The Effects of Exercise Training on Sympathetic Neural Activation in Advanced Heart Failure
A Randomized Controlled Trial

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OBJECTIVES
The goal of this study was to test the hypothesis that exercise training reduces resting sympathetic neural activation in patients with chronic advanced heart failure.

BACKGROUND
Exercise training in heart failure has been shown to be beneficial, but its mechanisms of benefit remain unknown.

METHODS
Sixteen New York Heart Association class II to III heart failure patients, age 35 to 60 years, ejection fraction $\leq 40\%$ were divided into two groups: 1) exercise-trained ($n = 7$), and 2) sedentary control ($n = 9$). A normal control exercise-trained group was also studied ($n = 8$). The four-month supervised exercise training program consisted of three 60 min exercise sessions per week, at heart rate levels that corresponded up to 10% below the respiratory compensation point. Muscle sympathetic nerve activity (MSNA) was recorded directly from peroneal nerve using the technique of microneurography. Forearm blood flow was measured by venous plethysmography.

RESULTS
Baseline MSNA was greater in heart failure patients compared with normal controls; MSNA was uniformly decreased after exercise training in heart failure patients (60 ± 3 vs. 38 ± 3 bursts/100 heart beats), and the mean difference in the change was significantly ($p < 0.05$) greater than the mean difference in the change in sedentary heart failure or trained normal controls. In fact, resting MSNA in trained heart failure patients was no longer significantly greater than in trained normal controls. In heart failure patients, peak VO$_2$ and forearm blood flow, but not left ventricular ejection fraction, increased after training.

CONCLUSIONS
These findings demonstrate that exercise training in heart failure patients results in dramatic reductions in directly recorded resting sympathetic nerve activity. In fact, MSNA was no longer greater than in trained, healthy controls. (J Am Coll Cardiol 2003;42:854–60)

Neurohumoral activation, including activation of the sympathetic nervous system, typifies advanced heart failure (HF), and patients with the greatest sympathetic activation have the poorest survival (1,2). Sympathetic excitation activates the renin-angiotensin system, increases peripheral vasoconstriction, and lowers the ventricular fibrillation threshold, thereby directly contributing to end-organ hypoperfusion and sudden death risk (3). Virtually every pharmacologic therapy proven to increase survival in chronic HF, and, thus, mandated in its treatment, interrupts this neural humoral activation (4–7). Exercise training is being increasingly prescribed in HF, and has been found to improve functional class, exercise ability, and quality of life (8–10). Its mechanism of benefit is unknown. Exercise training partially reverses the skeletal myopathy of HF, and improves peripheral blood flow (11). The effects of exercise on autonomic function in HF have been studied using plasma norepinephrine levels, heart rate (HR) variability, and the whole body norepinephrine spillover technique (12–15), with conflicting results.

Gordon et al. (12) reported that eight weeks of two-legged knee extensor exercise improved exercise ability and quality of life in chronic HF patients, but did not reduce resting plasma norepinephrine levels. Other investigators found that eight weeks of training improved indexes of HR variability analyzed in both the time domain and the frequency domain (13,14). Adamopoulos and colleagues (15) extended these improvements to the circadian pattern of HR variability as well. These findings are consistent with a return of sympathetic-vagal balance after exercise training.
Using the whole body norepinephrine spillover technique, Coats et al. (14) reported a reduction in sympathetic activation after eight weeks of bicycle training. As these investigators noted, however, the norepinephrine spillover technique does not distinguish between augmented central sympathetic outflow and altered norepinephrine dynamics at the nerve terminal. In addition to these potential benefits of exercise training on restoring resting autonomic balance in HF, it is possible that the exaggerated sympathetic excitation (16) and regional vasoconstriction (17) during exercise in HF is reversed by exercise training, further improving exercise ability, quality of life, and even mortality. The purpose of our study was to use direct recordings of muscle sympathetic nerve activity (MSNA) to test the hypothesis that exercise training reduces resting sympathetic neural activation in patients with chronic advanced HF.

