Exercise training prevents the deterioration in the arterial baroreflex control of sympathetic nerve activity in chronic heart failure patients


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Groehs RV, Toschi-Dias E, Antunes-Correa LM, Trevizan PF, Rondon MU, Oliveira P, Alves MJ, Almeida DR, Middlekauff HR, Negrão CE. Exercise training prevents the deterioration in the arterial baroreflex control of sympathetic nerve activity in chronic heart failure patients. Am J Physiol Heart Circ Physiol 308: H1096–H1102, 2015. First published March 7, 2015; doi:10.1152/ajpheart.00723.2014.—Arterial baroreflex control of muscle sympathetic nerve activity (ABRMSNA) is impaired in chronic systolic heart failure (CHF). The purpose of the study was to test the hypothesis that exercise training would improve the gain and reduce the time delay of ABRMSNA in CHF patients. Twenty-six CHF patients, New York Heart Association Functional Class II-III, EF ≤ 40%, peak VO₂ ≤ 20 ml·kg⁻¹·min⁻¹ were divided into two groups: untrained (UT, n = 13, 57 ± 3 years) and exercise trained (ET, n = 13, 49 ± 3 years). Muscle sympathetic nerve activity (MSNA) was directly recorded by microneurography technique. Arterial pressure was measured on a beat-to-beat basis. Time series of MSNA and systolic arterial pressure were analyzed by autoregressive spectral analysis. The gain and time delay of ABRMSNA was obtained by bivariate autoregressive analysis. Exercise training was performed on a cycle ergometer at moderate intensity, three 60-min sessions per week for 16 wk. Baseline MSNA, gain and time delay of ABRMSNA, and low frequency of MSNA (LFMSNA) to high-frequency ratio (HFMSNA) (LFMSNA/HFMSNA) were similar between groups. ET significantly decreased MSNA. MSNA was unchanged in the UT patients. The gain and time delay of ABRMSNA were unchanged in the ET patients. In contrast, the gain of ABRMSNA was significantly reduced [3.5 ± 0.7 vs. 1.8 ± 0.2, arbitrary units (au)/mmHg, P = 0.04] and the time delay of ABRMSNA was significantly increased (4.6 ± 0.8 vs. 7.9 ± 1.0 s, P = 0.05) in the UT patients. LFMSNA to HFMSNA ratio tended to be lower in the ET patients (P < 0.08). Exercise training prevents the deterioration of ABRMSNA in CHF patients.

chronic heart failure; sympathetic modulation; arterial baroreflex control; exercise training

NEUROHUMORAL ACTIVATION is a marker in chronic systolic heart failure (CHF). Muscle sympathetic nerve activity (MSNA) is increased in moderate CHF patients compared with healthy individuals (25). This increase in MSNA is even greater in severe CHF patients (25), which suggests an association between sympathetic nerve activity and severity of heart failure. Although the increase in sympathetic activity plays an important role in the initial and compensatory phase of the cardiac dysfunction, its maintenance contributes to the worsening of the cardiac function, vasoconstriction, and prognosis in CHF patients (5, 8). The sustained increase in sympathetic nerve activity in CHF is a complex issue and little understood. Previous studies have shown that the sympathetic exacerbation involves alteration in the central nervous system and peripheral autonomic reflex control, including arterial baroreflex (ABR) control (19, 38, 39). ABR control is a primary and powerful inhibitory reflex of sympathetic nervous traffic during short-term variation of arterial pressure (23, 38). The effectiveness of the ABR control depends on the magnitude (gain) and latency (time delay) of the effectors’ response (33, 35). Observational study shows that an ABR control gain of less than 3.0 ms/mmHg increases the risk of cardiac mortality in CHF patients twofold (19), which is suggestive of powerful prognostic information in this variable.

Previous studies have shown that exercise training plays a remarkable role in CHF. Exercise training improves exercise tolerance and quality of life in CHF patients (11, 29). This amelioration in clinical status has been attributed to an improvement in skeletal myopathy (4, 10). Exercise training substantially reduces sympathetic nerve activity and, in consequence, vasoconstriction (16, 29). This change in neurovascular favors decreasing in muscle pro-inflammation and oxidative stress. The reduction in sympathetic nerve activity as a result of exercise training in CHF has been linked to an enhancement in ABR control. Experimental studies in pacing-induced heart failure rabbits demonstrated that exercise training significantly increased ABR (21). Similarly, exercise training significantly increased ABR control of renal sympathetic nerve activity in the ischemic model of HF rats (27, 28). However, the effects of exercise training on ABR control of sympathetic nerve activity in humans with CHF are unknown.

