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Exercise training bradycardia is largely explained by reduced intrinsic heart rate

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ABSTRACT

Introduction: Resting heart rate (RHR) declines with exercise training. Possible mechanisms include: 1) increased parasympathetic tone, 2) decreased responsiveness to beta-adrenergic stimulation, 3) decreased intrinsic heart rate or 4) combination of these factors.
Objective: To determine whether an increase in resting parasympathetic tone or decrease in response to beta-adrenergic stimulation contributes to the decrease in RHR with training.
Methods: 51 screened healthy subjects aged 18–32 (n = 20, mean age 26, 11 female) or 65–80 (n = 31, mean age 69, 16 female) were tested before and after 6 months of supervised exercise training. Heart rate response to parasympathetic withdrawal was assessed using atropine and beta-adrenergic responsiveness during parasympathetic withdrawal using isoproterenol.
Results: Training increased VO_2 max by 17% (28.7 ± 7.7 to 33.6 ± 9.20 ml/kg/min, P < 0.001). RHR decreased from 62.8 ± 6.6 to 57.6 ± 7.2 beats per minute (P < 0.0001). The increase in heart rate in response to parasympathetic withdrawal was unchanged after training (+37.3 ± 12.8 pre vs. +36.4 ± 12.2 beats per min post, P = 0.41). There was no change in the heart rate response to isoproterenol after parasympathetic blockade with training (+31.9 ± 10.9 pre vs. +31.0 ± 12.0 post beats per min, P = 0.56). The findings were similar in all four subgroups.
Conclusions: We did not find evidence that an increase in parasympathetic tone or a decrease in responsiveness to beta-adrenergic activity accounts for the reduction in resting heart rate with exercise training. We suggest that a decline in heart rate with training is most likely due to decrease in the intrinsic heart rate.
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1. Introduction

Athletes are thought to be among the healthiest members of society. Ironically, the incidence of arrhythmias, ranging from the benign to the pathological, is known to be higher in athletes [1]. Sinus bradycardia, defined by a resting heart rate <60 beats min^{-1}, is the most frequent rhythm disturbance in response to exercise training; the heart rate can be ~30 beats min^{-1} and even lower at night [2–5]. Possible mechanisms for the lower heart rate include: 1) increased parasympathetic tone [6,7]; 2) decreased responsiveness to beta-adrenergic stimulation [8–10]; 3) decreased intrinsic heart rate [11,12], which is defined as the heart rate under the simultaneous presence of beta-blockade with propranolol (0.2 mg/kg) and muscarinic receptor blockade with atropine (0.04 mg/kg) [13]; or 4) a combination of these factors. There has been conflicting evidence about the relative contributions of these possible causes.

In view of these uncertainties, this study examined whether there was evidence of either increased resting parasympathetic tone or a decreased response to beta adrenergic stimulation in a longitudinal exercise training study.

2. Methods

2.1. Subjects

51 rigorously screened sedentary healthy adult volunteers aged 18–32 (n = 20, mean age 26, 11 female) or 65–80 (n = 31, mean age 69, 16 female) were tested before and after 6 months of supervised endurance exercise training. Exclusion criteria included any history of angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, diabetes, current medication use (prescription or over the counter) other than hormone or thyroid replacement therapy, current smoking, exercise-limiting orthopedic impairment, or participation in a regular exercise program in the last year. Entry requirements included a normal hematocrit, creatinine, fasting blood glucose, total cholesterol, resting electrocardiogram, M-mode and two-dimensional echocardiogram, and Bruce protocol maximal

Abbreviations: RHR, resting heart rate; SD, standard deviation; bpm, beats per minute.
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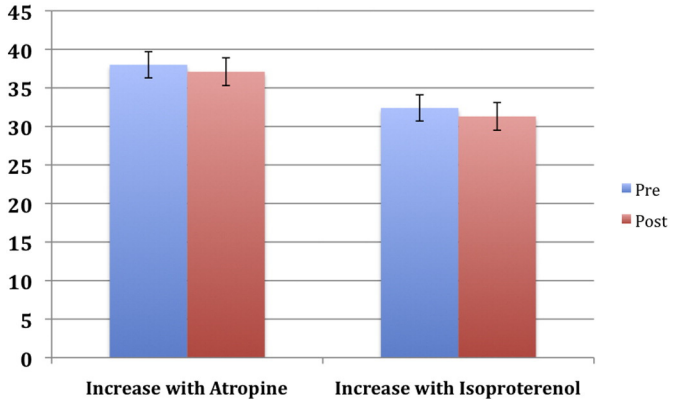

Fig. 1. Increase in heart rate before and after training in response to atropine (P = 0.41) and isoproterenol (P = 0.56). Values are means ± SD.

exercise test, including immediate post-exercise tomographic sestamibi imaging for all older subjects to rule out occult coronary disease. All older female subjects were on hormone replacement therapy. All subjects signed an informed written consent form approved by the University of Washington Human Subjects Committee.

