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 μg/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
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 ≥70 years with CHF as a result of dilated cardiomyopathy or ischemic heart disease were studied (NYHA class II to III). All patients had clinical, radiological, and echocardiographic signs of CHF and a reduced left ventricular ejection fraction (LVEF ≤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 (≥240 mg/dL; ≥6.2 mmol/L), ventricular tachyarrhythmias (Lown class >1Va), 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 (LVEF 71±1%). Healthy subjects had no evidence of hypertension and had normal findings on routine hematologic 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 temperature- and humidity-controlled room. All cardiovascular medications were withheld for ≥24 hours before the measurement of endothelium-dependent vasodilation. A right femoral artery puncture was performed under local anesthesia (1% lidocaine). A 7F multipurpose catheter was advanced into the left superficial femoral artery through a 0.038-in arterial sheath inserted into the right femoral artery. Small volume hand injections of contrast medium were performed to verify the position of the catheter tip in the left superficial femoral artery. Two days after invasive assessment of endothelial function, patients underwent symptom-limited ergospirometry with determination of maximal oxygen uptake. 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. Respiratory gas exchange was determined continuously throughout the exercise test as previously described.

### Follow-Up Studies

Invasive assessment of endothelium-dependent vasodilation as well as exercise testing were repeated after 6 months. Post-baseline measurements were taken, CHF patients were randomized to either a training group 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), Nω-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 µg/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.

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 (Xenetix, 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.
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%; NYHA class II) and 1 patient with ischemic cardiomyopathy in the control group (aged 62 years; LVEF 15%; NYHA class II/III) 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 µg/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 µg/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, Vₐo max (18.6 ± 1.3 versus 17.9 ± 1.7 mL · kg⁻¹ · min⁻¹, P = NS) and

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Training (n = 10)</th>
<th>Control (n = 10)</th>
<th>Healthy Subjects (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 ± 4</td>
<td>56 ± 3</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24 ± 4</td>
<td>23 ± 3</td>
<td>71 ± 1</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>69 ± 3</td>
<td>66 ± 3</td>
<td>54 ± 1</td>
</tr>
<tr>
<td>V(0)o max, mL · kg⁻¹ · min⁻¹</td>
<td>18.3 ± 1.2</td>
<td>17.6 ± 1.4</td>
<td>26.2 ± 1.0</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>199 ± 7</td>
<td>209 ± 8</td>
<td>217 ± 14</td>
</tr>
<tr>
<td>No. dilated/ischemic CMP</td>
<td>7/3</td>
<td>6/4</td>
<td>-</td>
</tr>
<tr>
<td>NYHA (No. in class II/III)</td>
<td>6/7</td>
<td>7/3</td>
<td>-</td>
</tr>
<tr>
<td>Duration of CHF, mo</td>
<td>43 ± 12</td>
<td>53 ± 18</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are mean ± SEM unless otherwise indicated. LVEDD indicates LV end-diastolic diameter; and CMP, cardiomyopathy.

### Table 2. Changes in Peripheral Blood Flow After Administration of Acetylcholine, L-NMMA, or Bolus Injection of Nitroglycerin in Patients With CHF and Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>CHF (n = 18)</th>
<th>Healthy Subjects (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine, µg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>32 ± 18</td>
<td>257 ± 32*</td>
</tr>
<tr>
<td>60</td>
<td>93 ± 48</td>
<td>520 ± 64*</td>
</tr>
<tr>
<td>90</td>
<td>151 ± 47</td>
<td>923 ± 134*</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>−48 ± 13</td>
<td>−172 ± 44*</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>1168 ± 119</td>
<td>1600 ± 130</td>
</tr>
</tbody>
</table>

Values are absolute and percentage change from baseline (0.9% saline), mean ± SEM. ΔPBF indicates change in peripheral blood flow; CHF, patients with chronic heart failure.

*P < 0.05 vs CHF.

Administration of L-NMMA, a selective inhibitor of NO synthase, reduced mean arterial blood flow by 172 ± 44 mL/min or −25 ± 6% (P < 0.05 versus baseline) (Table 2).
NYHA functional status (2.1±0.1 versus 2.0±0.0, P=NS) remained virtually unchanged.

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±0.37 mm for the control group; APV in the training group was 14.7±0.37 mm for the control group. The improvement of peripheral blood flow was significantly increased by 174% (from 152±71 mL/min; P<0.05 versus control group) (Figure 3). The intra-arterial application of 90 μg/min acetylcholine yielded an even more pronounced increase of peak blood flow velocity (r=0.85, P<0.001), suggesting that physical exercise improves peripheral blood flow by correct- ing endothelium-dependent vasodilation in peripheral resistance vessels. At the beginning of the study, the increase in lower limb blood flow in response to acetylcholine was significantly correlated with VO₂ attained during bicycle ergometry (r=0.55, P<0.02), indicating a relation between blunted endothelial function and exercise intolerance. Changes in VO₂ after 6 months were closely related to changes (6 months versus beginning) in acetylcholine-induced blood flow (r=0.64, P<0.005) (Figure 2).

