Exercise Training in Patients With Severe Left Ventricular Dysfunction

Hemodynamic and Metabolic Effects

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We studied the effects of exercise training in patients with chronic heart failure attributed to left ventricular dysfunction (ejection fraction, 24 ± 10%). Twelve ambulatory patients with stable symptoms underwent 4–6 months of conditioning by exercising 4.1 ± 0.6 hr/wk at a heart rate corresponding to 75% of peak oxygen consumption. Before and after training, patients underwent maximal bicycle exercise testing with direct measurement of central hemodynamic, leg blood flow, and metabolic responses. Exercise training resulted in a decrease in heart rate at rest and submaximal exercise and a 23% increase in peak oxygen consumption from 16.8 ± 3.8 to 20.6 ± 4.7 ml/kg/min (p < 0.01). Heart rate, arterial lactate, and respiratory exchange ratio were unchanged at peak exercise after training. Maximal cardiac output tended to increase from 8.9 ± 2.7 to 9.9 ± 3.2 l/min and contributed to improved peak oxygen consumption in some patients, although this change did not reach statistical significance (p = 0.13). Rest and exercise measurements of left ventricular ejection fraction, left ventricular end-diastolic volume, and left ventricular end-systolic volume were unchanged. Right atrial, pulmonary arterial, pulmonary capillary wedge, and systemic arterial pressures were not different after training. Training induced several important peripheral adaptations that contributed to improved exercise performance. At peak exercise, systemic arteriovenous oxygen difference increased from 13.1 ± 1.4 to 14.6 ± 2.3 ml/dl (p < 0.05). This increase was associated with an increase in peak-exercise leg blood flow from 2.5 ± 0.7 to 3.0 ± 0.8 l/min (p < 0.01) and an increase in leg arteriovenous oxygen difference from 14.5 ± 1.3 to 16.1 ± 1.9 ml/dl (p = 0.07). Arterial and femoral venous lactate levels were markedly reduced during submaximal exercise after training, even though cardiac output and leg blood flow were unchanged at these workloads. Thus, ambulatory patients with chronic heart failure can achieve a significant training effect from long-term exercise. Peripheral adaptations, including an increase in peak blood flow to the exercising leg, played an important role in improving exercise tolerance. The finding that blood lactate levels at submaximal exercise were reduced without improvements in cardiac output suggests that in patients with chronic heart failure, peripheral metabolic or vascular factors are important in determining the onset of lactate production and may, independent of central hemodynamics, influence exercise tolerance. (Circulation 1988;78:506–515)

Numerous studies during the past 3 decades have established that training in normal subjects leads to an increase in peak exercise oxygen consumption (VO₂). This may be achieved through both improvements in maximal cardiac output and peripheral adaptations.1–8 In normal subjects, these peripheral adaptations include an increase in systemic arteriovenous oxygen (Avo₂) difference at peak exercise, which is attributable, in part, to a redistribution of cardiac output to working skeletal muscles.2–4,7 Training induces a delay in the rise in blood lactate during exercise that occurs through altered skeletal muscle metabolism2,3,5 and has been related to improvements in exercise endurance at submaximal workloads.

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Although these adaptations to chronic exercise would be potentially beneficial in the presence of chronic heart failure, the physiological effects of exercise training have not been well defined in these patients. The central hemodynamic abnormalities in heart failure are accompanied by many secondary neurohumoral,9 skeletal muscle,10,11 and peripheral vascular changes that may alter or attenuate the effects of exercise training. Patients with heart failure because of decreased left ventricular systolic function demonstrate large end-diastolic volumes and have little contractile reserve.13,14 It has been suggested that training in these patients may induce further increases in left ventricular end-diastolic volume that would increase wall tension and may be detrimental to left ventricular function. Peripheral adaptations to training may also be altered in chronic heart failure.15 LeJemtel et al16 observed near-maximal leg oxygen extraction at peak exercise in sedentary patients with heart failure and suggested that training would not further increase peripheral oxygen extraction in this disorder.

Despite these potential limitations, previous studies in patients with cardiac disease and various degrees of left ventricular dysfunction performed at our institution17–19 and others20–25 have demonstrated improved exercise duration and functional class after exercise training. Based on these results, many patients with severe left ventricular dysfunction currently participate in cardiac rehabilitation programs. The present study was designed to clarify the role of exercise training in these patients by providing a detailed assessment of their central and peripheral hemodynamic and metabolic adaptations to long-term exercise. A secondary aim of the present study was to determine whether baseline hemodynamic variables predicted the response to training in this patient group.

