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State-of-the-Art Lecture

Influence of Exercise Training on Neurogenic Control of Blood Pressure in Spontaneously Hypertensive Rats

Eduardo Moacyr Krieger, Patrícia Chakur Brum, Carlos Eduardo Negrão

Abstract—Exercise training plays an important role in the reduction of high blood pressure. In this review, we discuss the effect of distinct intensities of exercise training on the reduction of high blood pressure in spontaneously hypertensive rats (SHR). In addition, we present some hemodynamic mechanisms and associated neural controls by which exercise training attenuates hypertension in SHR. Low-intensity exercise training is more effective in reducing high blood pressure than is high-intensity exercise training in SHR. The decrease in blood pressure is due to resting bradycardia, and in consequence, lower cardiac output. Sympathetic attenuation to the heart is the major explanation for the resting bradycardia. Recovery of the sensitivity of baroreflex control of heart rate, which is usually impaired in SHR, is an important neurogenic component involved in the benefits elicited by exercise training. (*Hypertension*. 1999;34[part 2]:720-723.)

Key Words: exercise ■ rats, inbred SHR ■ cardiac output ■ nervous system, sympathetic ■ bradycardia

Moderate-intensity exercise training has been used to lower high blood pressure in animals and humans.¹⁻⁷ However, the effects of distinct intensities of exercise training are not entirely understood, and the mechanisms underlying the postexercise training reduction in blood pressure are still inconclusive. In this presentation, we will review recent results from our laboratory indicating that low-intensity exercise training is more effective than high-intensity exercise training in lowering high blood pressure in spontaneously hypertensive rats (SHR). Also, it will be demonstrated that the reduction in blood pressure is related to a decrease in cardiac output rather than a decrease in peripheral resistance, and the possible role of neurogenic mechanisms to account for these alterations will be examined.

Training Intensity

To address the effect of distinct exercise training intensities on hypertension, we studied SHR submitted to exercise training for 18 weeks at 55% of the maximum oxygen consumption ($\dot{V}O_{2max}$) or at 85% of $\dot{V}O_{2max}$, which we called low- and high-intensity exercise training regimens, respectively.⁸ We found that low-intensity exercise training significantly reduced systolic, diastolic, and mean blood pressure in SHR. In contrast, high-intensity exercise training caused no change in blood pressure in SHR. In previous studies, other investigators demonstrated either that exercise training performed at 55% of $\dot{V}O_{2max}$ reduced high blood pressure in men⁹ or that exercise training performed at 55%

of $\dot{V}O_{2max}$ had a better effect on blood pressure than did exercise in excess of 75% of $\dot{V}O_{2max}$ in SHR.¹⁰ These results reinforce the idea that low-intensity exercise training rather than high-intensity exercise training is more effective in reducing blood pressure in hypertension.

Hemodynamic Alterations

The understanding of the mechanisms by which exercise reduces high blood pressure has been a challenge for most investigators, because exercise may reduce high blood pressure either by attenuating total peripheral resistance and/or by decreasing cardiac output. The rationale to expect that exercise training attenuates total peripheral resistance was emphasized in our previous study,¹¹ in which we demonstrated that exercise training in normotensive rats decreased renal sympathetic activity and α -noradrenergic responsiveness. Besides that, in hypertensive rats¹² and humans,¹³ exercise training reduced norepinephrine levels, and more recently, other investigators¹⁴ reported that exercise training decreased muscle sympathetic nerve activity in humans. These studies^{12,13} and others¹⁵ suggest that the reduction in total peripheral resistance after exercise training could be responsible for the decrease in blood pressure in hypertensive conditions. On the other hand, the rationale for the concept that exercise training decreases cardiac output came from the repeated demonstration of the presence of resting bradycardia after exercise training in rats¹⁶ and humans,¹⁷ which represents the most valuable marker for exercise training adaptation. Further-

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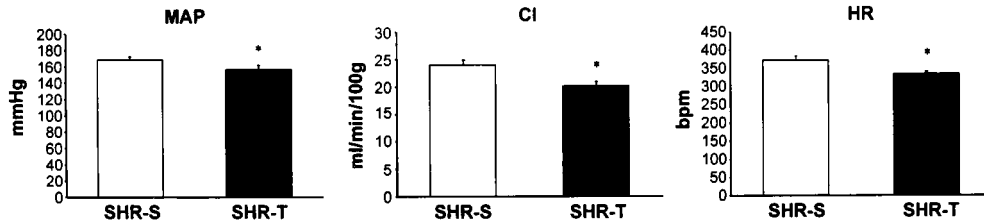


