Regular Physical Exercise Corrects Endothelial Dysfunction and Improves Exercise Capacity in Patients With Chronic Heart Failure

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Background—The purpose of this study was to determine the effects of systemic exercise training on endothelium-mediated arteriolar vasodilation of the lower limb and its relation to exercise capacity in chronic heart failure (CHF). Endothelial dysfunction is a key feature of CHF, contributing to increased peripheral vasoconstriction and impaired exercise capacity. Local handgrip exercise has previously been shown to enhance endothelium-dependent vasodilation in conduit and resistance vessels in CHF.

Methods and Results—Twenty patients were prospectively randomized to a training group (n = 10, left ventricular ejection fraction [LVEF] 24 ± 4%) or a control group (n = 10, LVEF 23 ± 3%). At baseline and after 6 months, peak flow velocity was measured in the left femoral artery using a Doppler wire; vessel diameter was determined by quantitative angiography. Peripheral blood flow was calculated from average peak velocity (APV) and arterial cross-sectional area. After exercise training, nitroglycerin-induced endothelium-independent vasodilation remained unaltered (271% versus 281%, P = NS). Peripheral blood flow improved significantly in response to 90 mg/min acetylcholine by 203% (from 152 ± 79 to 461 ± 104 mL/min, P < 0.05 versus control group) and the inhibiting effect of L-NMMA increased by 174% (from −46 ± 25 to −126 ± 19 mL/min, P < 0.05 versus control group). Peak oxygen uptake increased by 26% (P < 0.01 versus control group). The increase in peak oxygen uptake was correlated with the endothelium-dependent change in peripheral blood flow (r = 0.64, P < 0.005).

Conclusions—Regular physical exercise improves both basal endothelial nitric oxide (NO) formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with CHF. The correction of endothelium dysfunction is associated with a significant increase in exercise capacity. (Circulation. 1998;98:2709-2715.)

Key Words: endothelium-derived factors ■ nitric oxide ■ skeletal muscles ■ oxygen uptake ■ blood flow

Chronic heart failure (CHF) is associated with peripheral vasoconstriction.1,2 This has been attributed to activation of the sympathetic nervous system,3 the renin-angiotensin system,3 or the pituitary-vasopressin axis.4 However, recent findings revealed a potential contributory role of the vascular endothelium. Endothelium-derived relaxing factor (EDRF), lately identified as nitric oxide (NO),5,6 is released in response to both endocrine mediators (eg, acetylcholine and bradykinin7,8) and mechanical stimuli (eg, changes in blood flow velocity and endothelial shear stress9). The basal release of NO accounting for the biologic activity of EDRF5 has been shown to contribute to the control of regional blood flow in humans10 by using N^G-monomethyl-L-arginine (L-NMMA) as a selective inhibitor of the production of NO from L-arginine.11

Cell culture experiments have demonstrated that shear stress augments NO synthase expression in the endothelial cells.12,13 Chronic exercise training of dogs has been shown to be associated with an enhanced endothelium-dependent vasodilation in conduit coronary arteries and an increased NO production in isolated coronary microvessels.14,15 However, local forearm exercise training (ie, handgrip exercise) in patients with CHF yielded inconsistent results with regard to alterations of peripheral blood flow, despite an enhanced endothelium-dependent vasodilation in conduit16 or resistance vessels.17

See p 2652

Previous studies have demonstrated the beneficial effects of endurance training in patients with CHF, leading to an

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2709
improvement of submaximal and peak exercise capacity. As submaximal cardiac output remains essentially unchanged in these patients, improvement of exercise tolerance may have resulted from a decrease of peripheral vascular resistance in the lower limb and a corresponding redistribution of blood flow to the working muscles. It remains unclear, however, whether these functional adaptations are mediated by a correction of endothelial dysfunction, or by other as yet undefined mechanisms.

The objective of this investigation was to determine in patients with CHF (1) whether endothelial dysfunction in lower limb skeletal muscle may be normalized by a long-term exercise training program and (2) whether exercise-induced changes in endothelial function are associated with changes in maximal exercise tolerance.

