

# Effects of Exercise Training on Left Ventricular Function and Peripheral Resistance in Patients With Chronic Heart Failure

## A Randomized Trial

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UNTIL RECENTLY, EXERCISE INTOLERANCE among patients with chronic heart failure was regarded as a warning symptom precluding any strenuous physical activity to avert cardiac decompensation. During the last decade, however, it has become appreciated that this approach accelerates physical deconditioning and may worsen heart failure symptoms. Carefully designed endurance training programs can improve functional work capacity in patients with chronic heart failure.<sup>1-8</sup> Training benefits have been attributed in particular to peripheral adaptations, including enhanced oxidative capacity of the working skeletal muscle<sup>3,4,9</sup> and correction of endothelial dysfunction in the skeletal muscle vasculature.<sup>10-12</sup>

However, concerns have been raised that these peripheral adaptations in response to short-term exercise training may worsen left ventricular (LV) dimensions, contractile function, or both. Exercise training initiated early following an anterior Q-wave myocardial in-

**Context** Exercise training in patients with chronic heart failure improves work capacity by enhancing endothelial function and skeletal muscle aerobic metabolism, but effects on central hemodynamic function are not well established.

**Objective** To evaluate the effects of exercise training on left ventricular (LV) function and hemodynamic response to exercise in patients with stable chronic heart failure.

**Design** Prospective randomized trial conducted in 1994-1999.

**Setting** University department of cardiology/outpatient clinic in Germany.

**Patients** Consecutive sample of 73 men aged 70 years or younger with chronic heart failure (with LV ejection fraction of approximately 0.27).

**Intervention** Patients were randomly assigned to 2 weeks of in-hospital ergometer exercise for 10 minutes 4 to 6 times per day, followed by 6 months of home-based ergometer exercise training for 20 minutes per day at 70% of peak oxygen uptake (n=36) or to no intervention (control group; n=37).

**Main Outcome Measures** Ergospirometry with measurement of central hemodynamics by thermodilution at rest and during exercise; echocardiographic determination of LV diameters and volumes, at baseline and 6-month follow-up, for the exercise training vs control groups.

**Results** After 6 months, patients in the exercise training group had statistically significant improvements compared with controls in New York Heart Association functional class, maximal ventilation, exercise time, and exercise capacity as well as decreased resting heart rate and increased stroke volume at rest. In the exercise training group, an increase from baseline to 6-month follow-up was observed in mean (SD) resting LV ejection fraction (0.30 [0.08] vs 0.35 [0.09];  $P=.003$ ). Mean (SD) total peripheral resistance (TPR) during peak exercise was reduced by 157 (306) dyne/s/cm<sup>-5</sup> in the exercise training group vs an increase of 43 (148) dyne/s/cm<sup>-5</sup> in the control group ( $P=.003$ ), with a concomitant increase in mean (SD) stroke volume of 14 (22) mL vs 1 (19) mL in the control group ( $P=.03$ ). There was a small but significant reduction in mean (SD) LV end diastolic diameter of 4 (6) mm vs an increase of 1 (4) mm in the control group ( $P<.001$ ). Changes from baseline in resting TPR for both groups were correlated with changes in stroke volume ( $r=-0.76$ ;  $P<.001$ ) and in LV end diastolic diameter ( $r=0.45$ ;  $P<.001$ ).

**Conclusions** In patients with stable chronic heart failure, exercise training is associated with reduction of peripheral resistance and results in small but significant improvements in stroke volume and reduction in cardiomegaly.

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fraction reportedly leads to a deterioration in both global and regional function in patients with significant LV asynergy at baseline.<sup>13</sup> In this study, we investigated the influence of a long-term, ambulatory exercise training program involving patients with chronic heart failure on total peripheral resistance (TPR) at rest and during exercise, LV diameter, and stroke volume.

## METHODS

### Subjects

Seventy-three men aged 70 years or younger with chronic heart failure who were referred to the Leipzig Heart Center, Leipzig, Germany, for further diagnosis during 1994-1999 were enrolled in this trial if they met the following inclusion criteria: (1) documented heart failure by signs, symptoms, and angiographic evidence of reduced LV function (LV ejection fraction [LVEF] <0.40) as a result of dilated cardiomyopathy or ischemic heart disease; (2) physical work capacity at baseline greater than 25 W; and (3) clinical stability for at least 3 months before entry into the study.