Patients and Methods

Patient Population

Sixteen patients with chronic heart failure attributable to left ventricular dysfunction (ejection fraction, 24 ± 10%; range, 9–33%) agreed to participate in the study. Patients were 54 ± 10 years old; two were New York Heart Association functional Class I, eight were functional Class II, and six were functional Class III. Nine had coronary artery disease, and seven had idiopathic cardiomyopathy. Patients were clinically stable for at least 3 months before study and did not have claudication, chronic lung disease, orthopnea, or pulmonary rales. Mild exertional angina was present in five patients, but all maximal exercise studies were limited by dyspnea or fatigue. No patient had significant valvular heart disease by Doppler echocardiography or cardiac catheterization. Fifteen patients were taking diuretics, 14 were taking digoxin, and three were taking stable dosages of captopril for more than 4 months before entry into the study. Four patients occasionally took short-acting nitrates for angina. Captopril was discontinued during exercise training in one patient because of a rash and in another patient because of a decrease in symptoms. All other medication dosages remained stable during the study.

Study Protocol

All studies were performed under a research protocol approved by the institutional review boards of the Duke University and the Durham Veterans Administration medical centers. All subjects underwent a familiarization maximal bicycle exercise test 2–14 days before the study. Exercise testing was performed with a Fitron isokinetic bicycle (Lumex, Ronkowkoma, New York) with the workload beginning at 150 kilopond-meters (kpm)/min and advancing 150 kpm/min in 3-minute stages to a symptom-limited maximum. Heart rate was measured by continuous electrocardiographic monitoring. During exercise studies performed without an arterial catheter, blood pressure was measured with a sphygmomanometer at each workload.

Before and after training, patients were admitted to the Duke University Clinical Research Unit or the Durham Veterans Administration Medical Center for exercise testing with hemodynamic monitoring. Functional class was determined with the specific activity scale of Goldman et al.26 The morning after admittance (day 1), all cardiac medications were given at 7:00 AM, and patients were given light breakfasts. After administration of a local anesthesia, a 7F Swan-Ganz catheter was introduced into the right pulmonary artery through the right antecubital vein. A 5F thermodilution Swan-Ganz catheter was positioned in the femoral vein with the distal thermistor tip placed 12 cm above the inguinal ligament. Both catheters were positioned under fluoroscopic control. A plastic cannula was introduced percutaneously into the left brachial artery. Patients were then transferred to the exercise facility where hemodynamic, radionuclide, and gas exchange measurements were simultaneously obtained at rest in the sitting position and then at each workload during upright bicycle exercise to exhaustion at 9:30–11:00 AM.

After the baseline studies, patients were enrolled in the Duke University Preventive Approach to Cardiology rehabilitation program or a local accredited facility near their home. After an initial 3-week exercise period of progressively increasing intensity and duration, patients exercised for 1 hour three to five times each week at a heart rate corresponding to 75% of the peak VO2 determined from the initial hemodynamic study. Exercise consisted of stationary bicycle riding for 25–40 minutes, walking, jogging, and stair climbing.

Six weeks after the initial evaluation and monthly thereafter, patients underwent maximal bicycle exercise with expired gas analysis, and the training heart rate was adjusted if necessary. After 16–24 weeks of exercise training, patients underwent...
a repeat exercise evaluation that was performed exactly as the baseline study.

**Expired Gas Analysis**

Expired gas analysis was performed continuously during all exercise tests with a commercially available Sensormedics 4400 unit that was calibrated both daily and immediately before each study. Volume calibration was performed with a 3l calibration syringe (Sensormedics, Anaheim, California), and calibration of the O₂ and CO₂ analyzers was performed with 24.0% O₂ with 8.0% CO₂ and 100.0% N₂ (Sensormedics). On a weekly basis, the 4400 unit was connected to a sinusoidal artificial lung (Sensormedics), and a gas mixture of 12.0% O₂-8.0% CO₂ was introduced at precisely varied rates of 10 and 80 l/min. The resulting ventilation, VO₂, and VCO₂ values reported from the Sensormedics 4400 unit did not vary by more than 2% from expected values.