In the present study, we tested the hypothesis that exercise training would increase the ABR control of MSNA (ABRMSNA) in patients with CHF.

METHODS

Study Population

The study was approved by Scientific Research Committee of the Heart Institute (InCor) (SDC-4060/14/040) and Human Subject Protection Committee of the Clinical Hospital, University of Sao Paulo, Medical School (Plataforma Brasil, 31757714.4.0000.0068), and registered at www.ClinicalTrials.gov (NCT02219451). Patients were selected by database from randomized studies performed at the Unit
of Cardiovascular Rehabilitation and Exercise Physiology of the Heart Institute (InCor), Medical School, University of São Paulo.

Twenty-six CHF outpatients [age 30–70 years, Functional Class II to III, New York Heart Association, left ventricular ejection fraction (EF) ≤40%, and peak oxygen uptake (VO₂) ≤20 ml·kg⁻¹·min⁻¹, selected from other randomized studies of the Unit of Cardiac Rehabilitation and Exercise Physiology, Heart Institute (InCor), Medical School, University of São Paulo] were included in the study. The exclusion criteria were recent myocardial infarction or unstable angina (<3 mo), CHF duration (<3 mo), permanent pacemaker dependence, atrial fibrillation, skeletal muscle abnormality (e.g., arthritis), and participation in a regular exercise program. They were assigned to two groups: untrained (n = 13) and exercise-trained (n = 13).

Measurements and Procedures

Echocardiography. All patients underwent echocardiography before and after the protocol period follow-up in accordance with international standards (30). Left ventricular EF, end-diastolic volume (EDV), and end-systolic volume (ESV) were determined from the two-dimensional echocardiography by Simpson method (IE33, Philips Medical Systems, Andover, MA).

Cardiopulmonary exercise testing. As previously described (16, 36), all patients underwent maximal exercise capacity assessed during a maximal progressive exercise test on cycle ergometer (Ergoline, Spirit 150, Bitz, Germany), using a ramp protocol with work rate increments of 5–10 W every min until exhaustion. VO₂ and carbon dioxide production were determined by means of gas exchange on a breath-by-breath basis in a computerized system (model Vmax 229, SensorMedics, Buena Vista, CA). Peak VO₂ was defined as the maximum attained VO₂ at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm. Anaerobic threshold was determined to occur at the breakpoint between the increase in the carbon dioxide output and VO₂ or at the point in which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise. Respiratory compensation was determined to occur at the point at which ventilatory equivalent for carbon dioxide was lowest before a systematic increase and when end-tidal carbon dioxide partial pressure reaches a maximum value and begins to decrease (31). Cardiopulmonary exercise testing was conducted at baseline and after 4 mo of exercise training or untrained control period.

Muscle sympathetic nerve activity. MSNA was recorded directly from the peroneal nerve (multunit postganglionic) using a tungsten microelectrode by means of technique of microelectrodeography as previously described (37). In brief, the neural signals were amplified by a factor of 50,000 to 100,000 and band-passed filtered (700 to 2,000 Hz). For recordings and analysis, nerve activity was rectified and integrated (time constant, 0.1 s) to obtain a mean voltage display. Muscle sympathetic bursts were identified by visual inspection by the principal investigator and by two other investigators (C. E. Negrao and M. U. Rondon) blinded to the study protocol. MSNA were expressed as burst frequency (bursts per min) and burst incidence (bursts per 100 heart beats).

Arterial pressure, heart rate, and respiratory rate. Systolic, diastolic, and mean arterial pressure was measured noninvasively with an oscillometric beat-to-beat basis by a finger photoplethysmography device (Finometer Pro, Finapress Medical Systems, Amsterdam, The Netherlands). Heart rate (HR) was measured through ECG lead II, and respiratory rate was measured with a piezoelectric thoracic belt (model 1132, Pneumotrace II) placed around the upper abdomen.