Figure 1. Resting mean arterial pressure (MAP), cardiac index (CI), and heart rate (HR) in sedentary (SHR-S) and low-intensity exercise-trained (SHR-T) spontaneously hypertensive rats. Note that low-intensity exercise significantly decreases MAP, CI, and HR but that total peripheral resistance remained unchanged (from Reference 8). *Significantly different between groups, $P < 0.05$.

more, exercise training might reduce stroke volume, since it is proposed that exercise training may decrease total blood volume in hypertensive humans.¹⁸

To test whether exercise training reduces high blood pressure by provoking a decrease either in total peripheral resistance or in cardiac output, we studied the effects of a 18-week period of low-intensity exercise training on the hemodynamic responses in SHR.⁸ Cardiac output was evaluated by means of a flow probe implanted around the aortic arch and blood pressure by means of a cannula inserted into the carotid artery. Both parameters were recorded on a beat-to-beat basis at a frequency of 100 Hz for 30 minutes in quiet, conscious, unrestrained rats. Confirming our previous results, low-intensity exercise training significantly reduced high blood pressure in SHR. However, low-intensity exercise training had no effect on total peripheral resistance. In fact, the mechanism by which low-intensity exercise training decreased blood pressure was a reduction in cardiac output due to a lower resting heart rate (Figure 1).

Sympathetic Attenuation

To address the mechanisms by which low-intensity exercise causes bradycardia, we conducted an additional study to investigate the vagal and sympathetic activities that control heart rate in SHR.¹⁹ Vagal tone was estimated by the difference between the intrinsic heart rate (double blockade by methylatropine and propranolol) and the maximal bradycardia achieved after sympathetic blockade with propranolol. Sympathetic tone was evaluated by the difference between the intrinsic heart rate and the highest tachycardia observed after vagal blockade with methylatropine. From this study, we learned that low-intensity exercise training attenuated the sympathetic tone in SHR, but not the vagal tone, which remained unchanged. Therefore, the reduction in heart rate observed after low-intensity exercise training in SHR was directly related to a decrease in the sympathetic nerve activity to the heart. Remarkable was the fact that low-intensity exercise training actually normalized the increased sympathetic tone to the heart in SHR. As shown in Figure 2, the sympathetic tone in sedentary SHR was significantly enhanced when compared with that found in sedentary, normotensive control rats. After low-intensity exercise training, however, the sympathetic tone in SHR was very similar to that exhibited by the sedentary normotensive rats. These results clearly demonstrate that low-intensity exercise training brings the sympathetic tone to the normal level. Moreover, the cardiac acceleration of trained SHR during an acute session of dynamic exercise is restrained due to an attenua-

tion of the sympathetic activity associated with a decreased vagal withdrawal.¹⁹

Baroreflex Activity During Exercise

The fact that the elevation of blood pressure during exercise is accompanied by tachycardia rather than bradycardia has been interpreted as a demonstration that the baroreflex is "turned off" during exercise. However, there is evidence that baroreflex is actively involved in control of the circulation during exercise.²⁰ We evaluated the baroreflex sensitivity (BRS) of the bradycardiac responses to increases in blood pressure (phenylephrine) at rest and during exercise, and we found that in fact, the BRS was equally effective²¹ in both conditions. Moreover, in sinoaortic-denervated rats, the increase in blood pressure during dynamic exercise was more than double that found in control rats, while the tachycardiac response was similar. Thus, the arterial baroreflex restrains the increase in blood pressure but not the increase in heart rate during an acute bout of exercise. Another question is whether the autonomic changes induced by exercise training in hypertension are partially due to the influences exerted by baroreflex control on the cardiovascular system.

Influence of Training on BRS

An increased arterial BRS after exercise training has been observed in hypertensive subjects.^{22,23} In SHR during the