**Hemodynamic Measurements**

Right atrial, pulmonary, and systemic arterial pressures (systolic, diastolic, and electronically derived mean) were obtained with Hewlett-Packard pressure transducers and amplifiers and were continuously recorded as previously reported in our laboratory. Blood samples were taken at rest and in the last minute of each exercise stage and were chilled in an ice bath immediately after collection. Oxygen content and saturation of arterial, femoral, and mixed venous blood samples were measured on a calibrated Instruments Laboratories 282 CO-Oximeter (Lexington, Massachusetts). Arterial and femoral venous blood lactate concentrations were determined with a Calbiochem-Behring rapid lactate kit (San Diego, California).

**Radionuclide Angiography**

After in vivo labeling of red blood cells with 30 mCi technetium-99m, gated equilibrium radionuclide studies were acquired at rest and at each workload with a Searle LEM mobile V camera with a high-sensitivity 30° slant hole collimator interfaced with an A² computer (Medical Data Systems, Ann Arbor, Michigan) as previously described. Bolus injections of 1–5 ml saline were used to obtain two or three blood flow measurements at rest and in the last 90 seconds of each workload, which were then averaged. Previous studies by Sullivan et al. have shown a close relation near the line of identity between radionuclide flow measured with this catheter system and simultaneous paired electromagnetic flow probe measurements in a perfused canine preparation (r = 0.98, p<0.001). To determine the variability of this measurement in the femoral vein, three normal subjects and three patients with heart failure performed duplicate submaximal bicycle exercise tests separated by a 2-hour rest period with leg blood flow measurements. Regression of paired determinations showed an excellent correlation (r = 0.96, p<0.001) (Figure 1). The variability of duplicate exercise measurements was 16±9%. Previous studies by Sullivan et al. in 20 normal subjects have shown a linear relation between workload and leg blood flow (r>0.92, p<0.001), which agrees closely with data from Jorfeldt et al. using a continuous dye infusion method.

**Derived Variables**

Cardiac output was determined by the direct Fick technique. Stroke volume was obtained by dividing cardiac output by heart rate. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were calculated with the stroke volume (SV) derived from the Fick cardiac output and the left ventricular ejection fraction (LVEF) by radionuclide angiography:

\[
LVEDV = \text{Fick SV} / \text{LVEF}
\]

\[
LVESV = LVEDV - \text{Fick SV}
\]

This method is potentially limited by the presence of mitral regurgitation, which was not quantitated during exercise in our patients. Therefore, these calculated values were used to estimate absolute left ventricular volumes. Leg vascular resistance was calculated as mean arterial pressure minus right atrial pressure divided by leg blood flow and was expressed as millimeters mercury per liter per minute. Leg oxygen consumption and lactate production were calculated with the Fick principal. Systemic oxygen delivery was determined as cardiac output multiplied by arterial oxygen content.

**Statistical Analysis**

Intragroup comparisons were made with the Wilcoxon signed rank test to avoid potential errors from nonnormal distribution of data. Submaximal
exercise data for each variable at 150, 300, and 450 kpm/min were combined by calculating an area under the curve before performing paired analysis. All patients had data obtained at each of these workloads. To determine the relation of baseline variables and changes in these variables to the change in peak Vo2 with training, linear regression analysis was performed with the least-squares method. \( p<0.05 \) was considered to be statistically significant. Group data for each variable are expressed as mean \( \pm \) SD.

Results

Patients exercised for 4.1 \( \pm \) 0.6 hr/wk (range, 2.4–5.0 hr/wk). Four patients did not complete the training program and were excluded from analysis. One patient had sudden death unrelated to exercise, and one had an orthopedic injury that precluded further exercise. One patient developed progressing congestive heart failure in the 3rd month of training. Another patient complained of prolonged fatigue after exercising and dropped out of the study in the 3rd month without a change in his left ventricular ejection fraction, peak Vo2, or physical examination. Two patients underwent repeat hemodynamic testing after 4 months, two after 5 months, and eight after 6 months of training. There was no change in body weight for the group during the study. Training improved functional class from 2.4 \( \pm \) 0.6 to 1.3 \( \pm \) 0.7 (\( p<0.01 \)).

Maximal Exercise Endpoints

All patients exercised to a respiratory exchange ratio of more than 1.15 on all hemodynamic exercise studies. Training did not change the maximal exercise respiratory exchange ratio (1.32 \( \pm \) 0.14 vs. 1.36 \( \pm \) 0.15), arterial lactate (6.7 \( \pm \) 2.0 vs. 7.6 \( \pm \) 2.7 mM/l), or heart rate (145 \( \pm \) 14 vs. 146 \( \pm \) 14 min\(^{-1}\)) (all \( p = \) NS). These endpoints were consistent with the attainment of a maximal or near-maximal exercise effort during each exercise study.