Exclusion criteria were significant valvular heart disease, uncontrolled hypertension, diabetes mellitus, hypercholesterolemia ( $\geq 6$  mmol/L [232 mg/dL]), peripheral vascular disease, pulmonary disease, or musculoskeletal abnormalities precluding exercise training. All studies were performed according to a research protocol approved by the University of Leipzig Ethics Committee and all patients provided written informed consent before entry into the study.

### Intervention

Patients were randomly assigned to either a training group or an inactive control group using a list of random numbers. Both groups underwent invasive cardiopulmonary exercise testing and echocardiography at baseline and at 6-month follow-up.

To ensure close supervision, the initial phase of the exercise program was performed on an in-hospital basis. During the first 2 weeks, patients exer-

cised 4 to 6 times daily for 10 minutes using a bicycle ergometer. Workloads were adjusted so that 70% of the symptom-limited maximum oxygen uptake was reached. Before discharge from the hospital, peak symptom-limited ergospirometry was performed to calculate training target heart rate for home training, which was defined as the heart rate reached at 70% of the maximum oxygen uptake during symptom-limited exercise. On discharge from the hospital, patients were provided with bicycle ergometers for daily home exercise training. Patients were asked to exercise close to their target heart rate daily for 20 minutes every day for 6 months. In addition, they were expected to participate in at least 1 group training session of 60 minutes each week. Group sessions consisted of walking, calisthenics, and ball games.

Patients assigned to the control group continued their individually tailored cardiac medications and were supervised by their physicians. All examinations including exercise testing were repeated at 6-month follow-up.

### Assessments

**Cardiopulmonary Exercise Testing and Variables.** Prior to baseline measurements, all patients underwent a peak exercise test and participated in 1 group training session with 24-hour Holter monitoring to familiarize them with the examinations and to detect exercise-induced ventricular tachyarrhythmias.

Two days later, a catheter (Swan-Ganz 93A-131-7F, Edwards Laboratories, Santa Ana, Calif) was introduced into the right pulmonary artery through the right antecubital vein. Following a resting period of 30 minutes, exercise testing was performed on a calibrated, electronically braked bicycle in an upright position. Workload was increased progressively every 3 minutes in steps of 25 W beginning at 25 W. Exercise was terminated when patients were physically exhausted or developed severe dyspnea or dizziness. Hemodynamic and gas exchange measurements as well as blood samples were

simultaneously obtained at rest and at the end of each workload during bicycle exercise. Heart rate was measured by continuous electrocardiographic monitoring.

Cardiac output was obtained using a thermodilution catheter that was interfaced to a cardiac output computer (COM-2, Edwards Laboratories). Three measurements of cardiac output were made at rest and at the end of each workload. Stroke volume was calculated by dividing cardiac output by heart rate. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output and is expressed in  $\text{dyne/s/cm}^{-5}$ . Free and conjugated plasma catecholamine levels were analyzed by high-pressure liquid chromatography with amperometric detection as described by Weicker.<sup>14</sup>

Respiratory gas exchange data were determined continuously throughout the exercise test using a commercially available system (Oxycon Alpha, Erich Jaeger, Höchberg, Germany). The ventilatory threshold was defined as described elsewhere.<sup>15</sup>

**Echocardiography.** All patients underwent a complete resting echocardiographic study at both the initial and the final evaluations. Examinations were videotaped with a long apical 4-chamber view sequence for final analysis. End systolic and end diastolic diameters of the left ventricle were determined in the parasternal long axis. Three consecutive cardiac cycles were analyzed on an HP Sonos 5500 echocardiography system (Hewlett-Packard Inc, Andover, Mass) and averaged for each patient by an experienced cardiologist blinded to patient status and assignment. Left ventricular volume and LVEF were calculated in the apical 4-chamber view using the disk method.<sup>16</sup>

**Assessment of Lower-Limb Endothelial Function.** In a subgroup of 18 patients, endothelial function in the superficial femoral artery was assessed at baseline and 6-month follow-up as previously described.<sup>12</sup> Briefly, a 7F multipurpose catheter was advanced into the left superficial femoral artery through a 0.038-in arterial sheath in-

serted into the right femoral artery. Superficial femoral artery blood flow velocity was determined with a 0.018-in Doppler guide wire containing a 12-MHz pulsed Doppler ultrasonographic crystal at its tip (FlowMAP, Cardiometrics Inc, Mountain View, Calif). Serial angiography in the same projection (anterior-posterior view) was performed at the end of each infusion. Endothelial function was assessed at baseline (after 0.9% saline infusion for 5 minutes; after increasing doses of acetylcholine (30, 60, and 90  $\mu\text{g}/\text{min}$ ); after  $\text{N}^G$ -monomethyl-L-arginine infusion (20 nmol/min); and after a bolus injection of 0.5 mg of nitroglycerin. Because 1 of the previously described 18 patients refused invasive hemodynamic measurements, this subgroup analysis in the present study includes 17 patients.<sup>12</sup>