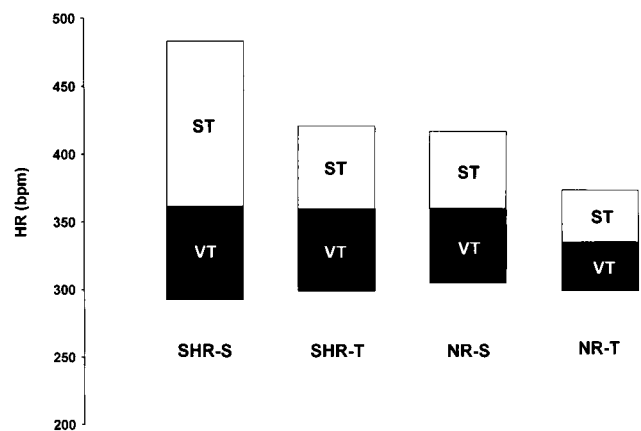


Figure 2. Sympathetic (ST) and vagal (VT) tone in sedentary normotensive rats (NR-S), exercise-trained normotensive rats (NR-T), sedentary spontaneously hypertensive rats (SHR-S), and low-intensity exercise-trained spontaneously hypertensive rats (SHR-T). Note that despite the fact that low-intensity exercise training in SHR did not reduce ST to the same level achieved in NR-T, it normalized the increased ST in SHR. In other words, low-intensity exercise training in SHR brings ST to a similar level found in NR-S (from References 16 and 19). HR indicates heart rate.

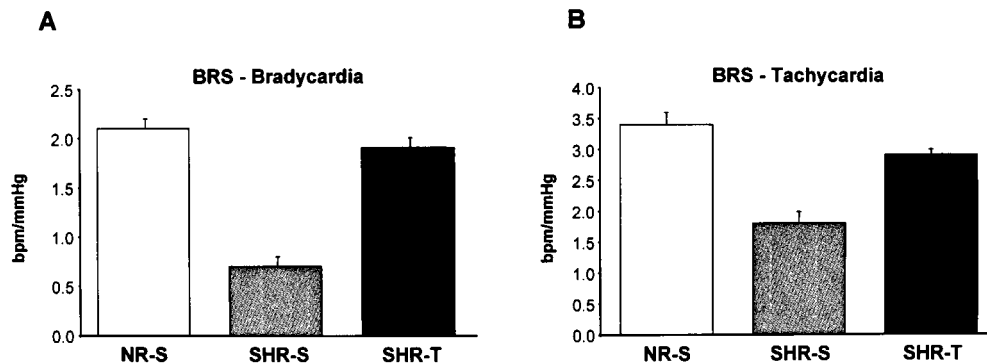


Figure 3. Baroreflex sensitivity (BRS) for bradycardia (A) and tachycardia (B) in sedentary normotensive rats (NR-S), sedentary hypertensive rats (SHR-S), and low-intensity exercise-trained spontaneously hypertensive rats (SHR-T). Note that low-intensity exercise training in SHR promoted an almost-complete restoration in BRS bradycardia and tachycardia (Figure drawn from data in Reference 24).

postexercise hypotension provoked by an acute bout of exercise, the BRS for bradycardiac responses was increased significantly (from 68% depression to 33% depression), while the BRS for tachycardiac responses remained depressed.²⁴ More interesting was the fact that low-intensity exercise training (50% of $\dot{V}O_{2\max}$ for 12 weeks) provoked a remarkable recovery of BRS for both bradycardiac and tachycardiac responses in SHR, which were 65% and 47% depressed, respectively, when compared with normotensive control rats.²⁴ In fact, low-intensity exercise training reduced these depressions to 18% and 17%, respectively, for bradycardiac and tachycardiac baroreflex responses (Figure 3).

An increase in vascular compliance was observed in humans²⁵ after exercise training. Increased shear stress during exercise may also enhance the release of endothelial factors.²⁶ All of these mechanisms may increase the sensitivity of the arterial baroreceptor afferents, thus increasing the BRS. In fact, we have observed an increase in baroreceptor gain sensitivity of the baroreceptor function curves in exercise training of normotensive rats.²⁷ However, we cannot exclude the possibility that exercise is associated with other alterations in the central and efferent components of the baroreflex pathway.

Future Studies

The revised data stress the necessity of additional studies, especially considering the following issues: (1) the mechanisms and the level of sympathetic attenuation produced by exercise training (afferent, central, and efferent pathways; alterations in target-organ sensitivity, etc); (2) whether the hemodynamic alterations promoted by sympathetic attenuation only involve a decrease in heart rate and cardiac output or whether they also promote a decrease in neurogenic tone that controls peripheral resistance; and (3) well-controlled studies in humans to analyze the beneficial effects of chronic exercise in hypertension and related risk factors (obesity, insulin resistance).

Concluding Remarks

The data that we have revised on the antihypertensive benefits of exercise training in SHR indicate the following:

- (1) Low-intensity but not high-intensity exercise training is effective in decreasing blood pressure in hypertension.
- (2) The decreases in heart rate and cardiac output at rest play an important role in promoting blood pressure reduction.
- (3) Sympathetic attenuation to the heart is one of the major alterations produced by exercise training.
- (4) The recovery of the sensitivity of baroreflex control of heart rate, which is usually impaired in SHR, is an important neurogenic component involved in the benefits elicited by exercise training.

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