Exercise training improves aortic depressor nerve sensitivity in rats with ischemia-induced heart failure

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Submitted 21 December 2005; accepted in final form 16 June 2006

Since the classical studies by Sullivan et al. (28, 29) in the late 1980s, evidence has accumulated supporting the beneficial effects of exercise training in heart failure. Exercise training substantially improves exercise tolerance in animal models of heart failure (21) and humans (8, 29). In addition, there is some evidence that exercise training significantly reduces the number of all-cause mortality in patients with heart failure (3). Sympathetic nerve activity is increased in heart failure. Although the mechanisms underlying this sympathetic excitation are not fully understood, patients with the greatest sympathetic neural activation have increased mortality. To some extent, the increased sympathetic nerve activity seems to be linked to the impairment in arterial baroreflex (9, 18) and cardiopulmonary reflex (9), mediated by abnormalities in the periphery at the level of the aortic and cardiopulmonary receptors (9). In a recent study (18), it has been documented that exercise training reduces renal sympathetic nerve activity (RSNA) in rabbit model of pacing-induced heart failure, which seems to be associated with the improvement of the arterial baroreflex. In the present investigation, we studied the effects of exercise training on aortic depressor nerve sensitivity during variation of arterial pressure in rat model of ischemia-induced heart failure.

We hypothesized that the improvement in the arterial baroreflex control after exercise training in ischemia-induced heart failure rats was associated with an enhancement in the aortic depressor nerve activity (AODN). MATERIALS AND METHODS

Animals. Twenty male Wistar rats from the Medical School of the University of São Paulo (180–200 g body wt) were studied. The heart failure rats were randomly assigned to exercise-trained (n = 11) and untrained (n = 9) groups. Nine normal control rats were also studied. They were fed a standard laboratory diet and water ad libitum, housed (2–3 rats/cage) in a temperature-controlled room (22°C) with a 12-h:12-h light-dark cycle. All animal experimental procedures were approved by the Ethical Committee for Human Research Protocols of the University of São Paulo Medical School (No. 067/00) in accordance with the Brazilian College of Animal Experimentation.

Myocardium infarction induction. The rats underwent surgical occlusion of the main descending branch of the left coronary artery, which resulted in myocardial infarction and, subsequently, heart failure. In brief, rats were anesthetized with a single injection of ketamine (50 mg/kg body wt, Parke-Davis) and xylazine (10 mg/kg body wt, Bayer) and then ventilated by a positive-pressure ventilator. The heart was exposed through a left intercostal thoracotomy. The left coronary artery was looped by a single nylon suture (7-0) ~1 mm from its origin and then gently tied. This procedure caused a clear demarcated cyanotic and bulged area of acute myocardium ischemia that corresponded to the area distally irrigated by the left coronary artery. The heart was then repositioned in the chest wall, and the air was removed by a syringe. Finally, antibiotic (20,000 U penicillin) was administered, and the rats were individually caged during a 24-h period.
period for recovery. The rats were kept for a 1-mo period until heart failure had developed.

Peak oxygen uptake. Oxygen uptake (\(V_\text{O}_2\)) was measured by means of a rapid-flow, open-circuit, indirect calorimeter as previously described by other investigators (4). After a 1-mo period after the heart surgery, the rats were submitted to a maximal exercise test to attain the peak \(V_\text{O}_2\). \(V_\text{O}_2\) was continually measured by means of expired gas analysis during a progressive exercise protocol (5 m/min increments every 3 min and no grade) performed on a motor treadmill. Peak \(V_\text{O}_2\) was defined as the highest \(V_\text{O}_2\) attained at the end of the exercise period when the rats could no longer maintain the running speed. Gas analysis was performed by means of carbon dioxide (CD-3A) and oxygen (S-3/Al) analyzers (AMETEK, Pittsburgh, PA). The maximal exercise test was performed at the beginning, at the fourth week to adjust the training intensity, and at the end of exercise training period.