### Statistical Analysis

All variables were calculated as mean (SD). Data were tested for normal distribution using the Kolmogorov-Smirnov test and for homogeneity of variances with the Levene test. Both intragroup and intergroup comparisons were made using 2-way repeated-measures analysis of variance followed by the Tukey post hoc test (SigmaStat 2.0.3 for Windows, SPSS Inc, Chicago, Ill). New York Heart Association functional class distribution was compared using the  $\chi^2$  test. A *P* value of less than .05 was considered statistically significant.

Linear regression analysis was used to determine the relationship between changes in peripheral vascular resistance and changes in stroke volume and end diastolic diameter as well as to assess the effect of changes in endothelial function and sympathetic drive on changes in peripheral vascular resistance.

Sample size calculation was based on the results of a pilot study with the same study protocol involving 10 patients with chronic heart failure. In this patient population, exercise training resulted in a reduction of TPR at peak exercise from a mean (SD) of 739 (410)

to 575 (188) dyne/s/cm<sup>-5</sup>. To detect a difference of 160 dyne/s/cm<sup>-5</sup> between groups at peak exercise after the intervention at 90% power with a 2-sided parametric test, a minimum sample size of approximately 70 patients was calculated.

## RESULTS

### Baseline Characteristics

No significant differences were observed between the 2 groups with regard to demographic or clinical data, including age, weight, LVEF, LV end diastolic diameter, New York Heart Association functional class, or maximum oxygen uptake. Drug treatment was not changed during the last 4 weeks before the study or during the study in any patient (excluding temporary medication changes during hospitalization) (TABLE 1).

### Dropouts and Clinical Events

In the exercise training group, 3 patients (LVEF, 0.21 [0.04]; maximum oxygen uptake [ $\text{O}_2\text{max}$ ], 17.8 [3.0] mL/kg/min) died of sudden cardiac death unrelated to exercise during the study period. These patients were compa-

rable with the other randomized patients with respect to duration of disease and hemodynamic parameters. After baseline testing, 1 patient was excluded from further analysis because of atrioventricular node reentrant tachycardia. One patient in clinically stable condition (LVEF, 0.38;  $\text{O}_2\text{max}$ , 20.8 mL/kg/min) withdrew consent after the baseline examination. Data for the remaining 31 patients were used for subsequent analyses. Two patients in clinically stable condition (LVEF, 0.31 [0.06];  $\text{O}_2\text{max}$ , 22.6 [3.3] mL/kg/min) refused right heart catheterization during the follow-up examination; therefore, data from invasive measurements are complete in 29 patients (FIGURE 1). During the study period, 2 patients (LVEF, 0.19 [0.08];  $\text{O}_2\text{max}$ , 16.5 [2.3] mL/kg/min) were admitted to the hospital because of temporarily worsening symptoms. These patients continued the training program after discharge.

In the control group, 2 patients died of sudden cardiac death during the study (LVEF, 0.13 [0.10];  $\text{O}_2\text{max}$ , 15.5 [2.0] mL/kg/min). An additional 2 patients withdrew consent after baseline

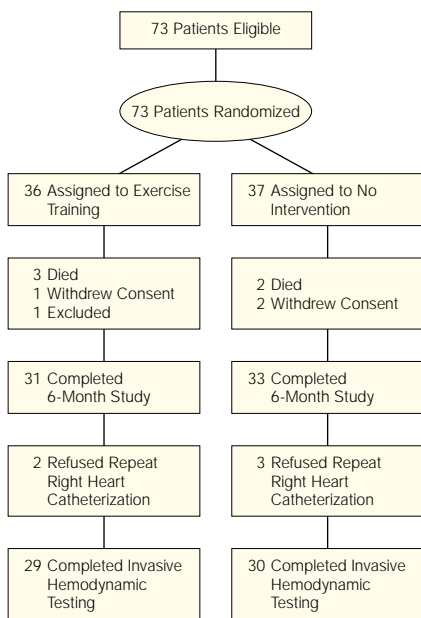
**Table 1.** Patient Clinical Characteristics

