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Exercise Training in Patients With Chronic Heart Failure Improves Endothelial Function Predominantly in the Trained Extremities

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The present study investigates whether lower-limb dominant exercise training in patients with chronic heart failure (CHF) improves endothelial function primarily in the trained lower extremities or equally in the upper and lower extremities. Twenty-eight patients with CHF were randomized to the exercise or control group. The exercise group underwent cycle ergometer training for 3 months while controls continued an inactive sedentary lifestyle. Exercise capacity (6-min walk test) and flow-mediated vasodilation in the brachial and posterior tibial arteries were evaluated. After 3 months, walking performance increased only in the exercise group (488±16 to 501±14 m [control]; 497±23 to 567±39 m [exercise, $p<0.05$]). The flow-mediated vasodilation in the brachial arteries did not change in either group (4.2±0.5 to 4.5±0.4% [control]; 4.3±0.5 to 4.6±0.4% [exercise]), but that in the posterior tibial arteries increased only in the exercise group (4.1±0.5 to 4.1±0.3% [control]; 3.6±0.3 to 6.4±0.6% [exercise, $p<0.01$]). Cycle ergometer training improved flow-mediated vasodilation in the trained lower limbs, but not in the untrained upper limbs. Exercise training appears to correct endothelial dysfunction predominantly by a local effect in the trained extremities. (*Circ J* 2003; **67:** 505–510)

Key Words: Chronic heart failure; Endothelial function; Exercise training; Flow-mediated vasodilation

Since the early 1980s, exercise training has been used as a therapeutic measure for patients with chronic heart failure (CHF) because those trials demonstrated that physical training improves aerobic work capacity and peak oxygen consumption in CHF patients[1–3] A more recent report documented that long-term moderate exercise training in CHF patients decreases hospital re-admissions and cardiac deaths, and improves exercise capacity and quality of life[4] The benefits of exercise training have been attributed to improvements in peripheral hemodynamics and the oxidative capacity of skeletal muscle rather than to improved cardiac function[5,6]

The endothelium plays an important role in peripheral perfusion during exercise by releasing vasodilatory factors[7–9] Recent studies have demonstrated that endothelium-dependent vasodilation is impaired in CHF patients[10–16] and that physical training contributes to the correction of endothelial dysfunction in these patients[17,18] Some investigators have reported that the improvement in endothelium-dependent vasodilation after exercise training is a local effect in the trained extremities, probably caused by the up-regulation of endothelial nitric oxide (NO) synthase as a consequence of regularly increased shear stress[18–20] Another researcher has shown that exercise training can correct endothelial dysfunction systemically by improving humoral and autonomic factors[21] However, the chief mechanism for the correction of endothelial dysfunction in CHF patients after exercise training remains unclear. The aim of the present study was to determine whether local or systemic vascular effects predominate in CHF patients who receive exercise training.

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Methods

Patients

The present study conformed to the guidelines established by the ethics committee of the Jichi Medical School, and written informed consent was obtained from all patients. The eligibility criteria were as follows: stable CHF caused by dilated cardiomyopathy or ischemic heart disease, New York Heart Association functional class 2 or 3, and left ventricular ejection fraction (LVEF) less than 40%. The diagnosis of heart disease and evaluation of LVEF were based on cardiac catheterization. The enrolled patients were randomized to either an exercise or control group. Patients in the exercise group underwent supervised cycle ergometer training for 2–3 days per week for 3 months and the controls were instructed to continue leading their normal sedentary life for the same time period. There were no significant differences in the 2 groups with respect to gender, diagnosis of heart disease, New York Heart Association functional class, LVEF, serum concentrations of cholesterol and humoral factors, and examined vessel diameter, except for age and exercise capacity (Table 1). The incidence of chronic atrial fibrillation was equal between the 2 groups (Table 1). Atrial fibrillation is indi-

