Exercise Training Increases Baroreceptor Gain Sensitivity in Normal and Hypertensive Rats

Patricia Chakur Brum, Gustavo José Justo Da Silva, Edson Dias Moreira, Fumio Ida, Carlos Eduardo Negrão, Eduardo Moacyr Krieger

Abstract—Exercise training attenuates arterial hypertension and increases baroreflex sensitivity in spontaneous hypertension. However, no information exists regarding the portion of the baroreflex arch in which this attenuation takes place. We tested the hypothesis that exercise training increases the afferent pathway sensitivity of baroreflex control in both normotensive and spontaneously hypertensive rats (SHR). Arterial pressure and whole-nerve activity of the aortic baroreceptor (multifiber preparation) were evaluated in 30 male rats assigned to 4 groups: sedentary and exercise-trained normotensive rats and sedentary and exercise-trained SHR. Exercise training was performed on a motor treadmill, 5 d/wk for 60 minutes, gradually progressing toward a speed of 26.8 m/min. Exercise training reduced mean arterial pressure in conscious exercise-trained SHR (183±4 versus 165±7 mm Hg). The relation between changes in aortic baroreceptor discharge and changes in systolic arterial pressure increased significantly in exercise-trained normotensive rats (2.09±0.1 versus 1.44±0.1%/mm Hg) and exercise-trained SHR (0.92±0.1 versus 0.71±0.1%/mm Hg) compared with their respective sedentary rats. Likewise, the average aortic baroreceptor gain sensitivity (calculated by logistic equation) was significantly higher in exercise-trained normotensive rats (2.25±0.1 versus 1.77±0.03%/mm Hg) and exercise-trained SHR (1.07±0.04 versus 0.82±0.05%/mm Hg) compared with their respective sedentary control rats. In conclusion, exercise training increases aortic baroreceptor gain sensitivity in normotensive and SHR, thus improving baroreceptor sensitivity, which may result in a more efficient arterial pressure regulation by the baroreflexes. (Hypertension. 2000;36:1018-1022.)

Key Words: exercise ■ baroreceptors ■ hypertension, arterial

Impairment of the baroreflex, associated with depression in afferent baroreceptor activity, is frequently observed in hypertension, atherosclerosis, and aging; these changes have been attributed to mechanoeelastic alterations as well as ionic and paracrine factors (for references, see Chapleau et al1). In spontaneously hypertensive rats (SHR), resetting of the baroreceptor with depressed sensitivity is observed.2 We have demonstrated that exercise training improves both the depressed baroreflex control of heart rate and reduces the level of arterial hypertension in SHR. After a 12-week period of low-intensity exercise training, the baroreflex sensitivity to bradycardia and tachycardia returned to near-normal values.3 However, the experimental approach used in that study allowed no conclusion regarding the portion of the reflex arch in which the exercise training acted to improve baroreflex sensitivity. Because afferent baroreceptor sensitivity is impaired in SHR,2 we hypothesize that exercise training may compensate for this impairment and thus improve baroreceptor sensitivity. Indeed, exercise training increases brachial and femoral artery compliance,4,5 which may alter baroreceptor sensitivity. Exercise training also induces an increase in the vasodilatory response to acetylcholine in SHR6 by releasing endothelial factors that act on the baroreceptor. Moreover, in some pathophysiological conditions (eg, heart failure), the attenuation in baroreflex sensitivity is due to an impairment in the aortic baroreceptor sensitivity.7,8 Therefore, to test the hypothesis that the afferent pathway of the baroreflex is involved in the increase in baroreflex sensitivity after exercise training, we studied the effects of low-intensity exercise training on the aortic baroreceptor gain sensitivity in normotensive rats and SHR.

Methods

Animal Care and Exercise Training Protocol
Sixteen male Wistar rats and 14 SHR (Medical School, University of São Paulo), weighing 180 to 200 g, were fed standard laboratory chow and water ad libitum while housed (2 to 3 per cage) in a temperature-controlled room (22°C) with a dark-light cycle of 12 to 12 hours. These rats were assigned to 4 groups: sedentary normo-
Baroreceptor Gain Sensitivity After Training

Brum et al

The Table shows the descriptive analysis of aortic baroreceptor function in normotensive rats and SHR. Exercise training did not change the systolic pressure threshold in normotensive rats or SHR. However, exercise training did significantly reduce the systolic pressure saturation and full arterial pressure range for baroreceptor activation in normotensive rats and SHR. In addition, an increased relation between changes in baroreceptor discharge and changes in SAP (%/mm Hg) was found in exercise-trained normotensive rats and SHR compared with their respective sedentary rat groups.

