Endothelial Dysfunction in Patients With Chronic Heart Failure: Systemic Effects of Lower-Limb Exercise Training

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OBJECTIVES We sought to analyze the systemic effects of lower-limb exercise training (ET) on radial artery endothelial function in patients with chronic heart failure (CHF).

BACKGROUND Local ET has the potential to improve local endothelial dysfunction in patients with CHF. However, it remains unclear whether the systemic effects can be achieved by local ET.

METHODS Twenty-two male patients with CHF were prospectively randomized to either ET on a bicycle ergometer (ET group, n = 11; left ventricular ejection fraction [LVEF] 26 ± 3%) or an inactive control group (group C, n = 11; LVEF 24 ± 2%). At the beginning of the study and after four weeks, endothelium-dependent and -independent vasodilation of the radial artery was determined by intra-arterial infusion of acetylcholine (ACh—7.5, 15 and 30 µg/min) and nitroglycerin (0.2 mg/min). The mean internal diameter (ID) of the radial artery was assessed using a high resolution ultrasound system (NIUS-02, Asulab Research Laboratories, Neuchâtel, Switzerland) with a 10-MHz probe.

RESULTS After four weeks of ET, patients showed a significant increase in the baseline-corrected mean ID in response to ACh (30 µg/min), from 33 ± 10 to 127 ± 25 µm (p < 0.001 vs. control group at four weeks). In the control group, the response to ACh (30 µg/min) remained unchanged. Endothelium-independent vasodilation was similar in both groups at the beginning of the study and at four weeks. In the training group, increases in agonist-mediated, endothelium-dependent vasodilation correlated to changes in functional work capacity (r = 0.63, p < 0.05).

CONCLUSIONS In patients with stable CHF, bicycle ergometer ET leads to a correction of endothelial dysfunction of the upper extremity, indicating a systemic effect of local ET on endothelial function. (J Am Coll Cardiol 2001;37:392–7) © 2001 by the American College of Cardiology

The last decade has witnessed a paradigmatic shift from the concept of chronic heart failure (CHF) as a “pump disorder” to the growing understanding of heart failure as a systemic neurohormonal disease, in which alterations of skeletal muscle and increased systemic vasomotor tone with impaired peripheral perfusion contribute to a reduced exercise capacity (1,2). Peripheral vasoconstriction in CHF has been explained by neurohormonal changes like activation of the sympathetic nervous system and the renin-angiotensin system (3,4). In recent years, however, the major role of the vascular endothelium in regulating local vasomotor tone has been revealed (5,6). Endothelial cells regulate vascular diameter by releasing nitric oxide (NO). Its production and release are influenced by endocrine mediators like acetylcholine (ACh) (through muscarinic receptors); mechanical, receptor-independent stimuli (shear stress); and the availability of the NO precursor, L-arginine. Different cardiovascular diseases (i.e., arterial hypertension, coronary artery disease, CHF) are associated with an attenuated vasodilatory response to ACh, as well as impaired flow-dependent vasodilation (FDVD) (7,8).

Cell culture experiments have indicated that shear stress induces an upregulation of the endothelial NO synthase (eNOS) (9). In animal studies, regular physical exercise training (ET) enhances endothelium-dependent vasodilation of conduit coronary arteries (10,11), suggesting that the in vitro results may be relevant for endothelial function in vivo. The positive effects of physical training on endothelial dysfunction could also be documented in patients with CHF. Local training interventions like handgrip exercise (12–14) or bicycle ergometer training improve local flow-dependent, endothelium-mediated vasodilation (15). However, these studies demonstrated only local effects of physical ET on endothelial dysfunction of the trained extremity.

It has been a matter of continuing debate whether there is a critical proportion of the whole body muscle mass that has to be trained to achieve systemic effects on endothelial function. Recently, it has been shown that 10 weeks of lower-limb endurance training in healthy subjects with normal endothelial function have systemic effects on agonist-mediated, endothelium-dependent vasodilation (16).