Characteristics	Exercise Training Group		Control Group	
	Baseline (n = 36)	6-Month Follow-up (n = 31)	Baseline (n = 37)	6-Month Follow-up (n = 33)
Age, mean (SD), y	54 (9)	54 (9)	55 (8)	54 (8)
Weight, mean (SD), kg	80.8 (13.0)	82 (12)	81.7 (12.7)	83.4 (11.4)
LVEF, mean (SD)	0.27 (0.09)	0.27 (0.09)	0.27 (0.09)	0.28 (0.09)
LV-EDD, mean (SD), mm	70 (10)	69 (10)	65 (9)	65 (9)
Dilated cardiomyopathy, No.	31	29	30	26
Ischemic heart disease, No.	5	2	7	7
$\dot{V}\text{O}_2\text{max}$ , mean (SD), mL/kg/min	18.2 (3.7)	18.2 (3.9)	17.7 (4.3)	17.7 (4.5)
NYHA functional class, No.				
I and II	26	30	28	25
III	10	1	9	8
Medications, No. (%)				
ACE inhibitors	34 (94)	29 (94)	35 (95)	31 (94)
Digoxin	26 (76)	22 (71)	23 (62)	21 (64)
Diuretics	28 (78)	24 (77)	29 (78)	28 (85)
Calcium channel blocker	6 (17)	5 (16)	2 (14)	2 (6)
$\beta$ -Blocker	3 (8)	3 (10)	6 (13)	6 (18)
Antiarrhythmic agents	2 (6)	2 (6)	3 (8)	1 (3)

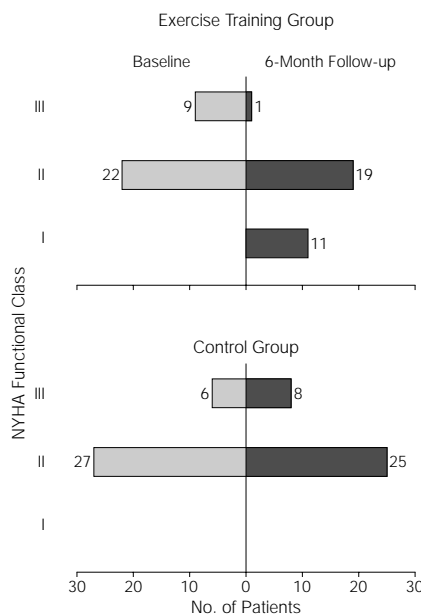
\*LVEF indicates left ventricular ejection fraction (assessed by angiography); LV-EDD, left ventricular end diastolic diameter (assessed by echocardiography);  $\dot{V}\text{O}_2\text{max}$ , maximum oxygen uptake (during peak exercise); NYHA, New York Heart Association; and ACE, angiotensin-converting enzyme.

examinations (LVEF, 0.23 [0.10]; O<sub>2</sub>max, 19.3 [0.6] mL/kg/min). Six-month follow-up examinations were

**Figure 1.** Patient Randomization and Study Withdrawals



**Figure 2.** New York Heart Association (NYHA) Functional Class



*P* < .001 for exercise training group vs control group at 6-month follow-up.

obtained for the remaining 33 patients. Invasive measurements (right heart catheterization) during follow-up were refused by 3 patients who were in clinically stable condition (LVEF, 0.16 [0.05]; O<sub>2</sub>max, 22.7 [12.0] mL/kg/min). Therefore, complete follow-up, including invasive data, was available for 30 patients (Figure 1). One patient had right heart failure during the study period and was readmitted to the hospital for an additional 2 weeks. Another patient was hospitalized because of temporarily worsening dyspnea. Both of these patients (LVEF, 0.22 [0.06]; O<sub>2</sub>max, 11.7 [0.6] mL/kg/min) continued the study after hospital discharge and complete 6-month follow-up measurements were obtained.

**Compliance With the Exercise Training Program**

In the exercise training group, attendance for the group training sessions was 60% (5%). Based on this result, the compliance for home training was estimated to be 60%, amounting to an average of approximately 20 minutes of subpeak exercise training per day.

**Exercise Capacity and Maximum Oxygen Uptake**

Improved New York Heart Association functional class was observed in the exercise training group but not in the control group (*P* < .001; FIGURE 2).

