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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 contribute 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 VO₂ 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 ($+37.3 \pm 12.8$ pre vs. $+36.4 \pm 12.2$ beats per min post, $p = 0.41$). There was no change in the heart rate response to isoproterenol after parasympathetic blockade with training ($+31.9 \pm 10.9$ pre vs. $+31.0 \pm 12.0$ post beats per min, $p = 0.56$). The findings were similar in all four subgroups.

Conclusions—We did not find evidence that 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 decline in heart rate with training is most likely due to decrease in the intrinsic heart rate.

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Conflict of Interest

There are no conflict interests for this study. The results of the present study do constitute endorsement by ACSM.

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.

METHODS

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 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.

Exercise training

The 6-month training program consisted of walking/jogging, bicycling, and stretching, each for 30min, 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.

Parasympathetic Withdrawal

Following placement of intravenous catheters, subjects rested supine in a quiet, dimly lit room for 30 minutes 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 (0.01mg/kg initially and repeated in 6 min).

Beta-Adrenergic Responsiveness to Isoproterenol

Five minutes following the second atropine dose, isoproterenol was started (7 and then 14 ng/kg/min $\times$ 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.

Statistical analysis

Results are expressed as the mean $\pm$ 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.

RESULTS

OVERALL RESULTS

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 ($P < 0.0001$).

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 (Figure 1).

Isoproterenol responses at baseline before training—There was also no change in the heart rate response to isoproterenol during parasympathetic blockade with training ($+31.9 \pm 10.9$ pre vs. $+31.0 \pm 12.0$ beats per min post, $P = 0.56$) (Figure 1).

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.

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.

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 et al [18], reviewed eleven studies on human beings and in summary, analysis of the heart rate in athletes after autonomic blockade showed resting bradycardia in athletes to be completely the result of decrease in intrinsic heart rate.

We extend the findings of prior studies by demonstrating that there is an apparent reduction in intrinsic heart rate with exercise training that occurs in both the young and old and in males and females. Neither age nor sex appears to influence this adaptation to exercise training.

Effect of training on intrinsic heart rate in animals

The most compelling evidence of a link between endurance exercise training and bradycardia in animals has been demonstrated in a recent publication by Dsouza et al. In this study which was done on rats, training-induced bradycardia was proven to be not a consequence of changes in the activity of the autonomic nervous system but caused by intrinsic electrophysiological changes in the sinus node. They demonstrated downregulation of pacemaker ion channels as a molecular explanation for this [19]. However one recent study debated that exercise training in rats also increases atrial acetylcholine, and vagal presynaptic NO-cGMP. It was concluded that in these animals not only decrease in intrinsic rate of pacemaker cells but also increase in cardiac parasympathetic activity contribute to training-bradycardia [20].

The study by Boyett et al [18] included a review of nine articles in animal models. In six of the nine studies, resting bradycardia was attributed to a decrease in the intrinsic heart rate. Previous studies on autonomic blockade have reported increased parasympathetic control of heart rate after endurance training [7, 20]. Conversely, in a cross-

sectional study by Katona et al. [11], a full dose of atropine (0.04 mg/kg) caused a significantly smaller rise in heart rate in athletes than in non-athletes suggesting that athletes had less parasympathetic control of heart rate compared to sedentary participants. The contradictory results of these studies could be due to a number of factors such as lack of uniform training or screening methods or the type of exercise. Our results suggest strongly that increased parasympathetic tone at rest does not account for the reduction in resting heart rate, since withdrawal of parasympathetic tone with atropine led to nearly identical increases in heart rate before and after training.

Another possible cause of the decline in resting heart rate might be decreased responsiveness to sympathetic stimulation. However, the heart rate response to isoproterenol was also unchanged by exercise training, suggesting that a reduction in response to sympathetic stimulation also is not a cause of the decline in resting heart rate with training. With training, most prior studies have shown no change in resting levels of catecholamines [21–26]. Thus any reduction due to altered sympathetic activity would likely be due to a reduction in responsiveness. Other studies of sympathetic stimulation before and after training in humans have also not suggested a reduction in isoproterenol responsiveness. For example, in a cross-sectional study of unconditioned and well-conditioned men by Williams et al [10], the same amount of isoproterenol caused similar heart rate increases in both groups, similar to our findings in the present longitudinal study. Taken together, these data show that decreased sympathetic responsiveness does not lead to the reduction in resting heart rate.