Exercise training. Low-intensity exercise training was performed on a motor treadmill during 8 wk, 5 days/wk. The running speed and distance of exercise were progressively increased to elicit 55% peak \(V_\text{O}_2\) and 60 min at the fourth week. This intensity was maintained during the rest of the 8-wk training period. All sedentary rats were exposed to treadmill exercise (5 min), three times a week, to become accustomed to the exercise protocol and handling.

** Hemodynamic measurements.** Twenty-four hours after the last exercise-training session, the rats were anesthetized with pentobarbital sodium (40 mg/kg body wt) for measurements of the left ventricular end-diastolic pressure (LVEDP). A fluid-filled catheter (PE-10) was inserted into the right carotid artery and then advanced into the left ventricle. LVEDP signals were recorded (4 kHz) on a beat-to-beat basis using AT/CODAS (DataQ Instruments). A strain-gauge transducer (Statham P23 Db) was used for arterial pressure measurement. The transducer signal was fed to an amplifier (GPA-4, model 2, Stemtech) and further to a 10-bit analog-to-digital converter. Only animals with LVEDP > 14 mmHg were included in the ventricular dysfunction group. The values of LVEDP were associated with an area of infarction of 40% (data not shown). After the LVEDP measurements were taken, the catheter was pulled back to the carotid artery, tunneled, and fixed to the neck of the animal for blood pressure measurements. Another catheter was inserted into the jugular vein (PE-10) for drug administration.

**Spectral analysis.** Pulse interval, systolic blood pressure, RSNA, and AODN fluctuations were assessed in the frequency domain, using autoregressive spectral analysis during a 10-min period (2, 20). In brief, continuous series of pulse interval, systolic blood pressure, RSNA and AODN, generated tachogram, systogram, RSNA neurogram and AODN neurogram series, respectively. Each of the series was divided in segments of 300 points, overlapped by 50%. The spectra of each segment were calculated via the Levinson-Durbin recursion, and the order of the model was chosen according to Akaike’s criterion. The oscillatory components of the spectra were quantified in low- (<0.2 Hz) and high-frequency (HF, 0.74 to 3.0 Hz) ranges (1). The oscillations of very LF (<0.02 Hz) were not quantified. The LF and HF spectral components of pulse interval, systolic blood pressure, RSNA, and AODN were expressed in arbitrary (as ms\(^2\), mmHg\(^2\), au\(^2\), and au\(^2\), respectively) and normalized units (au and nu, respectively). The normalized units were obtained by calculating the percentage of LF and HF variability in regard to the total power, after subtracting the power of the very LF component (15).

**Cross-spectral analysis.** Cross-spectral analysis was performed by means of bivariate autoregressive identification and was used to compute coherence, phase functions, and the magnitude of transfer function (from systolic blood pressure to RSNA and from systolic blood pressure to AODN). The coherence function was used to determine the linear regression between pulse interval, RSNA and AODN, and systolic blood pressure. We only used coherence function >0.5 in the central frequency within LF range (0.2–0.74 Hz) for analysis. After the coherence between two signals was verified, the \(\alpha\)-index and transfer function were analyzed to estimate the spontaneous baroreflex control of heart rate and RSNA, and spontaneous baroreceptor afferent sensitivity.

**Spontaneous baroreflex control of heart rate.** After coherence analysis, the baroreflex sensitivity was calculated using the \(\alpha\)-index within the LF range (\(\alpha\)-index = square root of the LF pulse interval/\(\alpha\) LF systolic blood pressure power ratio). This index is considered an estimate of spontaneous cardiac baroreflex sensitivity (25).

**Spontaneous baroreflex control of RSNA.** The baroreceptor-mediated control of RSNA was studied by means of the transfer function of closed-loop baroreflex arc (23). This linear system analysis predicts the input-output relations between two signals. Systolic blood pressure was considered the input variable, and RSNA, the output variable of the system.

**Spontaneous baroreceptor afferent sensitivity.** To estimate the spontaneous baroreceptor afferent sensitivity, we calculated the transfer function in LF range, considering systolic blood pressure as the input variable and AODN as the output variable. A 10-min-period data recording was used to calculate the magnitude of transfer function. Because the absolute value of the nerve activity varies according to the positioning and size of the electrode and the distance between electrodes, we expressed the RSNA and AODN sensitivity in arbitrary units (au).