It remains unclear, however, whether the systemic endothelial effects can also be achieved by local ET in patients with CHF, whose endothelial function is severely compromised. Therefore, the objective of the present study was to investigate whether lower-limb ET in patients with CHF...
has the potential to correct endothelial dysfunction of the upper extremity, indicating systemic rather than local changes of vascular function.

METHODS

Subjects. Twenty-two male patients age ≤70 years with CHF due to dilated cardiomyopathy or ischemic heart disease were studied. The diagnosis of heart disease was based on cardiac catheterization. Left ventricular ejection fraction (LVEF) was <40%, as assessed by left ventriculography. All patients were in stable clinical condition for three months before enrollment and had clinical, radiologic and echocardiographic signs of CHF (New York Heart Association [NYHA] functional class II/III). At baseline, a symptom-free exercise capacity of ≥25 W on bicycle ergometry was required.

Exclusion criteria included any conditions potentially affecting endothelial function, such as arterial hypertension (>160/90 mm Hg), hypercholesterolemia (total cholesterol >6.0 mmol/liter), diabetes mellitus (fasting glucose >6.5 mmol/liter) and current smoking. Patients with heart failure due to valvular heart disease were also excluded from the study.

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

At baseline, all patients performed a symptom-limited, maximal ET on a calibrated, electronically braked bicycle in an upright position. Work load was increased by 25 W every 3 min beginning at 25 W. Respiratory gas exchange was determined continuously throughout the ET, as previously described (15,17). Oxygen consumption was determined at a maximal work load and at the ventilatory threshold. The ventilatory threshold was defined as the oxygen uptake before the systematic increase in the ventilatory equivalent for oxygen, without a concomitant increase in the ventilatory equivalent for carbon dioxide (18).

One day after the maximal ET, endothelial function was studied in the fasting state in a quiet and temperature- and humidity-controlled room. All cardiovascular medications were withheld for >24 h before assessment of endothelium-dependent vasodilation.

Randomization. After baseline measurements, patients were randomized to either a training or control group.

The patients assigned to the training program stayed in the hospital for the period of the study. They exercised 6 times/day for 10 min on a bicycle ergometer under close supervision, at 70% peak oxygen consumption. The patients in the control group received their previous medications, continued their sedentary life-style and were supervised by their private physician.

High precision ultrasound and determination of arterial diameter. For intra-arterial infusion of ACh and nitroglycerin (NTG), a 20-gauge catheter was placed into the brachial artery. Vessel diameter was measured as previously described (14). In brief, after a rest period of 20 min in the supine position, the internal diameter (ID) of the radial artery was determined using a high precision A-mode tracking ultrasound system, which permits measurement of the vessel diameter with a precision of ±2 μm (NIUS-02, Asulab Research Laboratories, Neuchâtel, Switzerland). A 10-MHz transducer was positioned perpendicular to the radial artery about 5 cm proximal to the wrist, without direct skin contact. Blood flow velocity was recorded simultaneously using an 8-MHz Doppler probe (Doptek 2003, Deltex France SA, Montpellier, France). Blood flow (ml/min) was calculated as the average peak velocity × cross-sectional area.

Intra-arterial infusions. Baseline measurements of the arterial diameter were performed by infusing a 5% glucose solution (Glucosteril 5%, Pharmacia, Erlangen, Germany) at a constant rate of 1 ml/min for 5 min. Endothelium-dependent vasodilation was assessed using ACh (Miochol Ciba-Vision, Grossostheim, Germany) in increasing doses: 7.5, 15 and 30 μg/min were administered at a flow rate of 1 ml/min for 5 min at each concentration step.

For determination of FDVD, the brachial artery was occluded by inflating the blood pressure (BP) cuff to 50 mm Hg above the systolic BP for 5 min. The ID of the radial artery was recorded continuously for 2 min in 10-s intervals after deflation of the occlusion cuff. The maximal ID was recorded as a measure of FDVD.

