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Exercise Training and Heart Failure

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.

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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.

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Abbreviations and Acronyms

FBF = forearm blood flow
FVR = forearm vascular resistance
HF = heart failure
HR = heart rate
MSNA = muscle sympathetic nerve activity
NYHA = New York Heart Association
VO_2 = oxygen uptake

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 $\leq$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 plethysmography (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

Table 1. Baseline Physiologic Parameters

	HF—Exercise N = 7	HF—Sedentary N = 9	Normal Controls N = 8
Gender (M/F)	5/2	6/3	5/3
Weight (kg)	64.6 ± 4.8	61.4 ± 4.3	67.3 ± 3.6
HF etiology			
Coronary artery disease	1	0	
Idiopathic	5	5	
Chagas	1	4	
Medications			
ACEI	7	9	
Digoxin	7	9	
Furosemide	5	5	
Hydrochlorothiazide	2	2	
Spironolactone	3	3	
Beta-adrenergic blocker	0	0	
HF duration (yrs)	3.7 ± 0.3	3.4 ± 1	
Peak VO_2 (ml/kg/min)	14.8 ± 2	16.6 ± 2	27.5 ± 3*
Heart rate (beats/min)	77 ± 3	79 ± 7	67 ± 3*
MAP (mm Hg)	100 ± 4	98 ± 3	102 ± 3
LVEF (%)	35 ± 3	35 ± 3	73 ± 3*
MSNA (bursts/min)	46 ± 3	44 ± 4	27 ± 3*
(bursts/100 heart beats)	60 ± 3	56 ± 3	41 ± 4*
FBF (ml/min/100 ml tissue)	1.7 ± 0.2	2.1 ± 0.1	2.6 ± 0.2*
FVR (U)	61 ± 4	47 ± 7	40 ± 2*

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; VO_2 = oxygen uptake.

(ml/min/100 ml tissue) was determined on the basis of a minimum of four separate readings. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure by FBF. The reproducibility of FBF measured at different time intervals in the same individual expressed as ml/min/100 ml tissue in our laboratory is r = 0.93.

Cardiopulmonary exercise testing. Maximal exercise capacity was determined by means of a maximal progressive exercise test on an electromagnetically braked cycle ergometer (Medifit 400L, Medical Fitness Equipment, Maarn, Netherlands), with work rate increments of 15W and 30W every 3 min at 60 rpm until exhaustion for HF patients and normal controls, respectively. Oxygen uptake (VO_2) and carbon dioxide production were determined by means of gas exchange on a breath-by-breath basis in a computerized system (CAD/Net 2001, Medical Graphics Corporation, St. Paul, Minnesota). Peak VO_2 was defined as the maximum attained VO_2 at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm. This method is considered the gold standard for assessing patients' exercise capacity (21). Anaerobic threshold was determined to occur at the breakpoint between the increase in the carbon dioxide output and VO_2 (V-slope) (22) or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise (23). 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 and begins to decrease (24). The reproducibility of the peak VO_2 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 ≤ 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