**Experimental protocols (experiment 1): baroreflex control of heart rate and RSNA.** After 1 day of LVEDP measurements, baseline blood pressure was assessed. The rats were then anesthetized with pentobarbital sodium (40 mg/kg body wt) for RSNA measurements. The left kidney was exposed retroperitoneally through a left flank incision. The two tips of the electrodes were hooked on the nerve by placing the electrode between the renal nerve and the sheath. The third electrode was placed between the sheath and the tissue, which served as a grounding electrode. The exposed nerve and electrode were then embedded in a two-component silicone gel (Walker Sil-Gel 604). After this procedure, the incision was closed. The nerve was cut distally to the electrode positioning to exclude afferent influence in the signal recording. The RSNA signal was then integrated, using the diastolic blood pressure wave as a trigger, in an AT/CODAS acquisition system on a beat-to-beat basis. The RSNA and blood pressure signals were simultaneously recorded for a 10-min period, using AT/CODAS acquisition system (6 kHz). The RSNA was normalized to the maximum response obtained by means of intravenous bolus injection of sodium nitroprusside (32 \(\mu\)g/ml), which decreased blood pressure to 40–45 mmHg. The pulse-interval signal was obtained from the digitized arterial pressure signals (17). The baroreflex control of heart rate was evaluated by the relationship between pulse interval and spontaneous fluctuation of systolic blood pressure. The baroreflex control of RSNA was evaluated by the relationship between RSNA and spontaneous fluctuation of systolic blood pressure.

**Experimental protocols (experiment 2): aortic baroreceptor-systolic blood pressure relationship.** The left AODN was carefully isolated at its junction with the superior laryngeal nerve and placed on a bipolar platinum electrode. The nerve-electrode preparation was then embedded in silicone gel. The nerve activity was amplified in a differential amplifier (5–10 kHz of gain; AN502 Differential Amplifier, Tektronix, Oregon), filtered with a band-pass filter of 0.2–3.0 kHz, and further full-wave rectified. The RSNA signal was then integrated, using the diastolic blood pressure wave as a trigger, in an AT/CODAS acquisition system on a beat-to-beat basis. The AODN was cut distally to the heart to exclude effenter influence in the signal recording. The AODN and blood pressure signals were simultaneously recorded for a 10-min period, using AT/CODAS acquisition system (6 kHz). The AODN was then recorded after changes in blood pressure induced by phenylephrine. In brief, phenylephrine was administered to cause a sudden and marked increase in blood pressure, which increased neural...
activity to maximal level. The AODN was normalized as a percentage of the maximal discharge obtained after phenylephrine administration (16).

Statistical analysis. One-way ANOVA was used to test possible differences in spectral analysis components, transfer function, and spontaneous baroreflex control among untrained heart failure rats, exercise-trained heart failure rats, and normal control rats. When significance was found, the Scheffé’s post hoc comparison test was used. Significant differences were assumed to be at $P \leq 0.05$. Data are reported as means ± SE.

RESULTS

Baseline measurements. Hemodynamic and functional characteristics of untrained and exercise-trained ischemia-induced heart failure rats and normal controls are shown in Table 1. Left ventricular end-diastolic pressure was significantly higher in exercise-trained and untrained heart failure rats when compared with that in normal controls. There were no significant differences in left ventricular end-diastolic pressure between exercise-trained and untrained heart failure rats. Mean arterial pressure was significantly lower in untrained heart failure rats compared with that in normal controls but similar between untrained and exercise-trained heart failure rats. Mean blood pressure was similar between exercise-trained heart failure rats and normal controls. Heart rate levels were significantly lower in exercise-trained heart failure rats when compared with those in normal controls. There were no significant differences in heart rate between exercise-trained and untrained heart failure rats. Peak $V_O2$ levels were significantly higher in exercise-trained than in untrained heart failure rats but similar between exercise-trained heart failure rats and normal control rats.