Table 1 Characteristics of the Patients in the 2 Study Groups at Baseline

	Control group	Exercise group	p value
n (M/F)	14 (8/6)	14 (12/2)	NS
Age (years)	62±2	55±2	$p<0.05$
Diagnosis (DCM/IHD)	6/8	9/5	NS
Atrial fibrillation (n)	2	2	NS
NYHA class (2/3)	8/6	10/4	NS
Peak $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.7±0.9	18.0±1.3	$p<0.05$
Ventilatory threshold ($ml \cdot kg^{-1} \cdot min^{-1}$)	9.9±0.6	12.0±0.8	NS
Left ventricular ejection fraction (%)	33±2	29±2	NS
LDL cholesterol (mg/dl)	129±11	98±8	NS
HDL cholesterol (mg/dl)	45±3	41±3	NS
Norepinephrine (pg/ml)	654±90	456±123	NS
Endothelin-1 (pg/ml)	3.40±0.52	2.92±0.22	NS
Interleukin-6 (pg/ml)	3.56±0.94	3.22±0.80	NS
Brain natriuretic peptide (pg/ml)	386±83	281±92	NS
Vessel diameter (mm)			
Brachial arteries	4.16±0.22	4.53±0.17	NS
Posterior tibial arteries	2.66±0.14	2.76±0.16	NS
ACE inhibitors or ARBs (n)	10	13	NS
β-blockers (n)	7	10	NS
HMG-CoA reductase inhibitors (n)	7	4	NS

The vessel diameter reflects the end-diastolic dimension before cuff inflation. Statistical analysis was performed using the goodness test of fit for chi-square or unpaired t-test. DCM, dilated cardiomyopathy; IHD, ischemic heart disease; $\dot{V}O_2$, oxygen consumption; LDL, low density lipoprotein; HDL, high density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

cated as one of the factors that alter exercise-induced vasodilation[9] The use of cardiac medications, such as angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, and 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors were statistically equal at baseline in the 2 groups (Table 1). Changes in pharmacologic treatment during the test period was permitted only when the attending physician judged that it was necessary. We evaluated exercise capacity, humoral factors, and endothelial function at baseline and 3 months later in both groups. Endothelial function was assessed on the trained lower and untrained upper extremities in order to compare the local and systemic vascular effects induced by lower limb dominant exercise training.

Exercise Capacity

Prior to training, the exercise capacity of each patient was determined by both a symptom-limited cardiopulmonary exercise test and a 6-min walk test. During the exercise test, patients pedaled in the upright position on an electronically-braked cycle ergometer (Ergometer 2320®, Minato Medical Science Co, Ltd, Osaka, Japan) at a constant rate of 60 rpm. The work rate was increased by a 10 W/min ramp until severe subjective symptoms, such as shortness of breathing and leg fatigue, or signs of myocardial ischemia appeared. Expired air was continuously analyzed with a metabolic cart (AE-300S®, Minato Medical Science Co Ltd). The ventilatory threshold was determined by the V-slope method;[22] whereby the starting point of the non-linear increase in carbon dioxide output was measured. The cardiopulmonary exercise test was done only at baseline in order to determine the intensity of exercise training applied to each patient. The 6-min walk test was repeated before and after the 3 month test period to evaluate the change in exercise capacity. The walk test was performed as described in a previous study;[23] that is, patients were instructed to walk the length of a 50-m hospital corridor for 6 min until fatigue prevented them from continuing. An examiner followed the patient, but did not give any encouragement to continue exercising during the test.

Humoral Factors

Some investigators have indicated that vasoconstrictive or pro-inflammatory humoral factors cause endothelial dysfunction in CHF patients and are reduced by vigorous exercise training.[24–26] We measured norepinephrine, endothelin-1, and interleukin-6 concentrations before and after exercise training in order to evaluate exercise-induced systemic effects. In addition to those substances, the concentration of brain natriuretic peptide (BNP) was also examined to evaluate failing heart status. Blood was drawn from resting patients after one night of fasting. Norepinephrine and interleukin-6 were measured by high-performance liquid chromatography and chemiluminoenzyme immunoassay, respectively. Endothelin-1 and BNP were measured by radioimmunoassay.