Methods

Patient Selection

Twenty male patients aged $\leq 70$ years with CHF as a result of dilated cardiomyopathy or ischemic heart disease were studied (NYHA functional class II to III). All patients had clinical, radiological, and echocardiographic signs of CHF and a reduced left ventricular ejection fraction ($\text{LVEF} \leq 40\%$), as assessed by angiography. Patients were in stable clinical condition for 3 months before study entry. Symptom-free exercise capacity of $>25$ W on bicycle ergometry was required.

Exclusion criteria were diabetes mellitus, hypertension, overt atherosclerotic peripheral vascular disease, hypercholesterolemia ($\geq 240$ mg/dL; $\geq 6.2$ mmol/L), ventricular tachyarrhythmias (Lown class $>1$Va), chronic obstructive lung disease, and primary valvular heart disease.

A total of 6 age-matched men (aged 56±3 years), who were studied for nonspecific chest pain to rule out coronary artery disease, served as healthy controls. They were normal by physical examination, ECG, chest x-ray, 2-dimensional echocardiography, coronary angiography, and left ventriculogram ($\text{LVEF} \pm 1\%$). Healthy subjects had no evidence of hypertension and had normal findings on routine hematólogic and biochemical blood analyses. No previous major medical illness was reported (including diabetes or any other cardiovascular diseases), and they were on no medication during the study.

Study Protocol

The protocol of this study was approved by the Ethics Committee of the University of Leipzig, and written informed consent was obtained from all patients and subjects at the beginning of the study.

Baseline Studies

At baseline, patients were studied in a fasting state, in a quiet environment, and a corresponding redistribution of blood flow to the working muscles. It remains unclear, however, whether these functional adaptations are mediated by a correction of endothelial dysfunction, or by other as yet undefined mechanisms.

Follow-Up Studies

Invasive assessment of endothelium-dependent vasodilation as well as exercise testing were repeated after 6 months. After baseline measurements were taken, CHF patients were randomized to either a group training or an inactive nontraining control group. Patients assigned to the training program stayed on an intermediate care ward for the initial 3 weeks of the training program. Patients exercised 6 times daily for 10 minutes on a bicycle ergometer under close supervision at 70% of the heart rate at peak oxygen uptake. On discharge from the hospital, patients were lent a bicycle ergometer for use at home. They were asked to exercise close to their target heart rate twice daily for a total of 40 minutes, 5 days per week. In addition, they were expected to participate in 1 group training session per week. Patients assigned to the control group stayed on their previous medication, continued their sedentary lifestyle, and were supervised by their private physicians.

Doppler Guidewire Measurements and Calculation of Blood Flow

Superficial femoral artery blood flow velocity was determined with a 0.018-in Doppler guidewire containing a 12-MHz pulsed Doppler ultrasound crystal at its tip (FlowMAP, Cardiometrics, Inc) connected to a real-time spectral analysis system. For the purpose of this study, the tip of the Doppler guidewire was positioned close to an anatomic landmark, usually a side branch takeoff, to aid its precise positioning at follow-up. For measurement of femoral blood flow, average peak velocity (APV) was multiplied by the cross-sectional area of the vessel segment of interest, yielding flow in mL/min.

Intra-arterial Infusions

Saline, acetylcholine (100 mg/10 mL, Dispersa), $N^\beta$-monomethyl-L-arginine (L-NMMA) (Clinalfa), and nitroglycerin (1 mg/mL, Schwarz Pharma) were infused via the guiding catheter. The agents were given in the following order: (1) baseline (0.9% saline for 5 minutes); (2) increasing doses of acetylcholine (30, 60, and 90 $\mu$g/min); (3) L-NMMA infusion (20 nmol/min); and (4) bolus injection of 0.5 mg nitroglycerin into the left superficial femoral artery. The doses of acetylcholine were chosen based on previous observations by Katz et al.\textsuperscript{21}

Subsequent infusions were administered after 3-minute intervals when all variables had returned to prior baseline values. All drugs were infused with an infusion pump (Braun Inc) set to a flow rate of 2 mL/min.

