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

Rainer Hambrecht, MD
Stephan Gielen, MD
Axel Linke, MD
Eduard Fiehn, MD
Jiangtao Yu, MD
Claudia Walther, MD
Nina Schoene, MD
Gerhard Schuler, MD

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. Training benefits have been attributed in particular to peripheral adaptations, including enhanced oxidative capacity of the working skeletal muscle and correction of endothelial dysfunction in the skeletal muscle vasculature.

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 infarction ([MIF] 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−5 in the exercise training group vs an increase of 43 (148) dyne/s/cm−5 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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farction reportedly leads to a deteriora-
tion in both global and regional
function in patients with significant LV
asynergy at baseline.13 In this study, we
investigated the influence of a long-
term, ambulatory exercise training pro-
gram involving patients with chronic
heart failure on total peripheral resis-
tance (TPR) at rest and during exer-
cise, 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 Cen-
ter, Leipzig, Germany, for further di-
agnosis during 1994-1999 were en-
rolled in this trial if they met the
following inclusion criteria: (1) docu-
mented heart failure by signs, symp-
toms, and angiographic evidence of re-
duced LV function (LV ejection fraction
[LVEF] <0.40) as a result of dilated car-
diomyopathy or ischemic heart dis-
ease; (2) physical work capacity at base-
line greater than 25 W; and (3) clinical
stability for at least 3 months before en-
try into the study.

Exclusion criteria were significant
valvular heart disease, uncontrolled
hypertension, diabetes mellitus, hyper-
cholesterolemia (≥6 mmol/L [232 mg/
dL]), peripheral vascular disease,
pulmonary disease, or musculoskel-
etal abnormalities precluding exercise
training. All studies were performed ac-
cording 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 ei-
ther a training group or an inactive con-
trol group using a list of random num-
bers. Both groups underwent invasive
cardiopulmonary exercise testing and
echocardiography at baseline and at 6-
month follow-up.

To ensure close supervision, the ini-
tial phase of the exercise program was
performed on an in-hospital basis. Dur-
ing 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 symp-
tom-limited maximum oxygen uptake
was reached. Before discharge from the
hospital, peak symptom-limited erg-
spirometry was performed to calcu-
late 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 exer-
cise 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 ex-
pected to participate in at least 1 group
training session of 60 minutes each
week. Group sessions consisted of walk-
ing, calisthenics, and ball games.

Patients assigned to the control group
continued their individually tailored
cardiac medications and were super-
vised by their physicians. All examina-
tions including exercise testing were re-
pealed at 6-month follow-up.

**Assessments**

**Cardiopulmonary Exercise Testing and Variables.** Prior to baseline mea-
surements, 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 ex-
ercise-induced ventricular tachyar-
rhythmias.

Two days later, a catheter (Swan-
Ganz 93A-131-7F, Edwards Laborato-
ries, 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 up-
right position. Workload was in-
creased progressively every 3 minutes
in steps of 25 W beginning at 25 W. Ex-
ercise was terminated when patients
were physically exhausted or devel-
oped severe dyspnea or dizziness. He-
modynamic and gas exchange measure-
ments as well as blood samples were
simultaneously obtained at rest and at
the end of each workload during bi-
cycle exercise. Heart rate was mea-
sured by continuous electrocardio-
graphic monitoring.

Cardiac output was obtained using
a thermodilution catheter that was in-
terfaced 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 calcu-
lated by dividing cardiac output by heart
rate. Total peripheral resistance was
calculated as mean arterial pressure
divided by cardiac output and is ex-
pressed in dyne/s/cm². Free and con-
jugated plasma catecholamine levels
were analyzed by high-pressure liquid
chromatography with amperometric de-
tection as described by Weicker.14

Respiratory gas exchange data were
determined continuously throughout
the exercise test using a commercially
available system (Oxycon Alpha, Erich
Jaeger, Höchberg, Germany). The ven-
tilatory threshold was defined as de-
scribed elsewhere.15

**Echocardiography.** All patients un-
derwent a complete resting echocardi-
ographic study at both the initial and the
final evaluations. Examinations were
videotaped with a long apical 4-cham-
ber view sequence for final analysis. End
systolic and end diastolic diameters of
the left ventricle were determined in the
parasternal long axis. Three consecu-
tive cardiac cycles were analyzed on an
HP Sonos 5500 echocardiography sys-
tem (Hewlett-Packard Inc, Andover,
Mass) and averaged for each patient by
an experienced cardiologist blinded to
patient status and assignment. Left ven-
tricular volume and LVEF were calcu-
lated in the apical 4-chamber view us-
ing the disk method.16

**Assessment of Lower-Limb Endo-
thelial Function.** In a subgroup of 18
patients, endothelial function in the su-
perficial femoral artery was assessed at
baseline and 6-month follow-up as pre-
viously described.12 Briefly, a 7F mul-
tipurpose 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 µg/min); after Nω-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.12