One day after the measurement of basal arterial pressure, the rats were anesthetized with sodium pentobarbital (30 mg/kg) to permit recording of the arterial pressure and whole-nerve activity of the aortic baroreceptor. The level of anesthesia was adjusted to maintain the blood pressure near the values existing in the conscious state. Aortic fibers of the isolated left aortic nerve or an isolated branch of the left recurrent laryngeal nerve in the lower part of the neck were studied. There was no apparent difference in the results obtained from these two nerve fiber preparations.

The pressure–nerve activity relation, spanning low to high pressures, was measured during rapid changes in arterial pressure (10 to 15 seconds) induced by the withdrawal or infusion of blood (~2.0 mL) into the femoral artery. The arterial pressure (carotid artery) and baroreceptor activity were continuously monitored on an oscilloscope (Tektronix Storage Oscilloscope 5115) and simultaneously recorded on a tape recorder (Hewlett-Packard, 3960) for analysis. To quantify the whole-nerve activity, the nerve traffic was amplified (5A22N Differential Amplifier, Tektronix), full-wave rectified, and further integrated in an AT/CODAS acquisition system (10-kHz frequency), with the arterial pressure wave used as a trigger. Background noise was determined when the nerve activity was suppressed by decreasing arterial pressure with sodium nitroprusside. To allow comparisons among different groups of rats, aortic baroreceptor activity was expressed as a percentage of the maximal nerve activity (100% saturation).

Assessment of Arterial Pressure and Baroreceptor Nerve Activity Relation

Two approaches were used to evaluate the arterial pressure–nerve activity relation in sedentary and exercise-trained rats. The first approach consisted of a descriptive analysis of (1) the average values of $SP_{\text{a}}$, defined as the systolic pressure at which the baroreceptors initiated firing; (2) the average values of $SP_{\text{th}}$ that is, the pressure level at which continuous baroreceptor discharge was achieved during a rapid increase in arterial pressure; (3) the full arterial pressure range for baroreceptor activation, defined by the difference between $SP_{\text{a}}$ and $SP_{\text{th}}$; and (4) the calculated relation between changes in baroreceptor discharge (0% to 100%) and systolic arterial pressure (SAP) ($SP_{\text{a}}$ minus $SP_{\text{th}}$) (expressed as %/mm Hg). The second approach consisted of fitting the experimental data to a logistic sigmoid function, as previously described by others.13 This equation was adapted to fit the relation of SAP–baroreceptor activity that showed a high determination coefficient of 0.97±2%. The logistic equation was analyzed as follows: Baroreceptor activity $= P_1 + \{ (P_2)/1 + \exp [P_3(SAP - P_4)] \}$, in which $P_1$ is the maximum response of baroreceptor activity; $P_2$, the range of baroreceptor activity (maximum response minus minimum response, %); $P_3$, the coefficient to calculate the gain as a function of pressure; $P_4$, the BP$_{50}$, the mean arterial pressure at half of the range of baroreceptor activity; and SAP. The average gain or slope of the curve between two inflection points was given by the following equation: Gain $= P_3/(P_4 \times 5.62)$. 

Statistical Analysis

A 2-way ANOVA test for unpaired measurements was used to compare values from the basal levels of arterial pressure and heart rate and from the descriptive and the logistic analysis of baroreceptor function of aortic baroreceptor gain sensitivity to determine the effects of exercise training in normotensive rats and SHR. A value of $P \leq 0.05$ was considered significant. Data are reported as mean±SEM.