In the exercise training group, oxygen uptake at the ventilatory threshold increased by 3.4 (4.0) mL/kg/min, whereas it decreased by 0.4 (2.6) mL/kg/min in the control group (*P* < .001). During peak exercise, oxygen uptake increased by 4.8 (3.7) mL/kg/min vs an increase of 0.3 (2.8) mL/kg/min in the control group (*P* < .001) (TABLE 2). Concomitant significant increases in maximum ventilation, exercise time, and exercise capacity were observed in the exercise training group. In control patients, oxygen uptake at the ventilatory threshold and at peak exercise, as well as exercise time, and exercise capacity, remained unchanged. Exercise time to ventilatory threshold increased significantly in the exercise

training group from 296 (150) seconds to 454 (295) seconds, whereas it decreased in the control group from 319 (146) seconds to 301 (132) seconds (exercise training vs control group, *P* < .001).

**Central Hemodynamics**

After 6 months, resting heart rate in the exercise training group decreased by 9 (13) beats/min vs by 3 (11) beats/min in the control group (*P* = .04). Heart rate at peak exercise increased by 6 (12) beats/min in the exercise training group vs decreasing by 5 (14) beats/min in the control group (*P* = .001). In both groups, no changes were observed with respect to arterial blood pressure at rest. Exercise training led to a significant increase in resting stroke volume (+13 [19] mL vs -2 [16] mL in the control group; *P* = .002) and at peak exercise (+14 [22] mL vs +1 [19] mL in the control group; *P* = .03) (TABLE 3). In the exercise training group, 6-month changes in stroke volume during subpeak exercise did not reach statistical significance (89 [36] mL vs 98 [45] mL at 75 W; *P* = .07).

There was a trend toward an increase in resting cardiac output, from 4.9 (1.4) L/min to 5.2 (1.3) L/min (*P* = .14 vs baseline), whereas cardiac output during subpeak exercise remained essentially unchanged because the increase in stroke volume was offset by a concomitant decrease in heart rate. As a result of improved stroke volume and increased heart rate in the exercise training group, maximum cardiac output was enhanced significantly by 2.7 (3.3) L/min vs -0.3 (2.6) L/min in the control group (*P* < .001).

There were no significant changes observed in the control group with regard to heart rate, stroke volume, or cardiac output at rest and during exercise. Mean pulmonary artery pressure at rest and in response to exercise remained unchanged at 6-month follow-up compared with baseline in both groups.

**Echocardiographic Parameters**

After 6 months of exercise training, LV end diastolic diameters was signifi-

cantly decreased by 3 (6) mm vs an increase of 1 (4) mm in the control group ( $P < .001$ ) and LV end systolic diameter was decreased by 5 (7) mm vs an increase of 1 (6) mm in the control group ( $P < .001$ ), respectively. Decreases in LV diameters were accompanied by a significant reduction in LV end diastolic and end systolic volumes by 22 (53) mL vs an increase of 11 (41) mL in the control group ( $P = .008$ ) and by 24 (36) mL vs an increase of 1 (40) mL in the control group ( $P = .009$ ), respectively. Resting LVEF in the exercise training group improved from 0.30 (0.08) at baseline to 0.35 (0.09) at 6-month follow-up ( $P = .003$ ) (TABLE 4). Left ventricular end diastolic and end systolic diameters remained essentially unchanged at 6-month follow-up in the control group.

### Total Peripheral Resistance

Exercise training led to a significant decrease in resting TPR by 126 (485) dyne/cm<sup>-5</sup> vs an increase of 120 (433) dyne/cm<sup>-5</sup> in the control group ( $P = .04$ ). During peak exercise, TPR decreased by 158 (306) dyne/cm<sup>-5</sup> in the exercise training group vs an increase of 43 (148) dyne/cm<sup>-5</sup> in the control group ( $P = .003$ ) (Table 3 and FIGURE 3). During subpeak exercise in the exercise training group, TPR was not significantly changed for the 6-month follow-up (841 [317] dyne/cm<sup>-5</sup> vs 832 [311] dyne/cm<sup>-5</sup> at 75 W;  $P = .88$ ). No differences between baseline and follow-up tests were observed among control patients with regard to TPR at rest and during exercise.