Autonomic control. As previously described (22, 35), the beat-to-beat variability of MSNA, systolic arterial pressure (SAP), and respiratory activity were analyzed by an autoregressive frequency domain approach. This procedure enables the automatic quantification of the center frequency and the power of each component in absolute as well as in normalized units (nu) in very low (VLF: 0.003 to 0.04), low-(LF: 0.04 to 0.15 Hz), and high-frequency (HF: 0.15 to 0.40 Hz) ranges. Furthermore, the ratio of LF of MSNA (LF/MSNA) and HF of MSNA (HF/MSNA) was calculated for estimation of the LF/MSNA
HF/MSNA (22, 35).

Arterial baroreflex control. As previously described in detail (35), the transfer function analysis, using the bivariate autoregressive identification procedure, allows evaluating ABR function of MSNA. This procedure permits the measurement of gain, coherence (κ²), and phase shift (Φ) of transfer function between an input and an output signals. The gain of the transfer function quantifies the intensity of the response of the output signal (MSNA) per unit of spontaneous change of the input signal (SAP), being expressed in arbitrary units per millimeters of mercury (au/mmHg). The coherence measures the strength of the linearity between the oscillations at the same frequency band in both variability signals and was accepted when >0.5. The phase shift quantifies the phase offset between the oscillations in both variability signals (the SAP changes precede MSNA changes) and was accepted when it was between 0 and -Π (radians) (35). The gain value is considered as a spontaneous index of sensitivity of ABR/MSNA (35). The time delay of ABR, an index that quantifies the latency of the baroreflex response, was calculated as previously described (35). In brief, considering that the phase shift is the product between the time delay and the angular frequency (ω), the time delay of ABR/MSNA in the LF range was quantified according to the following equation:

\[ \text{time delay} = \Phi_\omega \frac{1}{\omega} \]  

In which \( \omega \) is equal to the product between central frequency of LF band and 2π. The time delay was expressed in seconds (35).

Exercise training. The exercise training protocol was conducted for 4 mo, as previously described (11, 16, 36). In brief, it consisted of three 60-min exercise sessions/week. Each exercise session consisted of 5-min stretching exercises, 30-min of cycling on an ergometer bicycle in the first 15 days, and up to 40 min in the rest of the period, 10 min of local strengthening exercises, 5 min of cool down with stretching exercises. The exercise intensity was established by heart rate levels that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test. During the exercise sessions, when a training effect was observed, as indicated by a decrease by 8% to 10% in heart rate, the bicycle work rate was increased by 0.25 or 0.5 km/h to return to the target heart rate levels. Subjects underwent exercise training under supervision at the Heart Institute. The untrained patients were instructed to avoid any regular exercise program but advised to maintain their daily activities. The physical activity status was followed every 3–4 wk at the clinic examination. At the end of the study, the patients randomized to the untrained group were invited and encouraged to participate of exercise training program under supervision in the Heart Institute (InCor), Medical School, University of São Paulo.

Experimental Protocol

The experimental protocol was performed in a quiet and thermoneutral room at approximately the same time of the day, and all the subjects were instructed to not interrupt their cardiac medications. The subject was placed in the supine position, and electrocardiogram electrodes were placed on the chest and the cuffs for arterial pressure measurement were placed on the left arm. After patient’s instrumentation, the signals of MSNA, arterial pressure, heart rate, and respiratory rate were registered with subjects in rest for a period of 10 min. The study was conducted before and after 4 mo of exercise training or follow-up, 24–48 h after the last exercise training session.

Statistical Analysis

The data are presented as means ± SE. A Chi-square (χ²) test was used to assess categorical data differences. The Kolmogorov–Smirnov and Levene’s test were used to assess the normality of distribution and homogeneity for each variable. Variables with normal distribution
Table 1. Baseline characteristics in the untrained and exercise-trained chronic heart failure patients

<table>
<thead>
<tr>
<th></th>
<th>UT</th>
<th>ET</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>49 ± 3</td>
<td>57 ± 3</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>28 ± 1</td>
<td>29 ± 1</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (77%)</td>
<td>12 (92%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Female</td>
<td>3 (23%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Functional Class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>12 (92%)</td>
<td>10 (77%)</td>
<td>0.27</td>
</tr>
<tr>
<td>NYHA III</td>
<td>1 (8%)</td>
<td>3 (23%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>CHF etiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>6 (46%)</td>
<td>3 (23%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic</td>
<td>3 (23%)</td>
<td>7 (54%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2 (15%)</td>
<td>1 (8%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Chagasic</td>
<td>2 (15%)</td>
<td>2 (15%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ß-Blocker</td>
<td>13 (100%)</td>
<td>13 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACEI/ARA</td>
<td>13 (100%)</td>
<td>13 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diuretics</td>
<td>13 (100%)</td>
<td>13 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>6 (46%)</td>
<td>5 (38%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Digitalis</td>
<td>0</td>
<td>1 (8%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Statins</td>
<td>5 (38%)</td>
<td>7 (54%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (46%)</td>
<td>5 (38%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 13 patients. UT, untrained; ET, exercise-trained; BMI, body mass index; NYHA, New York Heart Association; CHF, chronic heart failure; ACEI/ARA, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonist.