Quantitative Angiography

Serial angiography in the same projection (antero-posterior view) was performed at the end of each infusion period and after the administration of nitroglycerin. A nonionic contrast agent (Xenotix, Guerbet Inc) was manually injected at low pressure through the guiding catheter. The mean diameter of a 10-mm segment of the infused vessel was measured 2 to 3 mm distal to the tip of the Doppler guidewire. The artery of interest was centered, magnified, and digitized for subsequent computer analysis. Diameter measurements were performed in 2 consecutive end-diastolic frames and averaged. With the contrast-filled distal catheter used as the calibration standard, the minimal lumen diameter and reference diameter were determined with an edge-detection algorithm (Medis Inc).

Statistical Analysis

All data are expressed as mean±SEM. Both absolute values and percentage changes from baseline were used for statistical analysis and yielded similar $P$ values. Intragroup comparisons (beginning versus 6 months) were performed using the nonparametric Wilcoxon’s signed-rank test. Statistical analysis was performed by ANOVA followed by Student-Newman-Keuls test. Linear regression analysis was used to determine the relation of changes of oxygen uptake to changes in endothelium-dependent vasodilation. A value of $P<0.05$ was considered statistically significant.
### Results

**Baseline Characteristics**

At baseline, patients in the control group did not differ significantly from those in the training group with respect to age, etiology of heart failure, NYHA functional class, duration of heart failure, LVEF, or left ventricular end-diastolic diameter (Table 1). One patient with ischemic cardiomyopathy assigned to the training group (aged 67 years; LVEF 16%; maximum oxygen consumption [\(\dot{V}O_2\)max] 19.9 mL · kg\(^{-1}\) · min\(^{-1}\); NYHA class II) and 1 patient with ischemic cardiomyopathy in the control group (aged 62 years; LVEF 15%; [\(\dot{V}O_2\)max] 14.1 mL · kg\(^{-1}\) · min\(^{-1}\)) died during the study period. Both events were unrelated to the study protocol. The remaining 18 patients who completed the study were included in the analysis.

**Medical Treatment**

Patients were on angiotensin-converting enzyme inhibitors (100% in both groups), diuretics (training group 82%; control 70%), and digoxin (training 73%, control 70%, P = NS). Drug treatment did not change between 4 weeks before enrollment and study termination.

**Compliance With the Exercise Training Program**

In the exercise group, mean attendance for the group training sessions was 69.7 ± 9.0%. On the basis of this result, the compliance for home training was estimated to be ≈ 70%, amounting to an average of 25 minutes exercise training per day.

**Baseline Lower Limb Blood Flow in Healthy Subjects and in Patients With CHF**

**Healthy Subjects**

At baseline, a resting leg blood flow of 673 ± 62 mL/min was measured in healthy subjects. Arterial infusion of acetylcholine at a rate of 90 \(\mu\)g/min caused only minor (although significant) changes in superficial femoral artery diameter (0.64 ± 0.11 mm, \(P<0.05\) versus baseline). However, a substantial increase in blood flow velocity was observed (from 23.0 ± 2.5 to 44.0 ± 3.5 cm/s, \(P<0.01\) versus baseline), more than doubling the calculated mean blood flow (from 673 ± 62 mL/min to 1596 ± 30 mL/min, +144%, \(P<0.01\) versus baseline).

**CHF Patients**

Patients with CHF, both in the training and control groups, demonstrated a reduced resting leg blood flow at baseline compared with healthy subjects (435 ± 30 versus 673 ± 62 mL/min, \(P<0.05\)). The arterial infusion of acetylcholine (90 \(\mu\)g/min) caused small but significant changes in superficial femoral artery diameter (0.52 ± 0.09 mm, \(P<0.05\) versus baseline). Calculated blood flow showed only a slight, dose-dependent increase from 435 ± 127 to 586 ± 223 mL/min (+39%, \(P<0.05\) versus baseline) (Table 2). The extent of blood flow reduction during infusion of L-NMMA was attenuated in patients with CHF compared with healthy subjects (−48 ± 13 versus −172 ± 44 mL/min, \(P<0.05\)), suggesting a reduced basal release of NO in the peripheral vasculature of patients with heart failure. To determine whether CHF exerts any direct effects on vascular smooth muscle function, the vasodilator response to intra-arterial application of 0.5 mg nitroglycerin was examined. The relative increase in blood flow was not significantly different between patients with CHF and healthy subjects (Table 2).