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

	Pre	Post	Mean Difference in the Change
Peak VO_2 (ml/kg/min)			
HF exercise	14.8 ± 2	20.6 ± 3*	5.8 ± 2†
HF sedentary	16.6 ± 2	17.5 ± 2	0.9 ± 1
Normal exercise	27.5 ± 3	33.3 ± 2*	5.8 ± 1†
NYHA functional class			
HF exercise	2.6 ± 0.2	1.3 ± 0.3*	(−)1.3 ± 0.2†
HF sedentary	2.5 ± 0.2	2.3 ± 0.2	(−)0.3 ± 0.2
Heart rate (beats/min)			
HF exercise	77 ± 3	65 ± 3*	(−)12 ± 5
HF sedentary	79 ± 7	76 ± 6	(−)3 ± 4
Normal exercise	67 ± 3	65 ± 3	(−)2 ± 2
MAP (mm Hg)			
HF exercise	100 ± 4	93 ± 3	(−)7 ± 3
HF sedentary	98 ± 3	99 ± 3	1 ± 4
Normal exercise	102 ± 3	94 ± 3	(−)7 ± 2
LVEF (%)			
HF exercise	35 ± 3	34 ± 2	2.4 ± 2
HF sedentary	35 ± 3	35 ± 2	(−)0.1 ± 2
Normal exercise	73 ± 3	73 ± 3	0 ± 1
FBF (ml/min/100 ml tissue)			
HF exercise	1.7 ± 0.2	3.0 ± 0.3*	1.3 ± 0.4†
HF sedentary	2.1 ± 0.1	1.7 ± 0.2	(−)0.4 ± 0.3
Normal exercise	2.6 ± 0.2	3.0 ± 0.2	0.4 ± 0.4
FVR (U)			
HF exercise	61 ± 4	33 ± 2*	(−)27 ± 6†
HF sedentary	47 ± 7	60 ± 7	13 ± 7
Normal exercise	40 ± 2	32 ± 2	(−)8 ± 3
MSNA (bursts/min)			
HF exercise	46 ± 3	24 ± 1*	(−)21 ± 4†‡
HF sedentary	44 ± 4	43 ± 3	(−)1 ± 1
Normal exercise	27 ± 3	26 ± 1	(−)2 ± 1
MSNA (bursts/100 heart beats)			
HF exercise	60 ± 3	38 ± 3*	(−)23 ± 3†‡
HF sedentary	56 ± 3	56 ± 2	(−)2 ± 2
Normal exercise	41 ± 4	40 ± 3	(−)1 ± 2

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.