Effects of Training on Vo2 and Central Hemodynamics

Peak Vo2 (Figure 2A) increased from 1.11 \( \pm \) 0.33 (16.8 \( \pm \) 3.7 ml/kg/min) to 1.40 \( \pm \) 0.40 l/min (20.6 \( \pm \) 4.7 ml/kg/min) (\( p<0.01 \)) after training; rest and submaximal exercise Vo2 were unchanged. The peak exercise workload increased from 520 \( \pm \) 105 (range, 450–750 kpm/min) to 613 \( \pm \) 119 kpm/min (range, 450–900 kpm/min) (\( p = 0.02 \)). Exercise time increased from 582 \( \pm \) 102 (range, 450–825 seconds)
Effects of Training on Peripheral Hemodynamics

One patient did not have leg blood flow measurements because of technical difficulties. There were no changes in the following five variables at rest or during submaximal exercise: leg blood flow, leg oxygen delivery, leg vascular resistance, leg AVO₂ difference (Figures 5A–5D), or leg VO₂. Blood flow to the single leg (Figure 5A) increased at peak exercise from 2.5±0.7 to 3.0±0.8 l/min (p<0.01), as did leg oxygen delivery (Figure 5B). There was a strong tendency for leg vascular resistance (Figure 5C) to decrease at peak exercise from 48±14 to 42±12 mm Hg/l/min (p=0.06). The leg AVO₂ difference at peak exercise (Figure 5D) tended to increase from 14.5±1.3 to 16.1±1.9 ml/dl (p=0.07). Thus, single leg VO₂ increased from 0.36±0.11 to 0.47±0.13 l/min (p<0.01) at peak exercise.

Figure 6 illustrates the effects of training on resting and exercise arterial, mixed venous, and femoral venous oxygen contents and saturations. Arterial oxygen content increased at rest and during submaximal exercise without a change in arterial oxygen saturation. This was because of a slight change in blood hemoglobin, which increased at rest from 14.0±0.8 to 14.9±0.9 g/dl (p<0.05). This increase was uniform for the group and was unrelated to the pretraining hemoglobin. Mixed venous and femoral venous oxygen saturations (Figure 6B) were unchanged at rest and during submaximal exercise but tended to be lower at peak exercise (both, p<0.015).
This slight but significant increase in hemoglobin and arterial oxygen content resulted in an unchanged systemic oxygen delivery at rest, despite a slight decrease in resting cardiac output. Oxygen delivery increased at peak exercise from 1.68 ± 0.59 to 1.90 ± 0.50 l/min (p < 0.05) but was unchanged at submaximal workloads.

**Metabolic Effects of Training**

Arterial and femoral venous lactate concentrations were markedly reduced during submaximal exercise (Figures 7A and 7B) but were unchanged at rest or maximal exercise after training. Similarly, training decreased femoral arteriovenous lactate difference and leg lactate production during submaximal exercise (Figures 7C and 7D) without changing these variables at rest or maximal exercise.

**Time Course of Training Effects**

There were no differences in peak $V_{O_2}$ measured during the familiarization study, the initial hemodynamic study, and the study on day 45 of the protocol (Figure 8). Peak $V_{O_2}$ increased significantly by day 75 of the study compared with baseline and continued to increase from day 75 to the post-training study from 1.28 ± 0.36 to 1.40 ± 0.40 l/min (p = 0.06). Several patients, however, demonstrated little or no change in peak $V_{O_2}$ after 75 days of training.

**Relation of Baseline Patient Characteristics to Response to Training**

There was no relation between the change in peak $V_{O_2}$ after exercise training and any hemodynamic variable measured during the baseline exercise study. Specifically, the resting or peak exercise LVEF, stroke volume, cardiac output, $V_{O_2}$, systemic AVo$_2$ difference, leg AVo$_2$ difference, or femoral vein oxygen saturation were unrelated to the response to training. Changes in exercise variables after training were related to the change in peak $V_{O_2}$ after training to determine the relative importance of individual mechanisms in determining the magnitude of the training response. Increased $V_{O_2}$ with training was related to the change in maximal cardiac output ($r = 0.60$, $p = 0.04$) (Figure 9A) but was not related to the change in systemic AVo$_2$ difference (Figure 9B), which was relatively homogenous for most
patients. Increased peak leg blood flow was closely related to the change in peak VO₂ (r = 0.70, p = 0.01) (Figure 9C). The average number of hours that each patient exercised each week appeared to be a strong determinant of increased peak VO₂ after training (r = 0.67, p = 0.01) (Figure 9D). There was no relation between the duration of exercise training and the change in peak VO₂.