Table 2. Effect of exercise training on hemodynamic and functional capacity in chronic heart failure patients

<table>
<thead>
<tr>
<th></th>
<th>UT Pre</th>
<th>UT Post</th>
<th>ET Pre</th>
<th>ET Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EF, %</strong></td>
<td>31 ± 1</td>
<td>35 ± 2</td>
<td>25 ± 1</td>
<td>27 ± 2</td>
</tr>
<tr>
<td><strong>EDV, ml</strong></td>
<td>67 ± 1</td>
<td>64 ± 1</td>
<td>73 ± 3</td>
<td>72 ± 3</td>
</tr>
<tr>
<td><strong>ESV, ml</strong></td>
<td>56 ± 1</td>
<td>51 ± 1</td>
<td>62 ± 3</td>
<td>58 ± 4</td>
</tr>
<tr>
<td><strong>HR, beats/min</strong></td>
<td>64 ± 3</td>
<td>62 ± 3</td>
<td>59 ± 2</td>
<td>60 ± 2</td>
</tr>
<tr>
<td><strong>SAP, mmHg</strong></td>
<td>129 ± 5</td>
<td>133 ± 6</td>
<td>124 ± 4</td>
<td>124 ± 4</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>70 ± 3</td>
<td>73 ± 3</td>
<td>67 ± 2</td>
<td>69 ± 3</td>
</tr>
<tr>
<td><strong>Peak VO₂, ml·kg⁻¹·min⁻¹</strong></td>
<td>91 ± 4</td>
<td>94 ± 5</td>
<td>88 ± 3</td>
<td>89 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. EF, left ventricular ejection fraction; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; VO₂, oxygen uptake. *P < 0.05, within group comparison; †P < 0.05, between group comparison.

and homogeneity were used parametric tests. Student’s t-test for unpaired data was only used to test the baseline differences between groups. Two-way ANOVA for repeated measures was used to verify the effects of exercise training or clinical follow-up. In case of significant difference, Scheffé’s post hoc was employed. Probability value of P < 0.05 was considered statistically significant.

RESULTS

Pretraining Measurements

Before training was started, baseline characteristics of untrained (n = 13) and exercise-trained (n = 13) CHF patients were taken and are shown in Tables 1 and 2. There were no differences between groups in age, body mass index, gender, functional class, etiology, medications, presence of hypertension, and diabetes (Table 1). In addition, there were no differences in left ventricular EDV and ESV, HR, arterial pressure, and peak VO₂. However, left ventricular EF was lower in the exercise-trained group (Table 2).

Before training was started, the untrained and exercise-trained groups were similar in resting MSNA burst frequency and burst incidence (Fig. 1). With regard to the LFMSNA, coherence; SAP, systolic arterial pressure; HF, high frequency; ab, absolute; au, arbitrary units; nu, normalized units; ω, central frequency; LFMSNA/HFMSNA, oscillatory pattern of muscle sympathetic nerve activity; k², coherence; SAP, systolic arterial pressure; Φ, phase shift.

Table 3. Effect of exercise training on sympathetic modulation and baroreflex control in chronic heart failure patients