2.2. Exercise training

The 6-month training program consisted of walking/jogging, bicycling, and stretching, each for 30 min, for a total of 90 min per session, three times per week in a closely supervised and monitored setting. Training began at 50% to 60% of heart rate reserve and increased to 80% to 85% by the third to fourth month. Maximal oxygen consumption was measured using an exercise treadmill test before and after the six months of training. Maximal oxygen consumption was measured using a maximal treadmill exercise test. VO_2 max was obtained by standard procedures as previously described [14]. The test ended when the subject could no longer continue walking or running. Mean expiratory respiratory exchange ratio on the pre- and post-tests indicated good effort.

2.3. Parasympathetic withdrawal

Following placement of intravenous catheters, subjects rested supine in a quiet, dimly lit room for 30 min and resting heart rate was measured early morning by obtaining a 12 lead EKG both before and after endurance training. Heart rate response to parasympathetic withdrawal was assessed following two bolus intravenous injections of atropine (atropine sulfate, Elkins-Sinn Inc., New Jersey) for a total of 0.02 mg/kg or up to 2 mg (0.01 mg/kg initially and repeated in 6 min).

2.4. Beta-adrenergic responsiveness to isoproterenol

Five minutes following the second atropine dose, isoproterenol was started (7 and then 14 ng/kg/min × 14 min each). The prior atropine controlled for possible differences in vagal activity before and after training, which could possibly influence the resting heart rate and the response to isoproterenol.

2.5. Statistical analysis

Results are expressed as the mean ± SD. Student's t test for paired samples was done to compare RHR before and after atropine or isoproterenol injections. Correlations between the variables were done by Stat View 5.0 (Abacus, Berkeley, California). A value of P < 0.05 was considered significant. In addition to assessing results in the entire cohort, subgroup analyses were done comparing the young (age 18–32) and older (65–80) groups and the males and females using analysis of variance for repeated measures.

3. Results

3.1. Overall results

3.1.1. Exercise training data

Training increased VO_2 max by 17% (28.7 ± 7.7 to 33.6 ± 9.2 ml/kg/min, P < 0.001). RHR decreased by 8% from 62.8 ± 6.6 to 57.6 ± 7.2 bpm (P < 0.0001).

3.1.2. Response to atropine

Prior to training, the heart rate increased by 37.3 ± 12.8 bpm in response to parasympathetic withdrawal (62.8 ± 6.6 to 100.1 ± 14.17). Following training, with atropine injection the HR increased by 36.5 ± 12.2 bpm (57.6 ± 7.2 to 94.1 ± 13.95, P = 0.41), which was not significantly different (Fig. 1).

3.1.3. Isoproterenol responses at baseline before training

There was also no change in the heart rate response to isoproterenol during parasympathetic blockade with training (+31.9 ± 10.9 pre vs. +31.0 ± 12.0 beats per min post, P = 0.56) (Fig. 1).

3.2. Subgroup results: age and sex difference

The young group had a significantly greater increase in heart rate with atropine compared to the older subjects (Table 1) (P < 0.0001). The younger group also had a non-significant increase in heart rate to isoproterenol (Table 2) (P = 0.06). There were no significant differences between females and males in the heart rate response to atropine, isoproterenol or training.

4. Discussion

This study investigated two possible causes of the decline in resting heart rate with exercise training, increased resting vagal activity and reduced responsiveness to sympathetic activity. In this study, exercise training was supervised in a gym for 6 months and the subjects achieved a significant 17% increase in VO_2 max which was associated with a 6% reduction in resting heart rate. Despite the significant decrease in resting heart rate, parasympathetic blockade with up to 2 mg of atropine caused the same increase in heart rate both before and after training. The heart rate after atropine remained reduced by 6 bpm, similar to the 6 bpm reduction in the RHR. Thus there was no evidence of increased resting vagal activity contributing to the reduction in resting heart rate.

4.1. Effect of training on intrinsic heart rate in humans

In humans, several studies have demonstrated a lower intrinsic heart rate with training. In cross-sectional studies comparing highly trained subjects to sedentary controls, intrinsic heart rate has also appeared to decrease [11,12,15–17]. In the only other longitudinal study, Sutton [17] showed that exercise training for an 8-week interval caused a significant reduction in intrinsic heart rate compared with control subjects. In the exercise group, those who had increased their aerobic capacity by more than 15 ml oxygen per kg per minute had a significant decrease in their intrinsic heart by a mean of 9 beats per minute. Boyett

Table 1
Heart responses to parasympathetic withdrawal in young and older groups before and after 6 months of exercise training.

	Pre-training			Post-training		
Mean ± SD	Rest	Atropine	HR increase	Rest	Atropine	HR increase
Young	65.6 ± 4.4	113.1 ± 8.7	47.8 ± 10.4	59.7 ± 5.0	107.1 ± 8.9	47.4 ± 7.8
Older	60.9 ± 7.3	91.3 ± 9.6	31.1 ± 8.8	56.1 ± 8.1	85.4 ± 9.1	29.8 ± 8.9

P value for young vs. older atropine response P < 0.0001 for both pre- and post-training.