**Effects of Exercise Training on Aerobic Exercise Capacity in Patients With CHF**

**Training Group**

After 6 months of regular physical exercise training, oxygen uptake at peak exercise increased by 26%, from 18.1 ± 1.2 to 22.8 ± 1.2 mL · kg\(^{-1}\) · min\(^{-1}\) in CHF patients (\(P<0.05\)). The NYHA functional status showed a tendency toward improvement from 2.4 ± 0.2 to 1.9 ± 0.1 (\(P=0.06\) versus baseline).

**Control Group**

In the control group of untrained CHF patients, \(\dot{V}O_2\)max (18.6 ± 1.3 versus 17.9 ± 1.7 mL · kg\(^{-1}\) · min\(^{-1}\), \(P=NS\) and...
Effects of Exercise Training on Lower Limb Blood Flow

**Baseline**
At the beginning of the study, there was no difference between the training and control groups with respect to vessel diameter and APV at baseline (saline infusion): vessel diameter for the training group was 6.06 ± 0.37 mm for the control group; APV in the training group was 14.7 ± 6.06 cm/s and in the control group was 11.4 ± 1.4 cm/s.

**Training Group**
After 6 months of aerobic exercise training, peripheral blood flow measured in the superficial femoral artery was significantly improved in response to 60 μg/min acetylcholine (by 187%; from 112 ± 92 to 321 ± 103 mL/min; P < 0.05 versus control group). The intra-arterial administration of 90 μg/min acetylcholine yielded an even more pronounced increase of 203% (from 152 ± 79 to 461 ± 104 mL/min; P < 0.05 versus control group) at 90 s, patients from the control group.

**Acetylcholine-induced increase in peripheral blood flow**
leads to a significant increase in agonist-mediated, endothelium-dependent blood flow (A) after acetylcholine infusion of 60 and 90 μg/min, whereas acetylcholine-induced increase of peripheral blood flow remained essentially unchanged (B) in patients of the control group. The improvement of peripheral blood flow was significantly increased by 174% (from 152 ± 79 to 461 ± 104 mL/min; P < 0.05 vs beginning; †P < 0.05 vs control group).

**NYHA functional status**
remained virtually unchanged.

**Table 3. Effect of Regular Physical Exercise on Peripheral Blood Flow Velocity**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Beginning, %</th>
<th>6 Months, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine, μg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>3 ± 3</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>60</td>
<td>13 ± 19</td>
<td>51 ± 24*</td>
</tr>
<tr>
<td>90</td>
<td>15 ± 15</td>
<td>73 ± 25†</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>-8 ± 6</td>
<td>-27 ± 4†</td>
</tr>
<tr>
<td>Nitroglycerin 212 ± 36</td>
<td>207 ± 32</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin 226 ± 33</td>
<td>239 ± 18</td>
<td></td>
</tr>
</tbody>
</table>

Values indicate percentage change in blood flow velocity vs baseline. Data are mean ± SEM. L-NMMA, N°-monomethyl-l-arginine.

*P < 0.05 vs beginning; †P < 0.05 vs control group.

After training, the inhibitory effect of L-NMMA on peripheral blood flow was significantly increased by 174% (from -46 ± 25 to -126 ± 19, P < 0.05 versus control group) compared with the beginning of the study (Figure 3).

**Figure 1.** Acetylcholine-induced increase of peripheral blood flow before (A) and after 6 months (B). Regular physical exercise leads to a significant increase in agonist-mediated, endothelium-dependent blood flow (A) after acetylcholine infusion of 60 and 90 μg/min, whereas acetylcholine-induced increase of peripheral blood flow remained essentially unchanged (B) in patients of the control group. #P < 0.05 vs beginning; †P < 0.05 vs control group.

**Figure 2.** Change (6 months vs beginning) in peak oxygen uptake (ΔVO₂max) was correlated with change (6 months vs beginning) in endothelium-dependent peripheral blood flow during acetylcholine infusion (90 μg/min). Indicating patients from the training group; ▲, patients from the control group.
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maximum increase in peripheral blood flow caused by the endothelium-independent vasodilator nitroglycerin was 271% (from 426±44 to 1587±232 mL/min, \(P<0.05\) versus baseline) at the beginning and 281% (from 469±41 to 1785±258 mL/min; \(P<0.05\) versus baseline) after 6 months (\(P=NS\)); this is similar to the effect of nitroglycerin in the control group.