METHODS

Study population. All subjects gave written informed consent for this study, which was approved by the Human Subject Protection Committee of the Heart Institute (InCor) and Clinical Hospital, University of São Paulo Medical School. Consecutive out-patients meeting the following inclusion/exclusion criteria were offered participation in the study: 1) age between 35 to 60 years, 2) no recent (<3 months) myocardial infarction or unstable angina, 3) stable HF duration >3 months, 4) no muscle skeletal abnormality (e.g., arthritis) prohibiting participation in an exercise program, 5) New York Heart Association (NYHA) class II to III HF, and 6) ejection fraction ≥40%.

Normal healthy volunteers between the ages of 35 to 60 years had normal history and physical examinations, were not involved in exercise training for six months, and were not taking any medications.

Study protocol. Patients with HF were randomized to the training group or sedentary control group. All normal control subjects were enrolled in the exercise training group. Resting MSNA was recorded in the fasting state in patients and normal controls within three weeks of initiating the exercise or sedentary programs, and within one week of concluding the exercise or sedentary programs. Subjects were positioned for microneurography, and a satisfactory nerve recording site from the peroneal nerve was obtained pre- and post-intervention. Blood pressure, forearm blood flow (FBF), and HR were measured noninvasively. After a 15-min rest period, 10 min of resting MSNA and HR were recorded; FBF and blood pressure were recorded for 2 min.

Exercise training program. The training program was based on several published protocols that have demonstrated a conditioning effect (8,13,14). Subjects underwent exercise training under supervision at the Heart Institute. The four-month training program consisted of three 60-min exercise sessions/week. Each exercise session consisted of 5 min stretching exercises, 25 min of cycling on an ergometer bicycle in the first month and up to 40 min in the last three months, 10 min of local strengthening exercises (sit-ups, push-ups, and pull-ups), 5 min of cool down with stretching exercises. The exercise intensity was established by HR levels that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test. In one patient the respiratory compensation point was not detectable. In that patient, the exercise training was determined at the anaerobic threshold. When a training effect was observed, as indicated by a decrease by 8% to 10% in HR during exercise, the bicycle work rate was increased by 0.25 or 0.5 kpm to return to the target HR levels. Aerobic exercise training duration increased progressively so that all patients could perform 40 min of bicycle exercise at the established intensity. Compliance was assessed as percentage of exercise sessions attended.

Sedentary program. Patients were instructed to avoid any regular exercise program or any nonsupervised exercise program. The patients were asked about exercise each visit to the hospital (approximately every three weeks).

Resting MSNA. Resting MSNA was recorded directly from the peroneal nerve using the technique of microneurography (18,19). Multiunit post-ganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode. Signals were amplified by a factor of 50,000 to 100,000 and bandpassed filtered (700 to 2,000 Hz). Nerve activity was rectified and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper. All recordings of MSNA met previously established and described criteria. Muscle sympathetic bursts were identified by visual inspection by a single investigator (C.E.N.) blinded to the study protocol, and were expressed as burst frequency (bursts per min), and bursts per 100 heart beats. The reproducibility of MSNA measured at different time intervals in the same individual expressed as bursts/min is r = 0.88, and expressed as bursts/100 heart beats is r = 0.91 (20).

FBF. Forearm blood flow was measured by venous occlusion plethysmography. The nondominant arm was elevated above heart level to ensure adequate venous drainage. A mercury-filled silastic tube attached to a low-pressure transducer was placed around the forearm and connected to a plethysmograph (Hokanson, Bellevue, Washington). Sphygmomanometer cuffs were placed around the wrist and upper arm. At 15-s intervals, the upper cuff was inflated above venous pressure for 7 to 8 s. Forearm blood flow