Results

Basal Levels of Arterial Pressure and Heart Rate

Systolic, diastolic, and mean arterial pressures were similar between sedentary rats and exercise-trained normotensive rats (129±2 versus 130±1; 105±1 versus 102±2 and 115±4 versus 113±3 mm Hg, respectively). In SHR, however, systolic, diastolic, and mean arterial pressures were significantly lower in the exercise-trained group compared with the sedentary group (192±9 versus 209±6; 140±6 versus 158±3; and 165±7 versus 183±4 mm Hg, respectively, $P<0.05$). Heart rate was significantly lower in the exercise-trained normotensive and SHR groups than in their respective sedentary groups (309±4 versus 340±3 bpm in normotensive rats, and 345±20 versus 383±10 bpm in SHR, respectively).

Aortic Baroreceptor Sensitivity

In normotensive rats, SAP was similar between the anesthetized and conscious conditions (128±3 versus 129±2 mm Hg in sedentary rats, and 128±1 versus 130±1 mm Hg in exercise-trained rats, respectively) as well as in SHR (196±7 versus 209±6 in sedentary rats and 199±10 versus 192±9 mm Hg in exercise-trained rats, respectively). These results show that the decreased arterial pressure observed in conscious exercise-trained SHR was no longer observed after anesthetization. Similarly, heart rate tended to be lower after anesthesia, so the significant difference between sedentary and exercise-trained groups observed in the conscious state was no longer observed (383±9 versus 361±9 bpm in SHR, and 280±14 versus 285±09 bpm in normotensive rats, respectively).
The Figure shows the logistic equation used to calculate the baroreceptor activity–SAP relation, the average gain, and the BP50 in sedentary and exercise-trained normotensive and SHR. In normotensive rats, the BP50 did not significantly differ between sedentary and exercise-trained rats (panel C; 128 ± 1 versus 131 ± 1 mm Hg, respectively). However, the average gain was significantly increased (27%) in exercise-trained normotensive rats compared with sedentary normotensive rats (panel B; 2.25 ± 0.19 versus 1.77 ± 0.03%/mm Hg, respectively). In SHR, exercise training significantly decreased the BP50 (panel C; 187 ± 5 versus 204 ± 5 mm Hg in exercise-trained and sedentary rats, respectively) and significantly increased (30%) the average gain (panel B; 1.07 ± 0.04 versus 0.82 ± 0.05%/mm Hg in exercise-trained and sedentary rats, respectively).

**Discussion**

The main and new finding in the present study is that dynamic exercise training increases the gain sensitivity of aortic baroreceptor function in normotensive rats and SHR. Bradycardia has been considered a good marker for exercise training adaptation in both normotensive11 and SHR12; thus, its presence in the conscious exercise-trained normotensive rats and SHR demonstrates the effectiveness of the exercise training used in the present study. We also found that exercise training significantly reduced arterial pressures in SHR. This finding confirms the results of our previous study12 in which we demonstrated that low-intensity exercise training decreases arterial pressures in SHR.

As we have thought, exercise training increases baroreceptor gain sensitivity in SHR, which has 2 pathophysiological implications. First, exercise training substantially improved aortic baroreceptor gain sensitivity in SHR, which is 40% depressed after the resetting of aortic baroreceptors in established hypertension.13,14 Second, the increase in baroreceptor discharge in exercise-trained SHR explains, at least in part, the 150% increase in baroreflex bradycardia and the 67%
increase in baroreflex tachycardia (which were depressed in
sedentary SHR) observed in our previous study. Moreover, the
central command or efferent pathway of the baroreflex
also may participate in this exercise-induced increase in
baroreflex sensitivity in SHR.

The present study shows that the effect of low-intensity
exercise training on aortic baroreceptor gain sensitivity is not
restricted to SHR but also occurs in normotensive rats. This
exercise training adaptation may play a role in the increased
baroreflex tachycardia reported by us in a previous study.
Surprising, however, was the fact that exercise training did
not increase baroreflex bradycardia in normotensive rats. The
discrepancy between the positive effect of exercise training
on aortic baroreceptor gain sensitivity and the depressed
baroreflex bradycardia can be explained by other alterations
occurring along the entire reflex arch. Chen et al. observed
an attenuation of baroreflex tachycardia in response to ind-
duced changes in arterial pressure in anesthetized rats
that had been submitted to daily spontaneous running. Because
the baroreceptor gain sensitivity was similar in exercise-
trained and sedentary rats, they attributed the baroreflex
attenuation to changes in the central component of the reflex
rather than a change in baroreceptor discharges. Alterna-
tively, the attenuation in baroreflex bradycardia may take
place in the efferent pathway of the reflex arch. In fact,
in a previous study, we found decreased bradycardiac responses
to progressive stimulation of efferent fibers of the vagal nerve
and increasing doses of methacholine in exercise-trained rats.
In addition, we demonstrated a decrease in the intrinsic heart
rate in exercise-trained normotensive rats, suggesting a sinus
node change after exercise training. Thus, the attenuation in
baroreflex bradycardia during arterial pressure increases in
exercise-trained rats may be explained by a decreased sensi-
tivity of the pacemaker cells, which overcomes the increased
sensitivities of baroreceptor function.