### TPR and LV Function

Changes in TPR at rest and during peak exercise were inversely correlated with changes in stroke volume at rest ( $r = -0.76$ ;  $P < .001$ ) and during peak exercise ( $r = -0.60$ ;  $P < .001$ ). The change in resting TPR was also significantly related to changes in LV end diastolic diameter ( $r = 0.45$ ;  $P < .001$ ).

### TPR and Endothelium-Dependent Peripheral Blood Flow

Exercise training improved agonist-mediated endothelium-dependent va-

sodilation of the skeletal muscle vasculature as assessed in a subgroup of patients with chronic heart failure, as reported previously.<sup>12</sup> In the present study, changes in acetylcholine-induced blood flow of the lower limb were significantly correlated with changes in TPR at peak exercise ( $r = -0.53$ ;  $P = .03$ ). However, no correlation was found between N<sup>G</sup>-monomethyl-L-arginine–

induced changes in peripheral blood flow and changes in resting TPR ( $r = 0.25$ ;  $P = .38$ ).

### Plasma Catecholamines

In the exercise training group, resting plasma epinephrine levels decreased significantly by 0.13 (0.28) nmol/L vs an increase of 0.03 (0.28) nmol/L in the control group ( $P = .03$ ). In the exercise

**Table 2.** Exercise and Gas Exchange Data\*

	Exercise Training Group (n = 31)			Control Group (n = 33)		
	Baseline	6-Month Follow-up	P Value†	Baseline	6-Month Follow-up	P Value‡
$\dot{V}O_2$ -VT, mL/kg/min	10.4 (3.4)	13.8 (4.9)	.002	11.4 (2.7)	11.0 (2.6)	<.001
$\dot{V}O_2$ max, mL/kg/min	18.2 (3.9)	23.0 (4.7)	<.001	17.8 (4.5)	18.1 (4.1)	<.001
$\dot{V}E$ max, L/min	60.7 (14.7)	75.8 (15.9)	<.001	62.6 (19.7)	60.9 (13.5)	<.001
Maximum RER	1.08 (0.14)	1.07 (0.15)	.45	1.09 (0.18)	1.05 (0.16)	.49
Exercise time, s	732 (206)	969 (277)	<.001	728 (229)	718 (211)	<.001

\*Data are mean (SD).  $\dot{V}O_2$ -VT indicates oxygen uptake at ventilatory threshold;  $\dot{V}O_2$ max, maximum oxygen uptake (during peak exercise);  $\dot{V}E$ max, maximum expired volume per minute; and maximum RER, respiratory exchange ratio during peak exercise.

†P values for comparison of 6-month follow-up data in exercise training vs control groups.

‡P values for comparison of change from baseline data in exercise training vs control groups.

**Table 3.** Hemodynamic Data\*

	Exercise Training Group (n = 29)			Control Group (n = 30)		
	Baseline	6-Month Follow-up	P Value†	Baseline	6-Month Follow-up	P Value‡
<b>At rest</b>						
Heart rate, beats/min	89 (16)	80 (17)	.04	91 (16)	88 (15)	.04
Arterial pressure, mm Hg	91 (12)	91 (11)	.03	95 (14)	98 (12)	.31
Cardiac output, L/min	4.9 (1.4)	5.2 (1.3)	.35	5.2 (1.4)	4.9 (1.0)	.08
Stroke volume, mL	56 (18)	69 (24)	.02	59 (19)	57 (14)	.002
Pulmonary artery pressure, mm Hg	21 (9)	18 (6)	.18	20 (11)	21 (10)	.03
Pulmonary vascular resistance, dyne/cm <sup>-5</sup>	397 (219)	304 (131)	.17	333 (228)	381 (232)	.01
Total peripheral resistance, dyne/cm <sup>-5</sup>	1612 (445)	1486 (390)	.07	1551 (386)	1671 (334)	.04
<b>During peak exercise</b>						
Heart rate, beats/min	154 (22)	160 (24)	.08	155 (22)	150 (23)	.001
Arterial pressure, mm Hg	115 (17)	117 (15)	.63	119 (19)	119 (14)	.53
Cardiac output, L/min	14.4 (6.2)	17.1 (6.1)	.04	14.2 (4.9)	13.9 (5.1)	<.001
Stroke volume, mL	95 (46)	109 (42)	.24	94 (35)	95 (41)	.03
Pulmonary artery pressure, mm Hg	46 (13)	44 (12)	.51	41 (14)	42 (15)	.37
Pulmonary vascular resistance, dyne/cm <sup>-5</sup>	350 (244)	266 (183)	.52	281 (191)	303 (219)	.02
Total peripheral resistance, dyne/cm <sup>-5</sup>	770 (373)	612 (219)	.03	751 (265)	794 (320)	.003

\*Data are mean (SD).