<table>
<thead>
<tr>
<th></th>
<th>UT Pre</th>
<th>UT Post</th>
<th>ET Pre</th>
<th>ET Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LFMSNA, au²</strong></td>
<td>43 ± 6</td>
<td>46 ± 6</td>
<td>30 ± 8</td>
<td>58 ± 9</td>
</tr>
<tr>
<td><strong>LFMSNA, nu</strong></td>
<td>42 ± 4</td>
<td>31 ± 6</td>
<td>35 ± 6</td>
<td>44 ± 4</td>
</tr>
<tr>
<td><strong>ω LF, Hz</strong></td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td><strong>HFMSNA, au²</strong></td>
<td>62 ± 11</td>
<td>108 ± 21</td>
<td>93 ± 37</td>
<td>76 ± 13</td>
</tr>
<tr>
<td><strong>HFMSNA, nu</strong></td>
<td>58 ± 4</td>
<td>69 ± 6</td>
<td>65 ± 6</td>
<td>56 ± 4</td>
</tr>
<tr>
<td><strong>ω HF, Hz</strong></td>
<td>0.30 ± 0.02</td>
<td>0.27 ± 0.02</td>
<td>0.24 ± 0.02</td>
<td>0.29 ± 0.02</td>
</tr>
<tr>
<td><strong>LFMSNA/HFMSNA</strong></td>
<td>0.8 ± 0.01</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td><strong>k² SAP-MSNA</strong></td>
<td>0.69 ± 0.05</td>
<td>0.67 ± 0.06</td>
<td>0.64 ± 0.05</td>
<td>0.64 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE. LF, low frequency; HF, high frequency; ab, absolute; au, arbitrary units; nu, normalized units; ω, central frequency; LFMSNA/HFMSNA, oscillatory pattern of muscle sympathetic nerve activity; k², coherence; SAP, systolic arterial pressure; Φ, phase shift.
Exercise training caused no change in left ventricular EF, EDV and ESV, HR, and arterial blood pressure (Table 2). Exercise training significantly increased peak VO$_2$ (Table 2). No changes were observed in the untrained group (Table 2). Exercise training significantly reduced resting MSNA burst frequency and burst incidence (Fig. 1). In contrast, no significant changes were found in the untrained group (Fig. 1). Exercise training did not change absolute or normalized LF$_{MSNA}$ and LF central frequency or absolute or normalized HF$_{MSNA}$ and HF central frequency. Exercise training tended to reduce LF$_{MSNA}$/HF$_{MSNA}$ ($P < 0.08$, Table 3). In the untrained group, no significant changes were observed in absolute and normalized LF$_{MSNA}$ and absolute and normalized HF$_{MSNA}$, and LF$_{MSNA}$/HF$_{MSNA}$ (Table 3).

With regard to arterial baroreflex control, the gain and time delay (response) of the ABR$_{MSNA}$ were unchanged in exercise-trained patients (Fig. 2). In contrast, in the untrained patients, the gain of the arterial baroreflex control was significantly reduced, whereas the time delay (response) of the arterial baroreflex control was significantly increased. SAP, systolic arterial pressure, *$P < 0.05$, within group comparison; † $P < 0.05$, between groups comparison.

**Effects of Exercise Training**

Exercise training caused no change in left ventricular EF, EDV and ESV, HR, and arterial blood pressure (Table 2). Exercise training significantly increased peak VO$_2$ (Table 2). No changes were observed in the untrained group (Table 2). Exercise training significantly reduced resting MSNA burst frequency and burst incidence (Fig. 1). In contrast, no significant changes were found in the untrained group (Fig. 1). Exercise training did not change absolute or normalized LF$_{MSNA}$ and LF central frequency or absolute or normalized HF$_{MSNA}$ and HF central frequency. Exercise training tended to reduce LF$_{MSNA}$/HF$_{MSNA}$ ($P < 0.08$, Table 3). In the untrained group, no significant changes were observed in absolute and normalized LF$_{MSNA}$ and absolute and normalized HF$_{MSNA}$, and LF$_{MSNA}$/HF$_{MSNA}$ (Table 3).

With regard to arterial baroreflex control, the gain and time delay (response) of the ABR$_{MSNA}$ were unchanged in exercise-trained patients (Fig. 2). In contrast, in the untrained patients, the gain of the ABR$_{MSNA}$ was significantly reduced and the time delay (response) of the ABR$_{MSNA}$ was significantly increased (Fig. 2). Thus the gain of the ABR$_{MSNA}$ was significantly lower and the time delay (response) was significantly higher in untrained patients compared with exercise-trained patients (Fig. 2). No significant changes in $k^2$ and $\Phi$ of the ABR$_{MSNA}$ were observed in untrained patients and exercise-trained patients (Table 3). Examples of individual raw data of arterial pressure, sympathetic neurogram, and cross-spectral analysis (gain, $k^2$, and $\Phi$) between MSNA and SAP variabilities in one untrained patient and one exercise-trained patient are displayed in Fig. 3.

