regulation and not as a consequence of changes in the intrinsic properties of the sinoatrial node.

**AUTHOR CONTRIBUTIONS**

G.E.B. drafted manuscript; G.E.B. edited and revised manuscript; G.E.B. approved final version of manuscript.

**DISCLOSURES**

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

**REFERENCES**