Sex—Few studies have examined sex differences in autonomic control. In general, it has been reported that males have a greater sympathetic influence on the heart rate while females have a greater parasympathetic control of heart rate [27, 28]. However, our results did not show any sex-related differences in responses to parasympathetic withdrawal or sympathetic stimulation either before or after exercise training in normal subjects.

Age—Our data included 31 participants who were from 65 to 80 years old. It has been established that the responses to parasympathetic withdrawal as well as sympathetic stimulation decline with aging [7, 29, 30 mental stress and isometric exercise in normal subjects.]. The present study provides further evidence that older adults exhibit diminished response to β -adrenergic stimulation and vagal blockade (Tables 1–2). Nevertheless, the heart rate adaptation to training was similar in both the young and older subjects. To our knowledge, this is the first study to examine training induced changes in the control of resting heart rate in older subjects.

It is possible that both metabolic and mechanical effects add to the lower intrinsic heart rate in healthy individuals following endurance training [11]. An increase in actomyosin adenosine triphosphatase activity is an indication of the biochemical adaptation of the myocardium to training [31]. The changes in cardiac dimensions with exercise training modify the mechanical stresses and strains applied to the pacemaker cells [32].

Limitations of this study include that we did not study intrinsic heart rate directly by using simultaneous parasympathetic and sympathetic blockade. In addition, these results apply to rigorously screened healthy subjects only. Responses in subjects with disease may differ.

CONCLUSION

In conclusion, the data of the present investigation suggest that neither an increase in resting parasympathetic tone nor a decrease in response to beta-adrenergic stimulation contribute to the decrease in resting heart rate with exercise training in humans. These results suggest the training induced reduction in resting heart rate is due to a decrease in the intrinsic heart rate via mechanisms which have not yet been fully defined.

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Abbreviations

RHR	Resting Heart Rate
SD	Standard Deviation
BPM	Beats Per Minute

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Figure 1. Increase in heart rate before and after training in response to atropine ($p=0.41$) and isoproterenol ($p=0.56$). Values are means $\pm$ SD.

Heart Responses to Parasympathetic Withdrawal in Young and Older Groups Before and After 6 Months of Exercise Training.

TABLE 1

	PRE TRAINING				POST TRAINING			
Mean $\pm$ SD	Rest	Atropine	HR Increase	Rest	Atropine	HR Increase		
Young	65.6 $\pm$ 4.4	113.1 $\pm$ 8.7	47.8 $\pm$ 10.4	59.7 $\pm$ 5.0	107.1 $\pm$ 8.9	47.4 $\pm$ 7.8		
Older	60.9 $\pm$ 7.3	91.3 $\pm$ 9.6	31.1 $\pm$ 8.8	56.1 $\pm$ 8.1	85.4 $\pm$ 9.1	29.8 $\pm$ 8.9		

P value for Young vs. Older Atropine Response $P < 0.0001$ for both pre and post training

Heart Responses to Isoproterenol in Young and Older Groups Before and After 6 Months of Exercise Training

TABLE 2

Mean $\pm$ SD	PRE TRAINING			POST TRAINING		
	Baseline	Isoproterenol	HR Increase	Baseline	Isoproterenol	HR Increase
Young	113.1 $\pm$ 8.7	148.8 $\pm$ 13.8	36.7 $\pm$ 10.5	107.1 $\pm$ 8.9	140.7 $\pm$ 11.0	33.6 $\pm$ 13.7
Older	91.3 $\pm$ 9.6	120.7 $\pm$ 13.9	29.6 $\pm$ 10.5	85.4 $\pm$ 9.1	114.8 $\pm$ 13.5	29.7 $\pm$ 11.0

P value for Young vs. Older Isoproterenol Response $P=0.06$ for both pre and post-training