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

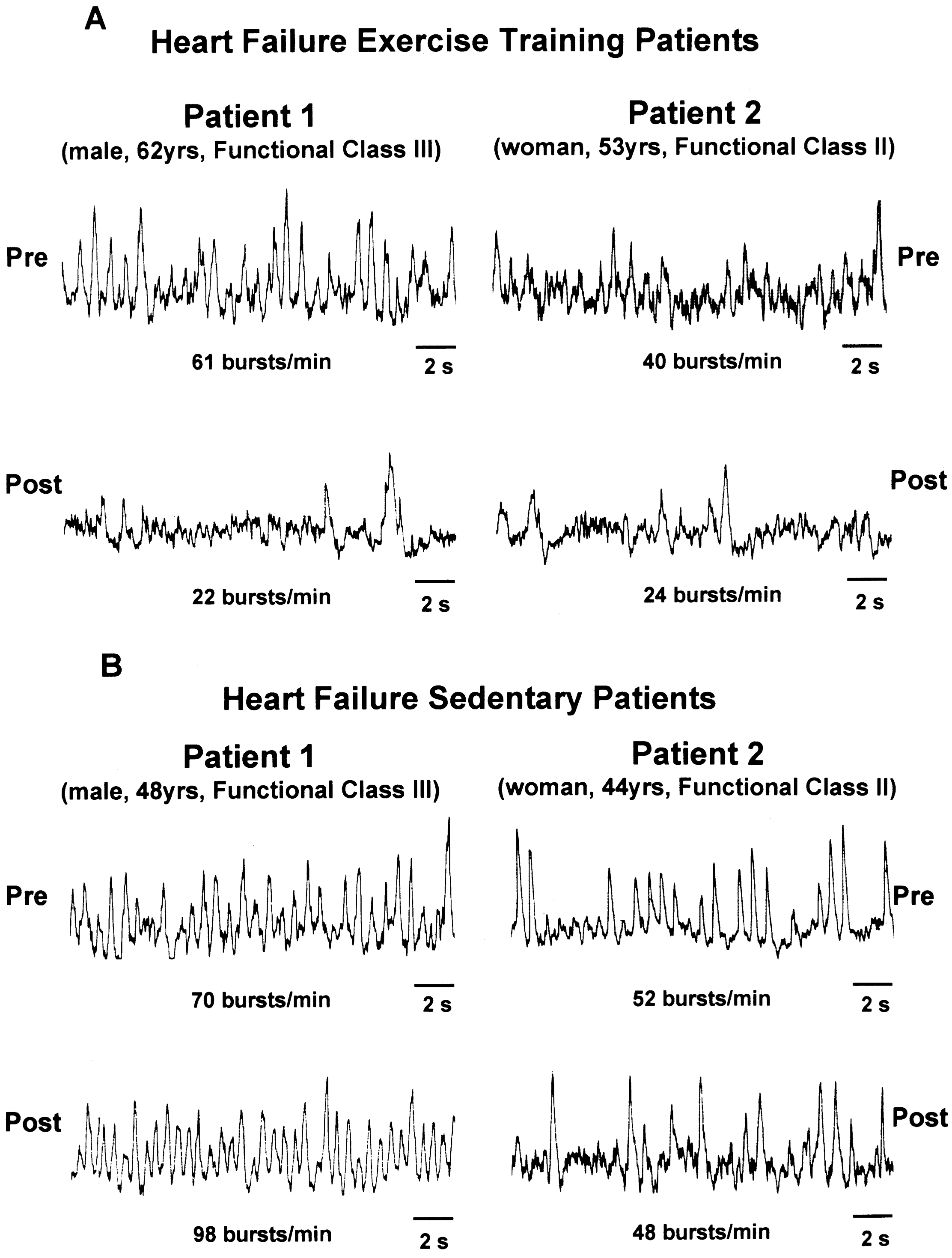

Figure 1. Sympathetic neurograms. **(A)** Heart failure patients, exercise group. Pre-training, muscle sympathetic nerve activity (MSNA) is markedly elevated. Post-exercise training, sympathetic nerve activity levels are reduced. **(B)** Heart failure patients, sedentary group; MSNA levels are markedly elevated before and after the sedentary period.

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

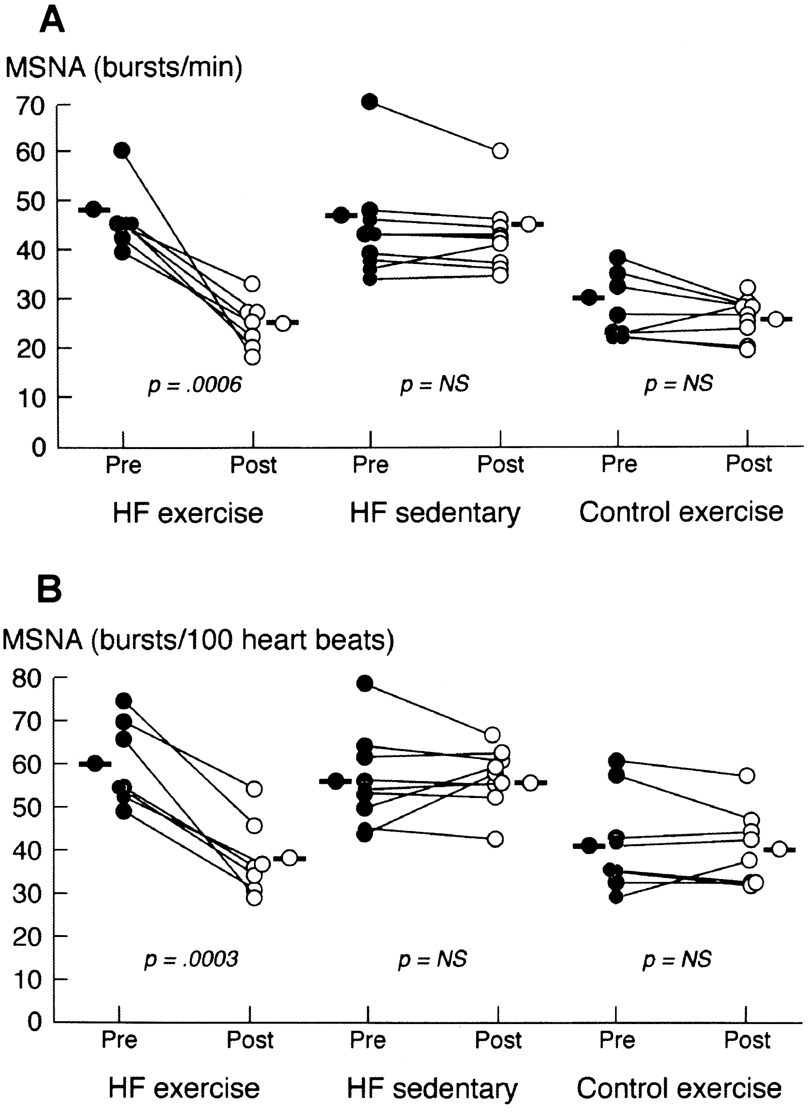

Figure 2. Muscle sympathetic nerve activity (MSNA) pre/post exercise/sedentary periods quantified as bursts/min **(A)** and bursts/100 heart beats **(B)**. Post-exercise training MSNA levels compared with pre-training MSNA levels in heart failure (HF) patients are uniformly and markedly reduced and are no longer higher than normal controls; MSNA remained unchanged in the HF sedentary group and the normal control exercise group.