†P values for comparison of 6-month follow-up data in exercise training vs control groups.

‡P values for comparison of change from baseline data in exercise training vs control groups.

**Table 4.** Echocardiographic Data\*

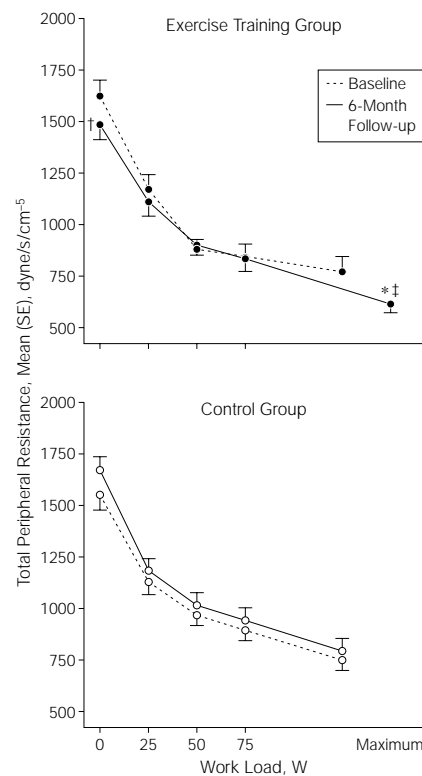
	Exercise Training Group (n = 31)		P Value†	Control Group (n = 33)		P Value‡
	Baseline	6-Month Follow-up		Baseline	6-Month Follow-up	
LV-EDD, mm	69 (10)	66 (10)	.78	65 (9)	66 (9)	<.001
LV-ESD, mm	60 (10)	55 (10)	.54	55 (9)	56 (9)	<.001
LV-EDV, mL	229 (75)	207 (85)	.55	207 (66)	218 (68)	.008
LV-ESV, mL	161 (65)	137 (66)	.46	147 (56)	148 (56)	.009
LVEF	0.30 (0.08)	0.35 (0.09)	.43	0.30 (0.09)	0.33 (0.09)	.47

\*Data are mean (SD). LV-EDD indicates left ventricular end diastolic diameter; LV-ESD, left ventricular end systolic diameter; LV-EDV, left ventricular end diastolic volume; LV-ESV, left ventricular end systolic volume; and LVEF, left ventricular ejection fraction.

†P values for comparison of 6-month follow-up data in exercise training vs control groups.

‡P values for comparison of change from baseline data in exercise training vs control groups.

**Figure 3.** Total Peripheral Resistance at Different Workloads During Ergospirometry



Data are for ergospirometry performed at baseline and 6-month follow-up. Asterisk indicates  $P = .03$  vs control group; dagger,  $P = .04$  for change from baseline vs control group; and double dagger,  $P = .003$  for change from baseline vs control group.

training group at 6-month follow-up, there was a trend toward decreased plasma norepinephrine levels at rest (2.9 [2.8] nmol/L at baseline vs 2.0 [1.3] nmol/L at 6-month follow-up) and during subpeak exercise (8.5 [4.7] nmol/L

at baseline vs 7.0 [4.4] nmol/L at 6-month follow-up). Changes in epinephrine and norepinephrine were not significantly correlated with changes in TPR. In the control group, there was no change in plasma catecholamine levels over time, either at rest or during exercise.

**COMMENT**

In this randomized trial, we evaluated the effects of 6 months of exercise training in patients with stable chronic heart failure and moderate-to-severe LV dysfunction. Three key findings emerged. First, aerobic endurance training leads to an increase in LV stroke volume at rest and during exercise and to a small but significant decrease in LV end diastolic diameter and volume. Cardiac output at rest and during subpeak exercise remains essentially unchanged. Second, long-term exercise training is associated with a considerable reduction of TPR at rest and, in particular, at peak exercise. In addition, we found a correlation between improved endothelium-dependent vasodilation of the skeletal muscle vasculature and reduction of total peripheral resistance during exercise. Third, changes in TPR are related to changes in stroke volume and LV end diastolic diameter. These results suggest that in patients with stable chronic heart failure, regular physical exercise for 6 months is associated with a significant afterload reduction. This beneficial training effect leads to a small but significant improvement in LV stroke volume and reduction in cardiomegaly.