RSNA, expressed as a percentage of maximal RSNA, was significantly lower in exercise-trained heart failure rats when compared with that in untrained rats. There were no significant differences in RSNA between exercise-trained heart failure rats and normal control rats (Fig. 1).

Spectral power analysis. The data of spectral power of pulse interval, systolic blood pressure, RSNA, and AODN in untrained and exercise-trained heart failure rats and normal controls are shown in Table 2. Exercise-trained heart failure rats had significantly lower absolute and normalized LF component of pulse interval when compared with untrained heart failure rats but similar to normal control rats. In contrast, exercise-trained heart failure rats had significantly higher normalized HF component of pulse interval when compared with that in untrained heart failure rats.

Table 1. Hemodynamic and functional characteristics in normal control rats and untrained and exercise-trained heart failure rats

<table>
<thead>
<tr>
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<th>Normal Control</th>
<th>Untrained Heart Failure</th>
<th>Exercise-Trained Heart Failure</th>
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<tbody>
<tr>
<td>LVEDP, mmHg</td>
<td>2.8 ± 0.7</td>
<td>15.6 ± 0.3*</td>
<td>15.5 ± 0.4*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>114 ± 4</td>
<td>101 ± 4*</td>
<td>107 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>344 ± 12</td>
<td>332 ± 7</td>
<td>306 ± 6*</td>
</tr>
<tr>
<td>Peak $V_O2$, ml/kg·min⁻¹</td>
<td>66 ± 3</td>
<td>53 ± 2*</td>
<td>65 ± 1†</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n$, number of rats. LVEDP, left ventricle end-diastolic pressure; MAP, mean arterial pressure; $V_O2$, oxygen uptake. *$P < 0.05$ vs. normal control; †$P < 0.05$ vs. untrained heart failure group.

Table 2. Spectral power analysis of pulse interval, systolic blood pressure, RSNA and AODN in normal control rats and untrained and exercise-trained heart failure rats

<table>
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<td>LF, ms²</td>
<td>0.07 ± 0.01</td>
<td>4.35 ± 0.6*</td>
<td>0.21 ± 0.06†</td>
</tr>
<tr>
<td>LF, nu</td>
<td>1.21 ± 0.1</td>
<td>0.84 ± 0.2</td>
<td>1.17 ± 0.2</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>57.6 ± 3.0</td>
<td>21.6 ± 5.0*</td>
<td>56.1 ± 9.0*</td>
</tr>
<tr>
<td>HF, nu</td>
<td>43.0 ± 1.1</td>
<td>30.1 ± 2.5*</td>
<td>46.7 ± 0.4†</td>
</tr>
<tr>
<td>AODN</td>
<td>76.1 ± 3.0</td>
<td>64.7 ± 26.0</td>
<td>95.1 ± 19.0</td>
</tr>
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</table>

The absolute LF component of systolic blood pressure was significantly lower in exercise-trained heart failure rats when compared with that in untrained heart failure rats. There were no significant differences in the absolute LF component of systolic blood pressure between exercise-trained heart failure rats and normal control rats. The absolute HF component of systolic blood pressure was similar among groups.

The absolute and normalized LF component of RSNA was significantly increased in exercise-trained heart failure rats when compared with that in untrained heart failure rats. There were no significant differences in absolute and normalized LF component of RSNA between exercise-trained heart failure rats and normal control rats.

Fig. 1. Renal sympathetic nerve activity (RSNA), calculated by a percentage of maximal activity of RSNA achieved during reduction in arterial blood pressure with sodium nitroprusside, in normal control rats and untrained and exercise-trained heart failure (HF) rats. RSNA is significantly lower in exercise-trained HF rats when compared with that in untrained HF rats. *$P < 0.05$ vs. normal control; †$P < 0.05$ vs. untrained HF rats.