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). The only a small proportion of flow increase, both at the beginning (10±2%) and after 6 months (10±3%).

Acetylcholine-induced increase in peripheral blood flow correlated with acetylcholine-induced increase in average peak blood flow velocity (r=0.85, P<0.001), suggesting that physical exercise improves peripheral blood flow by correcting endothelium-dependent vasodilation in peripheral resistance vessels. At the beginning of the study, the increase in lower limb blood flow in response to acetylcholine was significantly correlated with VO₂ attained during bicycle ergometry (r=0.55, P<0.02), indicating a relation between blunted endothelial function and exercise intolerance. Changes in VO₂ after 6 months were closely related to changes (6 months versus beginning) in acetylcholine-induced blood flow (r=0.64, P<0.005) (Figure 2).

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). The

### TABLE 3. Effect of Regular Physical Exercise on Peripheral Blood Flow Velocity

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Training Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine, μg/min</td>
<td>30 3±3 8±5</td>
<td>30 −2±5 3±4</td>
</tr>
<tr>
<td></td>
<td>60 13±19 51±24*</td>
<td>60 7±6 6±5</td>
</tr>
<tr>
<td></td>
<td>90 15±15 73±25†</td>
<td>90 13±7 10±6</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>−8±6 −27±4*†</td>
<td>−13±4 −8±3</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>212±36 207±32</td>
<td>226±33 239±18</td>
</tr>
</tbody>
</table>

Values indicate percentage change in blood flow velocity vs baseline. Data are mean±SEM. L-NMMA, N⁶-monomethyl-L-arginine.

*P<0.05 vs beginning; †P<0.05 vs control 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 application 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) (Figure 1). The improvement of peripheral blood flow after physical exercise training was mainly the result of a significant increase in blood flow velocity from 1.6±2.4 to 7.6±3.4 cm/s (P<0.05 versus control group) at 60 μg/min acetylcholine, and from 2.0±2.0 to 10.9±3.4 cm/s (P<0.05 versus control group) at 90 μg/min acetylcholine (Table 3). The extent of conduit vessel dilation accounted for...
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with CHF can be restored by long-term aerobic exercise
endothelium-dependent arteriolar vasodilation in patients
application of NO. These results suggest that impaired
muscle cells of the peripheral vasculature to exogenous
Regular exercise did not alter the responsiveness of smooth
Arteriolar Vasodilation
3. No Effects on Endothelium-Independent
vessels.

N
2. Improvement of Basal NO Formation

Figure 3. Change in peripheral blood flow in response to
administration of L-NMMA at the beginning of the study and
after 6 months. Reduction of peripheral blood flow induced by
L-NMMA infusion was significantly augmented after regular
physical exercise training. \( \#P<0.05 \) vs beginning; \( \ast P<0.05 \) vs control; \( \ast\ast P<0.05 \) vs CHF-training and CHF-control.

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 base-
line) 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 signifi-
cantly 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 \( N^\text{G}\)-mono-
methyl-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 de-
rangement 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 acetylcho-
line infusion accurately determines the vasodilation capacity
of resistance vessels. Our findings with regard to lower limb
peripheral vasculature are in agreement with previous stud-
ies,\(^2,21–24\) 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 corre-
lates with blood flow measurements obtained by venous
occlusion plethysmography, the current finding is in agree-
ment with previous work by Katz et al\(^2\); they demonstrated a
reduction in blood flow velocity by \(~40\%\) 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 reduc-
tion 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 func-
tion is impaired in CHF. These findings are in accord with
clinical trials\(^22\) and with experimental studies that demon-
strated 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 de-
crease in blood flow induced by L-NMMA was similar in
patients with CHF and normal subjects, indicating a pre-
served basal release of NO from endothelium.\(^23,27\) The differ-
ences 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
partiallly related to endothelial dysfunction of peripheral resistance and conduit vessels. In the present study, acetylcholine-induced increase in blood flow of the lower limb was blunted compared with healthy subjects. Regular physical exercise led to an increase in endothelium-dependent peripheral perfusion of 203% and to a decrease in peripheral perfusion after L-NMMA infusion of 174%. These findings suggest that the improvement in peripheral blood flow was attributed to an enhanced formation and/or release of NO at basal conditions and after stimulation.

**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.

**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.

**Acknowledgment**

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**References**


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