Endothelial Function

Experienced investigators (N Kobayashi and T Iwasawa) analyzed the endothelial function, unaware of which group a patient was enrolled in. The change in vascular endothelial function in the upper and lower extremities was evaluated as an index of systemic and local vascular effects, respectively, of lower limb dominant exercise training. Endothelial function was assessed by flow-mediated vasodilation (FMD) following reactive hyperemia. First, we examined the brachial arteries in longitudinal section just above the antecubital fossa using 15-MHz ultrasound equipment (SONOS 5500, Philips Medical Systems, Best, The Netherlands). Doppler measurements provided the waveforms of intravascular blood flow. Computer software installed in the ultrasound apparatus traced the waveforms automatically and calculated mean blood flow velocities. The vessel diameter was measured on a ultrasound screen as a media-to-media distance at end-diastole (Fig 1). Next, a pneumatic cuff was inflated on the forearm for 5 min at

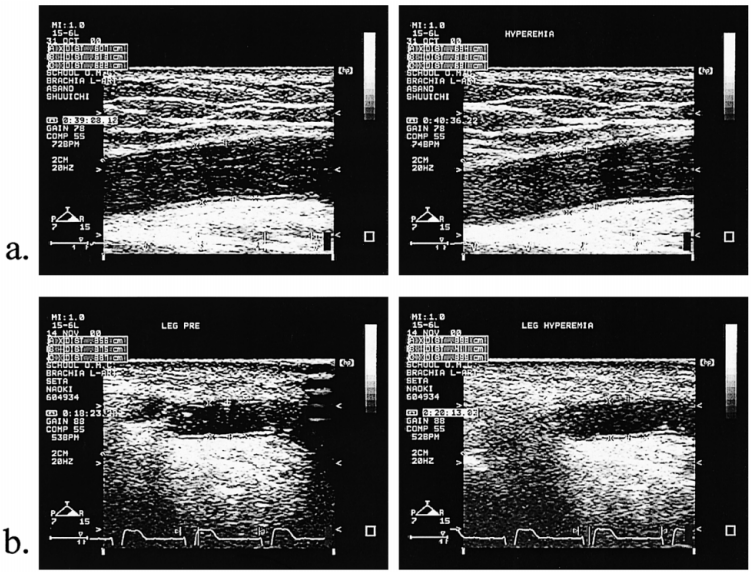

Fig 1. Two-dimensional ultrasound images of the brachial arteries (a) and posterior tibial arteries (b) at baseline (Left) and during reactive hyperemia following cuff deflation (Right). Flow-mediated vasodilation was defined as the percent increase in vessel diameter measured by the media-to-media distance. A vessel's diameter was determined by the mean value of 3 points on the ultrasound screen in order to minimize the measurement error.

a pressure of 200 mmHg. In this state, peripheral tissue ischemia promotes microvascular relaxation that reduces the afterload in limb circulation. Following cuff deflation, accelerated blood flow (reactive hyperemia) promotes the vasodilatory effect in the brachial artery. We measured intravascular blood flow velocities and vessel diameter at 30 and 60 s following cuff deflation, respectively, in the same manner as at baseline. Reactive hyperemia was calculated as the percent increase in mean blood flow velocities after cuff deflation. The value of FMD was defined as the percent increase in vessel diameter following reactive hyperemia. The location of the measurement was marked on the skin to ensure that the same section of artery was measured at baseline and after cuff deflation. In order to minimize the error in measurement, the vessel diameter was determined by the mean value of 3 points on the ultrasound screen. Fifteen minutes after evaluation of the upper limb, we evaluated FMD in the posterior tibial arteries (Fig 1). The measurements of blood flow velocities and vessel diameters were performed in the same manner as for the brachial arteries. A pneumatic cuff was inflated and deflated on the calf. Posterior tibial arteries are tortuous compared with the brachial artery, so we carefully selected a straight portion near the medial malleolus. In some patients, it was difficult to visualize the posterior tibial arteries as clearly as the brachial arteries and in those cases with obscure media layers, vessel diameters were measured between the inner margins of the adventitia.