Table 2. Spectral power analysis of pulse interval, systolic blood pressure, RSNA and AODN in normal control rats and untrained and exercise-trained heart failure rats

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</tr>
<tr>
<td>LF, au²</td>
<td>57.6 ± 3.0</td>
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<td>HF, au²</td>
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</tr>
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</table>

Values are means ± SE; $n$, number of rats. RSNA, renal sympathetic nerve activity; AODN, aortic depressor nerve activity; LF, low-frequency component; HF, high-frequency component; nu, normalized units; au², arbitrary units. *$P < 0.05$ vs. normal control group; †$P < 0.05$ vs. untrained heart failure group.
exercise-trained heart failure rats

In contrast, the normalized HF component of RSNA was significantly decreased in exercise-trained heart failure rats when compared with that in untrained heart failure rats. In addition, no significant differences in the normalized HF component of RSNA were observed between exercise-trained heart failure rats and normal control rats.

The absolute and normalized LF component of AODN was significantly increased in exercise-trained heart failure rats when compared with that in untrained heart failure rats, and no significant differences were observed in the absolute and normalized LF component of AODN between exercise-trained rats and normal control rats. The absolute HF component of AODN was similar among groups. However, the normalized HF component of AODN was significantly decreased in exercise-trained heart failure rats when compared with that in untrained heart failure rats. In addition, there were no significant differences in the normalized HF component of RSNA between exercise-trained heart failure rats and normal control rats.

The coherence function of RSNA and AODN, and systolic blood pressure are shown in Table 3. The coherence function between RSNA and systolic blood pressure was similar among all three groups. However, the coherence function was significantly lower in exercise-trained heart failure rats when compared with that in untrained heart failure rats. In addition, there were no significant differences in the normalized HF component of RSNA and systolic blood pressure were also similar among groups.

The spontaneous baroreceptor sensitivity of heart rate by means of α-index (LF component) was significantly increased in exercise-trained heart failure rats when compared with that in untrained heart failure rats, but it was similar between exercise-trained heart failure rats and normal control rats (Fig. 2A). Similarly, both the spontaneous baroreceptor sensitivity of RSNA and AODN by means of the transfer function (LF component) were significantly greater in exercise-trained heart failure rats when compared with those in untrained heart failure rats. However, they were similar between exercise-trained heart failure rats and normal control rats (Figs. 2B and 3).

**DISCUSSION**

The novelty of this study is that exercise training increases AODN sensitivity in ischemia-induced heart failure rats. In addition, exercise training significantly improves baroreflex control of heart rate and RSNA in ischemia-induced heart failure rats. Although these findings suggest an association between the increase AODN sensitivity and the improvement in baroreflex control, its cause-effect relationship is unknown.

The consistent findings of reduced sympathetic nerve activity after exercise training (18, 26) may lead to an increase in quality of life with exercise (3), possibly reducing the mortality

### Table 3. Coherence and phase of gain of spontaneous baroreflex control of RSNA and spontaneous baroreceptor afferent AODN in normal control rats and untrained and exercise-trained heart failure rats

<table>
<thead>
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<th>Exercise-Trained Heart Failure</th>
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<tbody>
<tr>
<td>RSNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coherence</td>
<td>0.85±0.03</td>
<td>0.55±0.02*</td>
<td>0.72±0.03†</td>
</tr>
<tr>
<td>Phase, radians</td>
<td>−2.24±0.4</td>
<td>−2.04±0.1</td>
<td>−2.31±0.12</td>
</tr>
<tr>
<td>AODN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coherence</td>
<td>0.80±0.02</td>
<td>0.71±0.07</td>
<td>0.70±0.06</td>
</tr>
<tr>
<td>Phase, radians</td>
<td>−0.34±0.04</td>
<td>−0.51±0.04</td>
<td>−0.53±0.24</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rats. *P < 0.05 vs. normal control group; †P < 0.05 vs. untrained heart failure group.

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**AJP-Heart Circ Physiol • VOL 291 • DECEMBER 2006 • www.ajpheart.org**

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[Figures and diagrams are not included in this text format.]

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of patients with heart failure, although the definite answer to this prognosis must wait for the results of future studies.