Endothelium-independent vasodilation was determined using NTG (Glyceroltrinitrat, Schwarz Pharma, Monheim, Germany) at a dose of 0.2 mg/min and a flow rate of 1 ml/min. Between each intervention, the infusions were stopped for 2 min to allow the radial artery diameter to return to baseline values.

Statistical analysis. All data are expressed as the mean value ± SEM. The data were tested for normal distribution using the Kolmogorov-Smirnov test, and for homogeneity of variances using Levene’s test.

Absolute values, baseline-corrected IDs (difference between ID during infusion of the respective agonist and ID during glucose infusion) and percent changes from baseline were used for statistical analyses. Both intragroup and intergroup comparisons were made using two-way repeated
measures analysis of variance (ANOVA), followed by the Tukey post hoc test. For the ANOVA procedure, both the results of the test for the interaction between group and time and the results of the Tukey post hoc test are reported. In case of non-normal distribution, intragroup comparisons were performed using the Wilcoxon signed-rank test; intergroup comparisons were done using the Mann-Whitney U test.

The relation between changes in endothelium-dependent vasodilation and increases in peak oxygen consumption was assessed by linear regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. At baseline, patients in the training and control groups did not differ significantly in terms of age, etiology of heart failure, NYHA functional class, LVEF or left ventricular end-diastolic diameter. They had similar values for blood glucose, total cholesterol and systolic arterial pressure. RR diast andcontrol groups did not differ significantly in terms of Table 2.

Drug treatment was not changed in any patient between at therapy did not differ significantly between the two groups. Medical were on digoxin and 59% were on beta-blockers. Medical treatment was not changed in any patient between at therapy did not differ significantly between the two groups.

Baseline measurements. At the beginning of the study, a slight but significant difference in vessel diameter between the training and control groups was noted during glucose infusion: training group 3.42 ± 0.12 mm versus control group 2.99 ± 0.13 mm (p < 0.05). However, patients in the training and control groups had similar responses to ACh, NTG and flow (Table 3), as assessed by the percent change in radial artery diameter. There were no significant differences in oxygen uptake at the ventilatory threshold (11.5 ± 0.9 vs. 11.5 ± 0.9 ml/kg per min) or at peak exercise (16.0 ± 1.2 vs. 16.9 ± 1.3 ml/kg per min) between training and control groups.

Vasodilative responses to ACh. After four weeks of ET, ACh-mediated, endothelium-dependent vasodilation increased significantly from 33 ± 10 to 127 ± 25 μm (p < 0.001 vs. control group at four weeks), from 114 ± 31 to 290 ± 47 μm (p < 0.001 vs. control group at four weeks) and from 184 ± 57 to 453 ± 63 μm (p < 0.001 vs. control group at four weeks) at 7.5, 15 and 30 μg/min of ACh, respectively. In the control group, the response to ACh remained virtually unchanged during the study period (Fig. 1).

Vasodilative response to NTG. Bicycle ergometer training did not change the endothelium-independent vasodilatory capacity of the radial artery. In the training group, infusion of NTG led to a comparable increase in the ID of the radial artery at beginning and end of the study (594 ± 47 vs. 602 ± 56 μm, p = 0.563). In parallel, the endothelium-independent vasodilative capacity remained unchanged in the control group.

Flow-dependent vasodilation. Four weeks of bicycle ergometer training were associated with a significant increase in FDVD, from 374 ± 57 to 570 ± 76 μm (p < 0.01 vs. control group at four weeks); in the control group, FDVD remained essentially unchanged (344 ± 20 μm at the beginning of the study vs. 351 ± 22 μm at four weeks).