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 contributor 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 neurohumoral 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

1. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies Of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724–9.
2. Cohn JN, Levine B, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
3. Middlekauff HR, Mark AL. The treatment of heart failure: the role of neurohumoral activation. Int Med 1998;37:112–22.
4. Task Force on Practice Guidelines. Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. J Am Coll Cardiol 2001;38:2101–13.
5. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
6. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
7. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.
8. Keteyian SJ, Levine AB, Brawner CA, et al. Exercise training in patients with heart failure: a randomized controlled trial. Ann Intern Med 1996;124:1051–7.
9. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173–82.
10. Tyni-Lenne R, Gordon A, Europe E, Jansson E, Sylven C. Exercise-based rehabilitation improves skeletal muscle capacity, exercise tolerance, and quality of life in both women and men with chronic heart failure. J Cardiac Fail 1998;4:9–17.
11. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation 1988;78:506–15.
12. Gordon A, Tyni-Lenne R, Jansson E, Kaijser L, Theodorsson-Norheim E, Sylven C. Improved ventilation and decreased sympathetic stress in chronic heart failure patients following local endurance training with leg muscles. J Cardiac Fail 1997;3:3–12.
13. Kilavuori K, Toivonen L, Naveri H, Leinonen H. Reversal of autonomic derangement's by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J 1995;16:490–5.
14. Coats AJS, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992;85:2119–31.
15. Adamopoulos S, Ponikowski P, Cerquetani E, et al. Circadian pattern of heart rate variability in chronic heart failure patients: effects of physical training. Eur Heart J 1995;16:1380–6.
16. Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma norepinephrine response to exercise in patients with congestive heart failure. N Engl J Med 1962;267:650–4.
17. Middlekauff HR, Nitzsche EU, Hoh CK, et al. Exaggerated renal vasoconstriction during exercise in heart failure patients. Circulation 2000;101:784–9.
18. Delius W, Hagbarth KE, Hongell A, Wallin BG. Maneuvers affecting sympathetic outflow in human muscle nerves. Acta Physiol Scand 1972;84:82–94.
19. Vallbo AB, Hagbarth KE, Torebjork HE, Wallin BG. Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. Physiol Rev 1979;59:919–57.
20. Fagius J, Wallin BG. Long-term variability and reproducibility of human muscle nerve activity at rest, as reassessed after a decade. Clin Auton Res 1993;3:201–5.
21. Cohen-Solal A. Cardiopulmonary exercise testing in chronic heart failure. In: Wasserman K, editor. Exercise Gas Exchange in Heart Disease. Armonk, NY: Futura Publishing Company, 1996:17–38.
22. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
23. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 1973;33:236–43.
24. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. In: Wasserman K, Hansen JE, Sue DY, Whipp BJ, editors. Measurement of the Physiological Response to Exercise. Philadelphia, PA: Lea & Febiger, 1987:27–46.
25. Svedenhag J, Wallin BG, Sundlof G, Henriksson J. Skeletal muscle sympathetic activity at rest in trained and untrained subjects. Acta Physiol Scand 1984;120:499–504.
26. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;6:1239–49.
27. Ferguson DW, Berg WJ, Roach PJ, Oren RM, Mark AL. Effects of heart failure on baroreflex control of sympathetic neural activity. Am J Cardiol 1992;69:523–31.
28. Floras JS. Arterial baroreceptor and cardiopulmonary reflex control of sympathetic outflow in human heart failure. Ann NY Acad Sci 2001;940:500–13.
29. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. Circulation 1996;93:940–52.
30. Belardinelli R, Georgiou D, Scocco V, Barstow TJ, Purcaro A. Low intensity exercise training in patients with chronic heart failure. J Am Coll Cardiol 1995;26:975–82.
31. Azevedo ER, Kubo T, Mak S, et al. Nonselective versus selective beta-adrenergic receptor blockade in congestive heart failure: differential effects on sympathetic activity. Circulation 2001;104:2194–9.