**DISCUSSION**

The major and new finding of the present study is that exercise training prevents the reduction in the gain and the increase in the time delay of the ABR$_{MSNA}$ in CHF patients. Since an impaired baroreflex control portends a worse prognosis in heart failure, these findings may have implications for improved overall survival in patients with CHF following exercise training.

ABR control modulates sympathetic nerve activity at rest and in response to acute changes in blood pressure (14, 18). This autonomic control that originates in the carotid sinus and aortic arch travels through the glossopharyngeal and vagal nerves to the central nervous system (34, 38) and inhibits efferent sympathetic nerve activity during acute increases of blood pressure (26). Conversely, during a fall in blood pressure, this inhibitory influence is acutely withdrawn. At rest the ABR exerts a tonic inhibitory effect on resting MSNA. The efficiency of the ABR depends on the magnitude (gain) and latency (time delay) of the arterial baroreceptors response (7). The ABR is impaired in chronic systolic CHF (15, 17), explaining, at least in part, the increased resting sympathetic nerve activity in heart failure. In the present study, the ABR$_{MSNA}$ was significantly decreased over time in the untrained group, despite no apparent worsening in cardiac disease. This mismatch between ABR$_{MSNA}$ and clinical status raises the possibility that the deterioration in baroreflex control precedes the changes in clinical status. Exercise training prevents the deterioration in the ABR$_{MSNA}$. ABR$_{MSNA}$ was unchanged in exercise-trained patients over time. In the animal model of heart failure, exercise training has been shown to improve ABR sensitivity (20, 21).

Another interesting piece of information in the present study was the fact that exercise training reduced resting MSNA. These findings suggest that the reduction in sympathetic nerve activity after exercise training in CHF patients is not only mediated by increase in ABR sensitivity but may also be modulated by chemoreflex control and/or ergoreflex control. Exercise training normalizes renal sympathetic nerve activity responses during variation of oxygen partial pressure (32). In a recent study, we found that exercise training improved mechanoreflex and metaboreflex control of MSNA in patients with CHF (3). To our knowledge, this is the first demonstration that exercise training prevents the reduction in ABR$_{MSNA}$ function in CHF patients.

The effect of the exercise training on the sympathetic nerve activity in humans with CHF has been extensively replicated. Exercise training decreases MSNA regardless of age, gender, and β-blockers (1, 2, 16). The present study confirms these previous findings. Our paradigm significantly reduced MSNA in patients with CHF. These findings have clinical implications, since MSNA is an independent predictor of mortality in patients with CHF (5).

The present study provides no information regarding the mechanisms by which exercise training preserved ABR$_{MSNA}$ in CHF patients. However, it is reasonable to suspect that exercise...
training preserved endothelial function and arterial stiffness. Reduction in arterial compliance (6, 13), which impairs the efficiency of arterial baroreceptors to translate the spontaneous oscillations in arterial pressure in CHF, is enhanced by exercise training (9, 12). We cannot exclude the central component of baroreflex pathway. Exercise training normalizes central angiotensin II concentration and angiotensin II type 1 receptor messenger RNA (20). In addition, exercise training decreased messenger RNA and protein expression of angiotensin II type 1 receptors in the rostral ventrolateral medulla in heart failure rabbits (24). This information is not available in our study. However, we can speculate that exercise training prevented the burden in the central nervous system caused by CHF.

**Limitations**

The baseline difference in left ventricular EF between groups might suggest that we were dealing with patients in different stages of cardiac dysfunction. This seems unlikely because left ventricular EF was not the only criteria to select patients to the study. Medications and peak $\dot{V}O_2$ were not different between untrained and exercise-trained patients, which strengthen the clinical similarity between groups. In addition, exercise training or clinical follow-up did not affect left ventricular EF. In contrast, an increase in peak $\dot{V}O_2$ and preservation of ABR$_{MSNA}$ were only observed in the exercise-trained patients.

**Perspectives**

The preservation of ABR sensitivity by exercise training is an important finding and has clinical implications. ABR control has been associated with increased risk of cardiac death in CHF patients (19). Since deterioration in ABR control takes place even in a short period (16 wk), early initiation and continuous maintenance of an exercise training program in CHF patients is of paramount importance.

In conclusion, exercise training preserves the deterioration in the ABR$_{MSNA}$ function in CHF patients.
GRANTS
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DISCLOSURES
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AUTHOR CONTRIBUTIONS

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