Exercise capacity. Four weeks of aerobic ET led to a significant increase in oxygen consumption at the ventilatory threshold and at peak exercise, by 19 ± 5% (from 11.5 ± 0.9 to 13.4 ± 0.9 ml/kg per min, p < 0.001 vs. beginning of study; p = 0.004 for interaction [ANOVA]) and by 21 ± 2% (from 16.0 ± 1.2 to 19.4 ± 1.4 ml/kg per min, p < 0.001 vs. beginning of study; p < 0.001 for interaction [ANOVA]), respectively. In the control group, oxygen consumption at the ventilatory threshold and at peak exercise did not change between the beginning and end of the study (11.5 ± 0.8 vs. 11.3 ± 0.8 ml/kg per min and 16.9 ± 1.2 vs. 16.3 ± 1.3 ml/kg per min). One patient in the control group did not tolerate the mouth piece of the ergospirometer during exercise; therefore, complete respiratory data are available in 10 control subjects.

Correlation between improvement of endothelial function and exercise capacity. Changes in agonist-mediated, endothelium-dependent vasodilation (ACh [30 μg/min]) induced by ET were significantly correlated with changes in peak oxygen consumption (r = 0.63, p < 0.05) (Fig. 2).

Table 1. Patient Characteristics

<table>
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<th>Training Group (n = 11)</th>
<th>Control Group (n = 11)</th>
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<tr>
<td>Age (yrs)</td>
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<td>59 ± 3</td>
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<tr>
<td>Etiology of CHF</td>
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<td></td>
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<tr>
<td>DCM</td>
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</tr>
<tr>
<td>IHD</td>
<td>5</td>
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<tr>
<td>NYHA functional class (II/III)</td>
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<td>8/3</td>
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<td>LVEDD (mm)</td>
<td>65 ± 2</td>
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<tr>
<td>LVEF (%)</td>
<td>26 ± 3</td>
<td>24 ± 2</td>
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<td>Blood glucose (mmol/liter)</td>
<td>5.6 ± 0.2</td>
<td>5.3 ± 0.3</td>
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<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>5.2 ± 0.2</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>RR diast (mm Hg)</td>
<td>83 ± 2</td>
<td>78 ± 2</td>
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<tr>
<td>RR syst (mm Hg)</td>
<td>128 ± 3</td>
<td>123 ± 5</td>
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</table>

Data are shown as the mean value ± SEM or number of subjects.

CHF = chronic heart failure; DCM = dilated cardiomyopathy; IHD = ischemic heart disease; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RR diast = diastolic arterial pressure; RR syst = systolic arterial pressure.

Table 2. Medical Treatment

<table>
<thead>
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<td>ACE inhibitors</td>
<td>11 (100%)</td>
<td>11 (100%)</td>
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<td>Diuretics</td>
<td>9 (82%)</td>
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<td>Digoxin</td>
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<td>5 (45%)</td>
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<tr>
<td>Beta-blockers</td>
<td>5 (45%)</td>
<td>8 (73%)</td>
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</table>

Data are presented as the number (%) of subjects.

ACE = angiotensin-converting enzyme.
DISCUSSION

The present study may extend our current concept of the effects of ET on vascular endothelial function in two regards: 1) regular ET on the cycle ergometer has systemic effects on endothelial function in patients with CHF; and 2) improvement in the endothelium-dependent vasodilative capacity is correlated with an increase in exercise capacity after four weeks of regular ET.

Effects of ET on endothelium-dependent vasodilation.

In patients with CHF, endothelium-dependent vasodilation of peripheral vessels is impaired (7), possibly as a result of impaired eNOS activity (8,15). Physical ET increases shear stress by intermittently augmenting pulsatile flow along the endothelium. During handgrip exercise, the increase in pulsatile flow remains restricted to the forearm vessels. In bicycle ergometer training, however, the trained muscle mass exceeds the critical proportion necessary to achieve systemic cardiovascular effects. Although one is inclined to presume that the highest increase in blood flow—and thus the most pronounced shear stress effects—will be in the vasculature supplying the exercised muscles, the increases in heart rate and BP amplitude during the training program systematically increase pulsatile flow. In an independent parallel study, a 10-week program of aerobic and anaerobic ET in healthy young men led to a systemic enhancement of endothelial function (16). The present study extends these findings to pathologic states. To our knowledge, it is the first to prove the systemic effects of lower-limb ET in patients with CHF. Four weeks of bicycle ergometer ET at a submaximal level led to a significant improvement of endothelial function of the upper extremity. The vasodilatory response to ACh at the highest concentration increased 2.5-fold, whereas FDVD improved by 50%. Other factors potentially influencing vascular endothelial function, such as blood glucose, serum cholesterol levels and arterial BP, remained unchanged during the study period. A possible alternative hypothesis could be that ET induces changes in circulating humoral factors, which, in turn, affect endothelial function. However, no data on the short-term influences of ET on catecholamines, for example, in patients with CHF are available thus far.