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>FBF</td>
<td>Forearm blood flow</td>
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<tr>
<td>FVR</td>
<td>Forearm vascular resistance</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>MSNA</td>
<td>Muscle sympathetic nerve activity</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>VO₂</td>
<td>Oxygen uptake</td>
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Table 1. Baseline Physiologic Parameters

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<tr>
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<th>HF—Sedentary N = 9</th>
<th>Normal Controls N = 8</th>
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<td>6/3</td>
<td>5/3</td>
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<td>4</td>
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<tr>
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<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
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<tr>
<td>Furosemide</td>
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<td>5</td>
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<td>Hydrochlorothiazide</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Beta-adrenergic blocker</td>
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<td>0</td>
<td></td>
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<tr>
<td>HF duration (yrs)</td>
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<td>3.4 ± 1</td>
<td></td>
</tr>
<tr>
<td>Peak VO2 (ml/kg/min)</td>
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<td>16.6 ± 2</td>
<td>27.5 ± 3*</td>
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<td>Heart rate (beats/min)</td>
<td>77 ± 3</td>
<td>79 ± 7</td>
<td>67 ± 3*</td>
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<td>MAP (mm Hg)</td>
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<td>98 ± 3</td>
<td>102 ± 3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35 ± 3</td>
<td>35 ± 3</td>
<td>73 ± 3*</td>
</tr>
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<td>MSNA (bursts/min)</td>
<td>46 ± 3</td>
<td>44 ± 4</td>
<td>27 ± 3*</td>
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<tr>
<td>(bursts/100 heart beats)</td>
<td>60 ± 3</td>
<td>56 ± 3</td>
<td>41 ± 4*</td>
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<td>FBF (ml/min/100 ml tissue)</td>
<td>1.7 ± 0.2</td>
<td>2.1 ± 0.1</td>
<td>2.6 ± 0.2*</td>
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<tr>
<td>FVR (U)</td>
<td>61 ± 4</td>
<td>47 ± 7</td>
<td>40 ± 2*</td>
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Values are mean ± SD. *Value versus HF patients, p < 0.05.

ACEI = angiotensin-converting enzyme inhibitors; FBF = forearm blood flow; FVR = forearm vascular resistance; HF = heart failure; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MSNA = muscle sympathetic nerve activity; VO2 = oxygen uptake.

End-tidal carbon dioxide partial pressure reaches a maximum and begins to decrease (24). The reproducibility of the peak VO2 measured at a different time interval in the same individual expressed as ml/kg/min in our laboratory is \( r = 0.95 \).

Miscellaneous measurements. Arterial pressure was monitored noninvasively. Heart rate was monitored continuously through lead II of the electrocardiogram. Ejection fraction was determined from the two-dimensional echocardiography.

Statistical analysis. The data are presented as mean ± SEM. Statistical analysis was performed using paired Student t tests to compare within-group values before and after intervention, and unpaired Student t tests to make between-group comparisons. To determine if the mean delta value (pre/post) was the same in all three groups, one-way analysis of variance was used. In the case of significance, Scheffé’s post-hoc comparison was used to determine differences between groups. A p value of \( p \leq 0.05 \) was considered statistically significant.

RESULTS

Sixteen advanced HF patients and eight healthy volunteers were enrolled in this study. Heart failure patients were older than healthy volunteers (mean age, 53 ± 9 vs. 46 ± 5 years, \( p = 0.03 \)). Characteristics of patients and controls are displayed in Table 1. There were no differences between HF patients randomized to the exercise or sedentary groups in...
Exercise and Sympathetic Decrease in HF

The major new finding in this study is that exercise training results in dramatic reductions in directly recorded resting MSNA in chronic HF patients. In fact, we found that the sympathetic excitation characteristic of HF was reversed by exercise training, and sympathetic nerve activity levels were

any of the parameters measured. Normal controls had higher peak VO$_2$ (p = 0.0001), left ventricular ejection fraction (p = 0.0001), and FBF (p = 0.03), and lower HR (p = 0.04), MSNA (p = 0.001), and FVR (p = 0.01) than HF patients. All HF patients and normal controls completed the study. There were no adverse events. Medications were not altered during the study period.