Two recent studies in postinfarction patients with systolic dysfunction have demonstrated that exercise training may attenuate the unfavorable remodeling response and even improve ventricular function over time.<sup>5,6</sup> Although improved LV diastolic filling rate has been observed after exercise training in patients with dilated cardiomyopathy,<sup>17</sup> the long-term effect of exercise training on LV systolic function and cardiomegaly remains debatable.

The major goals of any therapy for chronic heart failure continue to be reduction of LV wall stress, increase of cardiac output, and reduction of afterload. An important finding of the present study was the observation that after 6 months of exercise training, stroke volume increased while at rest and, in particular, during peak exercise. Because resting heart rate significantly declined after 6 months of training, it could be argued that the lengthened diastolic filling period augmented stroke volume by the Frank-Starling mechanism. However, the decrease in LV end diastolic diameter strongly suggests that the reduction in heart rate cannot completely explain the increase in either LVEF or stroke volume.

In 1 of the first exercise training trials in patients with chronic heart failure, Sullivan et al<sup>1</sup> observed a trend toward an increase in stroke volume during exercise. Although more studies are needed in this area, the available evidence does not suggest that training causes any worsening of central hemodynamic responses to exercise. A recently published single-center study even postulated a reduction of mortality after exercise training.<sup>18</sup> Most studies have reported improved cardiac output response to exercise with no elevation of pulmonary artery pressure.<sup>1,3,6</sup> In the present study, both resting and peak exercise pulmonary vascular resistance were reduced after training therapy, indicating that the improvement in LV systolic function may have led to a decreased preload, that an improvement of endothelial function may also have affected pulmonary resistance vessels, or both.

A major finding of the present study was the observation that TPR decreased at rest and, in particular, during peak exercise in the exercise training group. Several mechanisms may be responsible for this reduction of TPR. First, endothelial dysfunction in chronic heart failure is characterized by a reduced endothelium-dependent vasodilation in response to acetylcholine and impaired ischemic vasodilation during reactive hyperemia.<sup>19,20</sup> During exercise, small resistance vessels exhibit a blunted vasodilatory capacity, which contributes to increased TPR and peripheral hypoperfusion. Recently, we demonstrated that exercise corrects endothelium-dependent vasodilation of the skeletal muscle vasculature after stimulation with acetylcholine and even improves basal endothelial nitric oxide formation.<sup>12</sup> In the subset of patients included in the present study, changes in endothelial function of the skeletal musculature of the lower limb were related to changes in TPR. This observation is consistent with the hypothesis that exercise therapy exerts its primary effects on the endothelial function of peripheral resistance vessels, contributing to the TPR reduction at rest and at peak exercise.

Second, peripheral vascular resistance also may be reduced by an attenuation of sympathetic activity and an increased vagal tone as noted after exercise training in healthy subjects and heart failure patients.<sup>21</sup> In the present study, however, changes in plasma catecholamine levels were not correlated with changes in TPR, indicating that training-induced afterload reduction is not solely caused by reduced plasma catecholamines.

The reduction in TPR after exercise training was significantly correlated to changes in stroke volume and LV end diastolic diameter, suggesting that an afterload reduction leads to an increase in stroke volume and reduction in cardiomegaly in patients with chronic heart failure. However, with regard to the formula used for calculating TPR, an inverse correlation between stroke volume and TPR is to be expected in the absence of major changes in blood pressure gradient and heart rate. Thus, the changes in LV stroke volume should be thought of as secondary effects of exercise therapy related to improved peripheral vasodilation.

Our study should be interpreted in light of several limitations. The study was conducted at only 1 center, in-

cluded only men, and was limited to a relatively young (mean age, 55 years) group of patients with chronic heart failure. The results may not be generalizable to all patients with chronic heart failure. Moreover, a relatively small proportion of patients in this study were taking  $\beta$ -blockers. We cannot predict from our data how these findings may apply to patient groups with more use of  $\beta$ -blockers for treatment of chronic heart failure.

In summary, the present study demonstrates that in addition to well-known peripheral adaptations, home-based exercise training in patients with chronic heart failure results in a considerable reduction of TPR, a small but significant improvement in LV stroke volume, and reduction in cardiomegaly. Although several questions regarding optimal training protocol and training intensity remain unanswered, the present findings may have important implications for rehabilitation of patients with chronic heart failure.

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