Our results contrast with those of a previous study by Demopoulos et al. (19), who failed to show any effect of bicycle ergometer training on endothelial function of the
untrained upper extremity. Several differences of the present study may explain the divergent findings: 1) ET was performed at a significantly lower intensity, which may not have had the effects on BP amplitude necessary to attain systemic effects; 2) the patients studied by Demopoulos et al. (19) were in more advanced stages of heart failure; and 3) their methodologic approach for measuring endothelial function differed from that of our study (forearm venous occlusion plethysmography vs. high resolution ultrasound).

**Correlation between endothelium-dependent vasodilation and exercise capacity.** In a previous study involving patients with CHF, we found a correlation between changes in endothelium-dependent vasodilation and changes in functional work capacity (15). In accordance with this observation, changes in endothelium-dependent vasodilatory capacity were related to changes in peak oxygen uptake in the present study. The correlation between improvement of endothelial vasodilatory function and functional work capacity implies that by improving endothelial dysfunction, exercised-induced peripheral perfusion is augmented, which, in turn, leads to a higher exercise capacity.

**Effects of ET on FDVD.** Endothelial dysfunction in CHF is not restricted only to agonist-mediated vasodilation; it also affects FDVD during reactive hyperemia (12). During reactive hyperemia, the maximal vasodilation occurs ~40 to 60 s after release of arterial occlusion (20). In animal as well as in human studies, it could be shown that FDVD is mediated partly by endothelium-derived NO (21–23). The proportion of FDVD inhibited by NG-monomethyl L-arginine (L-NMMA), an eNOS inhibitor, increases significantly after ET in patients with CHF (12,15). These results indicate an increased basal activity of eNOS after ET, which may be indicative of eNOS upregulation after training, as previously described in animal experiments (9,10).

Because endothelial factors contribute substantially to reactive hyperemia, we expected significant changes after ET. Maximal FDVD was significantly enhanced after ET by 54%.

**Effects of ET on endothelium-independent vasodilation.** Like other cardiovascular diseases, CHF is associated with increased oxidative stress. Reactive oxygen species, such as superoxide anions (O$_2^-$) rapidly scavenge NO, leading to an accelerated breakdown of NO, and consequently, an impairment of endothelial function (24,25). In a recently published clinical study, Hornig et al. (26) demonstrated that the early and late application of the radical scavenger vitamin C, improves flow-induced, NO-mediated vasodilation in forearm vessels of patients with CHF. In cell culture experiments, shear stress was associated with an upregulation of the cytosolic copper/zinc-containing superoxide dismutase, a free radical scavenger enzyme (27). Thus, the inactivation of NO by vascular superoxide anions or other reactive oxygen species may be attenuated after ET.

The fact that we did not find any differences in endothelium-independent vasodilation after training may indicate either that NTG was administered in sufficient excess above any reactive oxygen species or that a longer training intervention may be necessary to influence endothelium-independent vasodilation.

**Clinical implications.** In the present study, we demonstrated that four weeks of lower-limb aerobic ET corrects radial artery endothelial dysfunction in patients with CHF. The finding that the beneficial effects of training are not confined to the trained extremity indicates a systemic effect on endothelial function. Our study implies that endothelial dysfunction will be systemically improved as soon as a critical muscle mass is trained at a level sufficient to increase BP amplitude and shear stress. This message has important implications for ongoing trials investigating the effects of local ET in advanced stages of CHF.

**REFERENCES**