Compliance. Compliance with the exercise program was excellent, ranging from 85% to 98% of exercise sessions attended for both HF patients and normal controls.

Impact of exercise or sedentary period on physiologic parameters. Peak VO$_2$ and FBF significantly increased (p = 0.02 and p = 0.004, respectively), and FVR significantly decreased (p = 0.002) after exercise training in patients with HF (Table 2). Left ventricular ejection fraction did not change (p = 0.388). No parameters changed in the sedentary HF group. In trained normal control subjects, peak VO$_2$ increased (p = 0.01).

Examples of resting MSNA before and after exercise training are shown in Figure 1. Muscle sympathetic nerve activity as measured by bursts/min or bursts/100 heart beats was uniformly and dramatically decreased (p = 0.006 or p = 0.003, respectively) after training compared with baseline in HF patients (Table 2, Fig. 2) and was no longer greater than in trained, normal controls. In sedentary HF patients and in trained, healthy controls, resting MSNA did not change from baseline (p = 0.777 and p = 0.525, respectively). The mean difference in the change (Scheffé’s post-hoc comparisons) in MSNA was significantly greater in trained HF patients compared with sedentary HF patients (p = 0.01).

**DISCUSSION**

The major new finding in this study is that exercise training results in dramatic reductions in directly recorded resting MSNA in chronic HF patients. In fact, we found that the sympathetic excitation characteristic of HF was reversed by exercise training, and sympathetic nerve activity levels were

### Table 2. Physiologic Parameters Post/Pre-Exercise or Sedentary Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference in the Change</th>
<th>HF Exercise</th>
<th>HF Sedentary</th>
<th>Normal Exercise</th>
<th>HF Exercise</th>
<th>HF Sedentary</th>
<th>Normal Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$ (ml/kg/min)</td>
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<td>14.8 ± 2</td>
<td>16.6 ± 2</td>
<td>27.5 ± 3</td>
<td>20.6 ± 3*</td>
<td>17.5 ± 2</td>
<td>33.3 ± 2*</td>
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<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF exercise</td>
<td></td>
<td>2.6 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>102 ± 3</td>
<td>1.3 ± 0.3*</td>
<td>2.3 ± 0.2</td>
<td>5.8 ± 1†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td>77 ± 3</td>
<td>79 ± 7</td>
<td>67 ± 3</td>
<td>65 ± 3*</td>
<td>76 ± 6</td>
<td>65 ± 3</td>
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<tr>
<td>MAP (mm Hg)</td>
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<td>100 ± 4</td>
<td>98 ± 3</td>
<td>102 ± 3</td>
<td>93 ± 3</td>
<td>99 ± 3</td>
<td>94 ± 3</td>
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<tr>
<td>LVEF (%)</td>
<td></td>
<td>35 ± 3</td>
<td>35 ± 3</td>
<td>73 ± 3</td>
<td>34 ± 2</td>
<td>35 ± 2</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>FBF (ml/min/100 ml tissue)</td>
<td></td>
<td>2.1 ± 0.1</td>
<td>2.6 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>3.0 ± 0.3*</td>
<td>1.7 ± 0.2</td>
<td>0.4 ± 0.4</td>
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<td>FVR (U)</td>
<td></td>
<td>61 ± 4</td>
<td>60 ± 7</td>
<td>40 ± 2</td>
<td>33 ± 2*</td>
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<td>MSNA (bursts/100 heart beats)</td>
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<td>41 ± 4</td>
<td>38 ± 3*</td>
<td>56 ± 2</td>
<td>40 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Within group comparison, p < 0.05; † vs. HF sedentary value (mean difference in the change), p < 0.05; ‡ vs. normal exercise value (mean difference in the change), p < 0.05.

NYHA = New York Heart Association; other abbreviations as in Table 1.