Discussion

The present study demonstrates that ambulatory patients with chronic heart failure can achieve a significant training effect through a program of exercise conditioning. As has been demonstrated in normal subjects,¹²,⁴⁷ chronic exercise in our patients resulted in an increased peak VO₂, a delay in blood lactate accumulation during submaximal exercise, and a training bradycardia. The relative increase in peak VO₂ of 23% in our patients was comparable to that seen after conditioning in age-matched normal subjects.⁷,³³ The present study confirms previous investigations¹⁷⁻²⁵ that have demonstrated increases in exercise duration and improved functional class after training in patients with cardiac dysfunction. Our results also provide a detailed assessment of the central and peripheral hemodynamic and metabolic adaptations to training in patients with chronic heart failure.

Few published studies have examined exercise hemodynamics before and after training in patients with cardiac disease,²⁰,²¹,²⁴,²⁵,³⁴ and most have not quantitated LVEF or have included only a few subjects with severe left ventricular dysfunction. Varnauskas et al²⁰ and Detry et al²¹ demonstrated no improvement in exercise cardiac output or stroke volume in patients with coronary artery disease after training. In contrast, Frick and Katila²⁴ noted an increase in stroke volume and left ventricular preload after training in a small group of patients who had previous myocardial infarctions. However, these patients underwent supine exercise and had near-normal exercise stroke volume responses before training. Hagberg et al³⁴ and Paterson et al³⁵ have shown that patients with coronary artery disease can improve exercise stroke volume after 1 year of intense training. Studies by Ehsani et al²⁵ indicate that this intense training regimen may actually improve left ventricular contractility during exercise.

After 4–6 months of training, our patients did not demonstrate an improvement in left ventricular systolic function. As demonstrated in previous studies in cardiac patients²⁰,²¹,²³ and in normal subjects,⁷,⁸ resting stroke volume did not increase after training in our patients. However, exercise stroke volume tended to increase; although this was not statistically significant, it did compensate for the training bradycardia to maintain cardiac output during submaximal exercise. Maximal cardiac output also tended to increase after training; although this change also did not reach statistical significance, it was quantitatively similar to the change in peak systemic AVO₂ difference. As indicated by the relation between the change in cardiac output and the change in peak VO₂ with training (Figure 9A), our data suggest that central hemodynamic adaptations can contribute to improved maximal exercise performance after training in patients with left ventricular dysfunction.

Our patients demonstrated several important peripheral adaptations to chronic exercise. These changes are an important part of the training response in normal subjects¹⁻⁸ and are reflected as a decrease in submaximal blood lactate levels and an increase in peak systemic AVO₂ difference. Our results agree with previous studies⁷,²⁰,²¹,³⁵ that indicate that peak AVO₂ difference increases after training in cardiac patients and is an important mechanism leading to improved peak VO₂.

The increase in leg blood flow at peak exercise demonstrated in our patients after training was closely related to improved maximal exercise performance (Figure 9C). Because femoral blood flow is almost entirely directed to skeletal muscle during intense bicycle exercise,¹²,³² it is reasonable to assume that skeletal muscle blood flow was also

![Figure 9](http://circ.ahajournals.org/DownloadedFromImage.aspx?image_id=512)

**FIGURE 9.** Plots of relation of the change in peak VO₂ after training with the change in peak exercise hemodynamics after training and exercise compliance in patients with chronic heart failure. r, correlation coefficient.
unchanged during submaximal exercise and improved during maximal exercise in our patients. Musch et al. have demonstrated improved maximal exercise and unchanged submaximal exercise skeletal muscle blood flow in foxhounds after training with radiolabeled microspheres. Clausen et al. using a xenon washout technique, reported a similar increase in peak exercise skeletal muscle blood flow but noted a decrease in submaximal exercise blood flows after training. This is in contrast with our findings and with those of Henriksen and Saltin et al., which have demonstrated no decrease in leg blood flow at submaximal exercise after training with direct femoral blood flow measurements. This discrepancy may be related to limitations of the xenon washout technique, which may be accentuated by changes in muscle lipid content after training.