Control Group
With regard to vessel diameter and blood flow velocity at baseline, after acetylcholine or L-NMMA infusion and after nitroglycerin injection, there were no significant changes observed after 6 months versus the beginning of the study (Table 3).

Discussion
This is the first randomized study to investigate the effects of regular aerobic exercise training on endothelium-dependent vasodilation of the lower limb skeletal muscle vasculature and its clinical implications for patients with CHF. Three important messages emerge from this study:

1. Correction of Endothelium-Dependent Arteriolar Vasodilation
Leg blood flow during acetylcholine infusion was significantly enhanced by regular aerobic exercise. This is primarily due to an augmented endothelium-mediated vasodilation of the peripheral vasculature.

2. Improvement of Basal NO Formation
A significant decrease in peripheral blood flow by \(N^\text{G}\)-monomethyl-\(L\)-arginine, an inhibitor of NO synthase, suggests that regular exercise increases basal NO formation in resistance vessels.

3. No Effects on Endothelium-Independent Arteriolar Vasodilation
Regular exercise did not alter the responsiveness of smooth muscle cells of the peripheral vasculature to exogenous application of NO. These results suggest that impaired endothelium-dependent arteriolar vasodilation in patients with CHF can be restored by long-term aerobic exercise training, probably because of endothelial relaxing factors released in response to cell membrane shear stress induced by pulsatile blood flow. Moreover, correction of endothelial dysfunction in skeletal muscle vasculature of the lower limb after exercise training was associated with an enhanced exercise capacity. Thus, one fundamental hemodynamic derangement encountered in CHF may be at least partially corrected by exercise training-induced increase in blood flow.

Lower Limb Blood Flow in Healthy Subjects and Patients With CHF
The extent of dilation of the superficial femoral artery induced by acetylcholine and nitroglycerin was similar in healthy subjects and patients with CHF. Thus, in the present study, changes in superficial artery diameter are negligible and the assessment of peripheral blood flow after acetylcholine infusion accurately determines the vasodilation capacity of resistance vessels. Our findings with regard to lower limb peripheral vasculature are in agreement with previous studies \(^{21,24}\) that demonstrated impaired acetylcholine-mediated endothelium-dependent vasodilation in the forearm and in the coronary circulation of patients with CHF. As the mean blood flow velocity obtained by Doppler ultrasound closely correlates with blood flow measurements obtained by venous occlusion plethysmography, the current finding is in agreement with previous work by Katz et al\(^{22}\); they demonstrated a reduction in blood flow velocity by \(\approx 40\%\) in the superficial femoral artery in patients with CHF compared with normal subjects.

When L-NMMA was applied to inhibit basal NO-formation in the lower limb vasculature, a significant reduction of blood flow was observed in healthy control subjects, although it remained nearly unchanged in patients with CHF. Therefore, not just maximal but also basal endothelial function is impaired in CHF. These findings are in accord with clinical trials\(^{22}\) and with experimental studies that demonstrated impaired basal NO synthesis in vitro in isolated vascular rings and in vivo.\(^{25,26}\) However, the current findings contrast 2 previous studies which demonstrated that a decrease in blood flow induced by L-NMMA was similar in patients with CHF and normal subjects, indicating a preserved basal release of NO from endothelium.\(^{23,27}\) The differences between the results of these previous clinical studies and the present work may be related to differences in study protocol or in the severity of disease in the study cohorts.

Nitroglycerin was administered to assess the functional integrity of cGMP-dependent vasorelaxation in the vascular smooth muscle. In agreement with previous reports,\(^{21,25}\) the peripheral vasodilator response to nitroglycerin was slightly reduced in patients with CHF versus healthy subjects. Therefore, the present data suggest that abnormal cGMP-mediated vascular smooth muscle relaxation in patients with CHF may be partially responsible for the attenuated response to acetylcholine.\(^{21}\)

Improvement of Endothelium-Dependent Perfusion of the Lower Limb in Response to Exercise Training
CHF is characterized by peripheral vasoconstriction\(^1\) and abnormal vascular compliance.\(^{29}\) Both factors are at least
Several Mechanisms Are Involved in the Exercise-Induced Enhancement of Endothelial Function

1. In patients with CHF, local handgrip exercise improves flow-mediated vasodilation of the radial artery during hyperemia as well as agonist-mediated endothelium-dependent vasodilation of forearm resistance vessels. This is consistent with animal studies in dogs, which detected an improved endothelium-mediated of epicardial coronary arteries after short-term exercise-training and demonstrated increased NO synthase-expression.