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 2.03 for Windows, SPSS Inc, Chicago, Ill). New York Heart Association functional class distribution was compared using the χ^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^5. To detect a difference of 160 dyne/s/cm^5 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 [O2max], 17.8 [3.0] mL/kg/min) died of sudden cardiac death unrelated to exercise during the study period. These patients were comparable 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; O2max, 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]; O2max, 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]; O2max, 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]; O2max, 15.5 [2.0] mL/kg/min). An additional 2 patients withdrew consent after baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exercise Training Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 36)</td>
<td>6-Month Follow-up (n = 31)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54 (9)</td>
<td>54 (9)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>80.8 (13.0)</td>
<td>82 (12)</td>
</tr>
<tr>
<td>LVEF, mean (SD)</td>
<td>0.27 (0.09)</td>
<td>0.27 (0.09)</td>
</tr>
<tr>
<td>LV-EDD, mean (SD), mm</td>
<td>70 (10)</td>
<td>69 (10)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, No.</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Ischemic heart disease, No.</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>VO2max, mean (SD), mL/kg/min</td>
<td>18.2 (3.7)</td>
<td>18.2 (3.9)</td>
</tr>
<tr>
<td>NYHA functional class, No. I and II</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Medications, No. (%)</td>
<td>AC inhibitors</td>
<td>34 (94)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>26 (76)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28 (78)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6 (17)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3 (8)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

* indicates left ventricular ejection fraction (assessed by angiography); LV-EDD, left ventricular end diastolic diameter (assessed by echocardiography); VO2max, maximum oxygen uptake (during peak exercise); NYHA, New York Heart Association; and ACE, angiotensin-converting enzyme.
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]; \( O_2 \max \), 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]; \( O_2 \max \), 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/s/cm$^{-5}$ vs an increase of 120 (433) dyne/s/cm$^{-5}$ in the control group ($P=.04$). During peak exercise, TPR decreased by 158 (306) dyne/s/cm$^{-5}$ in the exercise training group vs an increase of 43 (148) dyne/s/cm$^{-5}$ 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/s/cm$^{-5}$ vs 832 [311] dyne/s/cm$^{-5}$ 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 vasodilation of the skeletal muscle vasculature as assessed in a subgroup of patients with chronic heart failure, as reported previously. 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$	extsuperscript{6}$-monomethyl-l-arginine-induced changes in peripheral blood flow and changes in resting TPR ($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

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**Table 2. Exercise and Gas Exchange Data*†‡**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Training Group (n = 31)</th>
<th>Control Group (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6-Month Follow-up</td>
</tr>
<tr>
<td>$V_{O2-\text{VT}}$, mL/kg/min</td>
<td>10.4 (3.4)</td>
<td>11.4 (2.7)</td>
</tr>
<tr>
<td>$V_{O2\text{max}}$, mL/kg/min</td>
<td>18.2 (3.9)</td>
<td>17.8 (4.5)</td>
</tr>
<tr>
<td>$V_{E}$, L/min</td>
<td>60.7 (14.7)</td>
<td>62.6 (19.7)</td>
</tr>
<tr>
<td>Maximum RER</td>
<td>1.08 (0.14)</td>
<td>1.09 (0.18)</td>
</tr>
<tr>
<td>Exercise time, s</td>
<td>732 (206)</td>
<td>728 (229)</td>
</tr>
</tbody>
</table>

*Data are mean (SD). $V_{O2-\text{VT}}$ indicates oxygen uptake at ventilatory threshold; $V_{O2\text{max}}$, maximum oxygen uptake (during peak exercise); $V_{E}$, maximum expired volume per minute; and maximum RER, respiratory exchange ratio during peak exercise.

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

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

**Table 3. Hemodynamic Data*†‡**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Training Group (n = 29)</th>
<th>Control Group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6-Month Follow-up</td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>89 (16)</td>
<td>91 (16)</td>
</tr>
<tr>
<td>Arterial pressure, mm Hg</td>
<td>91 (12)</td>
<td>95 (14)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.9 (1.4)</td>
<td>5.2 (1.3)</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>56 (18)</td>
<td>59 (19)</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mm Hg</td>
<td>21 (9)</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyne/s/cm$^{-5}$</td>
<td>397 (219)</td>
<td>333 (228)</td>
</tr>
<tr>
<td>Total peripheral resistance, dyne/s/cm$^{-5}$</td>
<td>1612 (445)</td>
<td>1551 (386)</td>
</tr>
</tbody>
</table>

During peak exercise

|                        |          |                   |              |          |                   |              |
| Heart rate, beats/min  | 154 (22) | 155 (22) | .08 | 150 (23) | .001 |
| Arterial pressure, mm Hg | 115 (17) | 119 (19) | .63 | 119 (14) | .53 |
| Cardiac output, L/min  | 14.4 (6.2) | 14.2 (4.9) | .04 | 13.9 (5.1) | <.001 |
| Stroke volume, mL      | 95 (46)  | 94 (35) | .24 | 95 (41) | .03 |
| Pulmonary artery pressure, mm Hg | 46 (13) | 41 (14) | .51 | 42 (15) | .37 |
| Pulmonary vascular resistance, dyne/s/cm$^{-5}$ | 350 (244) | 281 (191) | .52 | 303 (219) | .02 |
| Total peripheral resistance, dyne/s/cm$^{-5}$ | 770 (373) | 751 (265) | .03 | 794 (320) | .003 |

*Data are mean (SD).

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

‡$P$ values for comparison of change from baseline data in exercise training vs control groups.
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. Although improved LV diastolic filling rate has been observed after exercise training in patients with dilated cardiomyopathy, 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. 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. Most studies have reported improved cardiac output response to exercise with no elevation of pulmonary artery pressure. 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. 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. 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. 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, involved 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 β-blockers. We cannot predict from our data how these findings may apply to patient groups with more use of β-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.

**REFERENCES**