The increased peak leg blood flow in the present study was associated with no change in mean arterial blood pressure and a decrease in leg vascular resistance. Similar decreases in maximal vascular resistance have been demonstrated after chronic exercise in the trained limbs of normal subjects by Martin et al. and Sinoway et al. Several potential physiological adaptations to training have been identified that may be responsible for this and include reduced sympathetic vasoconstrictor activity and possibly an increased capacity for metabolic vasodilation. Although the present study does not define which mechanisms were responsible in our patients, the results indicate that maximal leg vascular resistance can be altered by a long-term intervention, exercise training, and that this may contribute to improved exercise tolerance.

The present study is one of the first to demonstrate a decrease in exercise blood lactate levels after an intervention in chronic heart failure. Our data indicate that this is mediated by a decrease in leg lactate production and suggest that skeletal muscle anaerobic metabolism was delayed after training. Reduced lactate production in exercising skeletal muscle has previously been demonstrated in animals and humans after exercise training.

Our patients demonstrated reduced exercise leg blood flow at matched submaximal workloads and at maximal exercise compared with normal subjects studied in our laboratory. This reduction in skeletal muscle blood flow during exercise represents a potent stimulus for early lactate production. By demonstrating decreases in leg lactate production after training without improved leg blood flow, our data indicate that mechanisms independent of hemodynamics were important in determining skeletal muscle metabolism during exercise in our patients. Several adaptations to training have been identified that could potentially explain this delay in anaerobic metabolism: vascular and biochemical adaptations in skeletal muscle, decreased adrenergic activity with exercise, changes in substrate delivery, or alterations in intramuscular blood flow distribution. Although our data do not define the mechanisms underlying the delayed lactate production in our patients, studies by Ferguson et al. have demonstrated that skeletal muscle adaptations similar to those seen in normal subjects can occur in patients with cardiac dysfunction after training.

The slight increase in arterial oxygen content noted in our patients has also been demonstrated by Varnauskas et al. and Detry et al. in patients with cardiac disease after training. Normal subjects increase both plasma volume and total hemoglobin with chronic exercise training and, consequently, do not alter hematocrit or arterial oxygen content. In contrast, Varnauskas et al. found no change in plasma volume in patients with cardiac dysfunction after training. This suggests that the increase in hemoglobin seen after training in our patients may be because of their inability to increase plasma volume, possibly attributable to diuretic use, while total hemoglobin increased.

The nine patients who achieved the greatest increase in exercise performance were highly motivated and demonstrated the best compliance with the exercise program, regularly training 4–5 hours each week. Subjects with only modest compliance did not achieve a significant training effect (Figure 9D). It appears that a threshold training stimulus may be present in patients with chronic heart failure and is similar to that described in normal subjects. However, the present study was uncontrolled, and those patients with lower compliance may represent a subgroup of patients who have abnormalities that limit their ability to both exercise regularly and improve with training.

No hemodynamic measurement from the baseline study could reliably predict the response to training. This may reflect the finding that several adaptations were responsible for the training response in our patients. Furthermore, delayed submaximal anaerobic metabolism was not dependent on any of the hemodynamic parameters measured and may be attributed to skeletal muscle adaptations. It should be emphasized that the patients in the present study were well compensated despite severe left ventricular dysfunction, so our results may not apply to patients with uncontrolled peripheral edema, pulmonary congestion, or more severe heart failure.

In conclusion, exercise training improved maximal exercise tolerance in ambulatory patients with chronic heart failure attributed to left ventricular systolic dysfunction and may represent a useful therapeutic option in stable patients with this disorder. A major element of the training response involved peripheral adaptations that included increased peak blood flow to active skeletal muscles and more efficient peripheral oxygen extraction. Although peripheral adaptations were important in the training response, increased hemoglobin and, in some patients, increased peak cardiac output also contributed to improved exercise performance. The onset of anaerobic metabolism was delayed after
training without improved submaximal exercise leg blood flow, suggesting that this response may be in part attributable to skeletal muscle adaptations. Although previous studies have shown that cardiac output and stroke volume abnormalities are strongly correlated with aerobic impairment in chronic heart failure, the present study indicates that peripheral vascular and metabolic function also play an important role in determining exercise tolerance in this disorder.

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