2. Chronic increase in blood flow also affects the release of prostaglandins. This may be particularly important in skeletal muscle microvasculature, in which prostaglandins are substantially involved in flow-mediated vasodilation.

3. Inactivation of NO by increased vascular superoxide or other oxygen-derived radicals also accounts for endothelial dysfunction in the human circulation. This may be counterbalanced by shear stress–induced expression of NO synthase and cytosolic copper/zinc–containing superoxide dismutase, a free radical scavenger.

4. Several other mechanisms may be involved in shear stress-induced vasodilation. Increases in flow enhance Ca influx in endothelial cells, which is necessary for both NO and prostaglandin synthesis. The sensitivity of the rheo- (flow) receptors and/or the cellular signal transduction pathways for the initiation of the synthesis of NO may be upregulated after exercise training.

Chronic exercise training leads to a significant increase in maximal oxygen uptake (26%). In the present study, changes in functional work capacity were significantly correlated with changes in agonist-induced endothelium-dependent blood flow. In rats, systemic inhibition of NO synthase during exercise and with L-NMMA significantly reduced blood flow to muscles with a high percentage of oxidative fibers but did not change blood flow to muscles with a high percentage of glycolytic fibers. Restoring endothelial function by chronic exercise training may contribute to the regulation of skeletal muscle blood flow as part of a coordinated system that preferentially supplies blood flow to oxidative muscles during submaximal exercise. These findings may at least partially account for the increase in oxidative enzyme capacity of the working skeletal muscle regularly observed in patients with CHF, which is closely related to the improved functional work capacity after exercise training. However, other mechanisms unrelated to blood flow are also proposed as potential mediators of the positive effects of exercise training: improvement of skeletal muscle metabolism, increase in mitochondrial volume density, and reduced activity of the muscle ergoreflex.

Limitations of the Study
To date, no consensus has been reached about the optimal exercise protocol for CHF patients. The protocol used in the present study was comparable to a number of previous training studies and less vigorous than a few others. On the basis of our previous experience with exercise training, we estimated that patient compliance would be in the range of 70%. Therefore, we set the goal of 40 minutes of home exercise training per day to achieve a minimum of 20 minutes submaximal exercise training per day in the majority of patients. In fact, given the patient compliance of 70% (as calculated from participation in group training sessions), the average exercise duration per week turned out to be ≈3 hours per week. The present study was designed to analyze the effects of aerobic endurance training on endothelial function in CHF. To draw an analogy to pharmacological studies, this was a phase 1 trial in the sense that the efficacy of the intervention was examined. Future studies will compare different levels of exercise training to determine the optimal protocol.

Although great care was taken to standardize flow measurements, we observed a considerable variation of values within the groups, as indicated by relatively large standard errors. However, the use of paired statistics, in which every patient serves as his own control, yielded significant intradividual blood flow differences before and after exercise training of CHF patients. In contrast, no change was observed in the untrained control group. It is known that up to 20% of CHF patients have normal peripheral blood flow at baseline. Obviously, this finding may partly explain the wide range of flow velocities within the groups because no strict linear relation between LVEF and the degree of reduction of peripheral perfusion could be identified.

Clinical Implications
The results of this study provide evidence that long-term aerobic exercise training in patients with CHF restores endothelial function of the skeletal muscle microvasculature of the lower limb. Therefore, a carefully and individually tailored program of physical activity should be made available to patients with CHF to reverse the deleterious effects of endothelial dysfunction, ie, increased peripheral resistance and reduced oxygen delivery to the working skeletal muscle. The present study demonstrates that chronic exercise training has the potential to correct peripheral endothelial dysfunction and to improve the debilitating key symptom of patients with CHF: exercise intolerance.

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