Although the mechanisms underlying the reduction in sympathetic nerve activity after exercise training in both animals and humans are unknown (18, 26), some recent findings provide important information in regard to the clarification of this complex physiological puzzle. Exercise training significantly improves arterial baroreflex sensitivity in paced-induced heart failure rabbits (18). This autonomic change may contribute to the reduced RSNA in heart failure animals and, more recently, muscle sympathetic nerve activity in humans with heart failure (18, 26). This idea can be extended to other cardiovascular diseases. In the rat model of spontaneous hypertension, exercise training increased arterial baroreflex control of heart rate (5, 27) and decreased sympathetic tonus on the heart (13).

In attempting to understand the mechanism by which exercise training improves arterial baroreflex control of heart rate and RSNA in the heart failure state, we investigated in the present study the effects of exercise training on the afferent portion of the arterial baroreflex arch by measuring the AODN sensitivity. We found that exercise training did increase the AODN sensitivity in rats with ischemia-induced heart failure. Thus it is possible that the improvement in arterial baroreflex control after exercise training is, in part, AODN sensitivity mediated. However, we cannot rule out the possibility that part of the enhancement in baroreflex control in heart failure after exercise training is associated with the reduction in plasma angiotensin II or endothelin levels. Previous studies (10, 11) have demonstrated that angiotensin II is enhanced in heart failure and attenuates baroreflex control of heart rate and sympathetic activity. Similarly, endothelin is elevated in the heart failure state (19).

The mechanisms involved in the improvement of AODN sensitivity are out of the scope of our study. However, it is reasonable to suggest an amelioration of blood vessels compliance as a candidate for AODN sensitivity in exercise-trained ischemia-induced heart failure rats. The enhancement in blood vessels compliance after exercise training has been previously reported by others (14). Another possibility is that the improvement of AODN sensitivity is due to an increase in cardiac function. A recent study (12) demonstrated that long-term exercise training is associated with an improvement in stroke volume and cardiac output in patients with advanced heart failure. The lowered resting heart rate in exercise-trained heart failure rats is indicative of an autonomic alteration. Moreover, HF component (cardiac vagal modulation) was greater in exercise-trained rats. Similar findings were previously demonstrated in humans with heart failure (8, 24).

Heart failure is characterized by enhanced neurovascular activation (animals and humans). Thus it would be reasonable to expect that heart failure rats had increased LF component of RSNA when compared with normal control rats. This was not the case in the present study. Heart failure rats had lowered LF component of RSNA when compared with normal control rats. Similar findings were observed in humans with heart failure in whom a LF component of intraneurale recording of muscle sympathetic nerve activity (22) was either present or absent in 91% of the patients. The explanation for the reduction or even absence in LF component in heart failure is unknown. One possibility is the arterial baroreflex impairment. Exercise training significantly improved spontaneous baroreflex sensitivity of RSNA in heart failure rats, which is consistent with augmented LF component of RSNA. Other effects of reduced LF component in heart failure may include central effects. The exaggerated catecholamine levels, angiotensin, and vasopressin may alter the autonomic regulatory functioning at the central level. In a previous study, exercise training dramatically reduced muscle sympathetic nerve activity in humans (26), which seemed centrally mediated.

We recognized several limitations in our study. The levels of LVEDP are suggestive of moderate left ventricular dysfunction. Thus we do not know whether the effects of exercise training on AODN sensitivity are maintained in rats with greater levels of LVEDP or more severe cardiac dysfunction. Because of the unfeasibility of AODN measurements in conscious animals, we cannot rule out the effects of anesthesia in our interpretations regarding AODN sensitivity. The reduction in RSNA after exercise training in heart failure rats might be even greater if RSNA was normalized to the maximum response seen after cigarette smoke or acute environmental stress (air-jet stress), because both elicited greater responses of RSNA than that seen after nitroprusside (6).

In conclusion, exercise training improves AODN sensitivity and arterial baroreflex control of heart rate and RSNA in ischemia-induced heart failure rats.

GRANTS
This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (01/00009–0) and in part by Fundação Zerbini. M. S. Brasileiro-Santos was supported by Universidade Federal de Pernambuco, Recife, Pernambuco, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

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