![Table 2](image-url)
no longer different from resting sympathetic nerve activity levels in trained, healthy controls. Muscle sympathetic nerve activity did not change after exercise training in normal controls, consistent with prior reports (25). These findings have important implications for the role of exercise in the treatment of HF.

Exercise training in patients with chronic congestive HF has been shown to improve endothelial function, vasodilation, and muscle blood flow, as well as NYHA functional class (8–11,26). As anticipated, in our study functional class was uniformly improved. Most importantly, central sympathetic neural outflow, measured directly using the technique

Figure 1. Sympathetic neurograms. (A) Heart failure patients, exercise group. Pre-training, muscle sympathetic nerve activity (MSNA) is markedly elevated. Post-exercise training, sympathetic nerve activity levels are reduced. (B) Heart failure patients, sedentary group; MSNA levels are markedly elevated before and after the sedentary period.
of microneurography, was found to be markedly reduced after exercise training. We also found that our exercise paradigm produced an increase in FBF and decrease in FVR after exercise training. This increased resting muscle blood flow may reflect the decline in resting sympathetic activation, but the underlying mechanisms were not investigated, and are beyond the scope of this study.

The mechanisms underlying the sympathetic activation in HF remain unknown. Several hypotheses have been advanced including baroreceptor dysfunction leading to attenuation of tonic inhibition of central sympathetic outflow (27,28). Alternatively, in the “muscle hypothesis,” abnormal skeletal metabolism may lead to increased ischemic metabolite release, thereby increasing muscle ergoreceptor sensitivity and increased central sympathetic outflow (29). Exercise training in patients with HF has been shown to improve the skeletal muscle abnormalities of HF, including reversal of muscle atrophy, increased mitochondrial enzyme content, and improved muscle metabolism (11,30). Although we are unable to identify the exact mechanism of this sympatholytic effect of exercise, we are confident that it is not due to a dramatic, or even modest, improvement in cardiac function because the ejection fraction remained stable throughout the study.

**Study limitations.** We recognize many limitations in this study. Although we found a dramatic reduction in sympathetic nerve activity directed to muscle, it is not feasible to measure sympathetic activity to other organs such as the heart or kidneys. Sympathetic activation to heart, kidney, and MSNA tend to parallel each other in animal models, and are governed by similar control mechanisms, so it is likely that exercise decreased sympathetic excitation to these organs as well. Nonetheless, the clinical relevance of these findings is without question, because MSNA is the largest

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**Figure 2.** Muscle sympathetic nerve activity (MSNA) pre/post exercise/sedentary periods quantified as bursts/min (A) and bursts/100 heart beats (B). Post-exercise training MSNA levels compared with pre-training MSNA levels in heart failure (HF) patients are uniformly and markedly reduced and are no longer higher than normal controls; MSNA remained unchanged in the HF sedentary group and the normal control exercise group.
contribution to serum norepinephrine levels, and it is the serum norepinephrine level that has been linked directly to prognosis in HF (2). In this study we measured resting, not exercising, MSNA. Although resting sympathetic levels have clear prognostic importance (2), we do not know from this study whether exercising MSNA was also reduced after training, thereby potentially contributing to the improvement in exercise tolerance. The exercise paradigm used in this study was rigorous; compliance within the general HF population remains to be assessed. Further studies will be required to investigate the optimal exercise program to optimize compliance without sacrificing the beneficial effects on the autonomic nervous system. Finally, HF patients in this study were not taking beta-adrenergic blockers. Azevedo et al. (31) reported that beta-adrenergic drugs do not alter central sympathetic outflow, so it is unlikely that the addition of beta-blockers would have an adverse effect, and, in fact, these therapies may be complementary.

Conclusions. Exercise training dramatically decreases central sympathetic nerve outflow measured directly. All pharmacologic therapies with beneficial effects on the neurohormonal system in patients with HF have also been shown to reduce mortality. Larger studies empowered to test the effects of exercise on mortality in HF are indicated.

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REFERENCES