The mechanisms involved in the increased afferent barore-
ceptor sensitivity after exercise training were not addressed in
the present study. However, some potential mechanisms may
explain the increased baroreceptor gain sensitivity after ex-
ercise training presently observed. According to the mecha-
noeastic concept, in the presence of increased vascular
compliance, the same pulse pressure can result in increased
baroreceptor activation. Because exercise training increases
intrinsic aortic compliance in rats and arterial compli-
ance in humans, we postulate that the improvement in
aortic baroreceptor gain sensitivity may be due to an increase
in aortic compliance. Although the increase in arterial com-
pliance is an attractive explanation for the enhancement of
baroreceptor gain sensitivity produced by exercise training, it
appears to apply to normotensive but not hypertensive rats.
This conclusion is based on the observation by Kingwell et
al. that exercise training does not increase arterial compli-
ance in SHR. Endothelial changes after exercise training is
another attractive hypothesis to explain the increase in aortic
baroreceptor gain sensitivity found in the present study. Both
the magnitude and frequency of shear stress on the endothelial
cells during exercise increase the release of endothelial
factors and/or the sensitivity of endothelial cells, which in
turn enhances baroreceptor ending activity. In fact, Yen et
al. reported that exercise training increases the vasodilatory
response to acetylcholine in SHR. The increase in aortic
baroreceptor gain sensitivity may be also explained by a
reduction nerve sympathetic nerve activity. Exercise training
reduces muscle sympathetic nerve activity and the spillover
of norepinephrine in humans and reduces the renal sympa-
thetic nerve activity in rats. These changes in sympathetic
nerve activity could modify the distensibility of the sinus
area and, in consequence, improve afferent baroreceptor
discharge in SHR. Alternatively, someone could raise the
question that the blood withdrawal or infusion used in the
present study could alter the activity of cardiopulmonary
receptor and thus affect the aortic baroreceptor gain sensitiv-
ity by interaction of reflex influences. However, this does not
appear to be the case. During hypotension/deactivation of
cardiopulmonary receptors and hence increase in sympathetic
nerve activity, no difference in the pressure threshold values
(Table) was found between sedentary and exercise-trained
rats. The marked difference in the gain sensitivity of the
afferent baroreceptor in both normotensive and hypertensive
rats was detected mostly in the upper part of baroreceptor
function curve.

In conclusion, low-intensity exercise training improves
aortic baroreceptor gain sensitivity, which explains, at least in
part, the increased baroreflex control after exercise training in
SHR. Furthermore, these exercise-training induced changes
in baroreflex sensitivity may have important implications in
buffering arterial pressure variations, given the reduced
buffering capacity associated with hypertension.

Acknowledgments
This study was supported by Financiadora de Estudos e Projetos (FINEP #866.93.0023.00), Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP #1995/4668-6 and #1997/0657-5), Conselho Nacional de Pesquisa (CNPq), and Fundação E.J. Zerbini. We also thank Katt Coelho Mattos for technical contributions, Mariana Curi for performing the statistical analysis throughout this study, and Mauro Roberto Ushizima for suggestions.

References


Exercise Training Increases Baroreceptor Gain Sensitivity in Normal and Hypertensive Rats

Patricia Chakur Brum, Gustavo José Justo Da Silva, Edson Dias Moreira, Fumio Ida, Carlos Eduardo Negrão and Eduardo Moacyr Krieger

Hypertension. 2000;36:1018-1022
doi: 10.1161/01.HYP.36.6.1018

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/36/6/1018

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/