Training Program

Patients in the exercise group underwent supervised physical training using computerized cycle ergometers (Ergomedic 818®; Monark Exercise AB, Varberg, Sweden). The training was performed 2–3 days per week in two 15-min sessions per day for 3 months. During training, we continuously measured the patients' heart rates with telemetry. In each session, the exercise speed was adjusted to maintain the heart rate equivalent to the ventilatory threshold level for 15 min. The ventilatory threshold level is equivalent to the upper limit of aerobic exercise and should not induce unfavorable conditions, such as acidosis or catecholamine increase. The heart rate corresponding to the ventilatory threshold level was also the target exercise speed in patients taking β-blockers throughout the training period. When it was difficult to determine the exercise intensity based on heart rate because of atrial fibrillation or alterations in medications, we used the rating of perceived exertion as an index of workload. In those cases, we regulated the exercise speed within the rating of 13 in the 20-grade Borg scale[27]

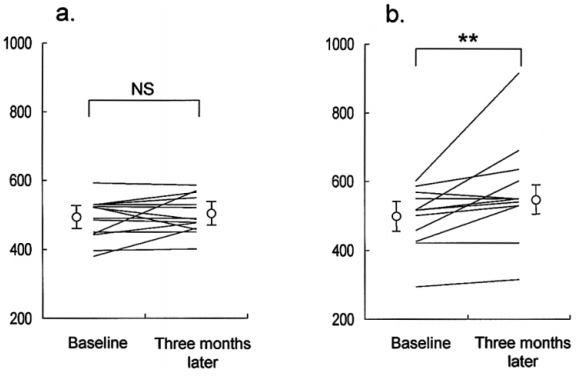

Fig 2. Change in distance covered during the 6-min walk test in the control (a) and exercise (b) groups. Walking performance improved in the exercise group, but not in the control group.

Statistical Analysis

All data are expressed as the group mean ± standard error. Patients' characteristics were compared between the control and exercise groups using the goodness test of fit for chi-square or unpaired t-test. After 3 months observation, we analyzed the transition in walking performance, humoral factors, and vascular function in each group using paired t-test. The percent increase in FMD was also compared between the control and exercise groups by each artery. Differences were considered statistically significant at $p<0.05$.

Results

All patients completed the protocol without exacerbation of heart failure requiring re-hospitalization.

Table 2 Vascular Examination Results at Baseline and 3 Months Later

	Control group		p value	Exercise group		p value
	Baseline	3 months later		Baseline	3 months later	
Upper limbs						
Mean flow velocity						
Resting state (cm/s)	16.8±1.6	16.6±1.4		19.4±2.4	21.2±1.8	
Cuff deflation (cm/s)	50.3±8.5	45.2±4.2		50.7±4.8	55.2±5.1	
Reactive hyperemia (%)	187±26	182±23	NS	179±33	92±27	NS
Vessel diameter						
Resting state (mm)	4.16±0.22	4.11±0.22		4.53±0.17	4.54±0.17	
Cuff deflation (mm)	4.33±0.22	4.29±0.22		4.73±0.17	4.74±0.18	
Flow-mediated vasodilation (%)	4.19±0.45	4.51±0.41	NS	4.34±0.45	4.56±0.43	NS
Lower limbs						
Mean flow velocity						
Resting state (cm/s)	17.8±3.5	14.2±2.4		19.9±2.9	22.9±3.9	
Cuff deflation (cm/s)	33.3±3.7	30.3±2.5		39.9±5.9	43.8±3.6	
Reactive hyperemia (%)	162±65	165±43	NS	142±47	202±92	NS
Vessel diameter						
Resting state (mm)	2.66±0.14	2.53±0.12		2.76±0.16	2.80±0.16	
Cuff deflation (mm)	2.77±0.14	2.67±0.12		2.86±0.16	2.98±0.16	
Flow-mediated vasodilation (%)	4.08±0.51	4.07±0.34	NS	3.64±0.26	6.44±0.56	p<0.01

Reactive hyperemia was calculateds the percent increase in mean flow velocity following cuff deflation. Flow mediated vasodilation was calculted as the percent change in vessel diameter following cuff deflation. Reactive hyperemia and flow mediated vasodilation were compared between baseline and 3 months later in each group (paired t-test). NS, not significant.

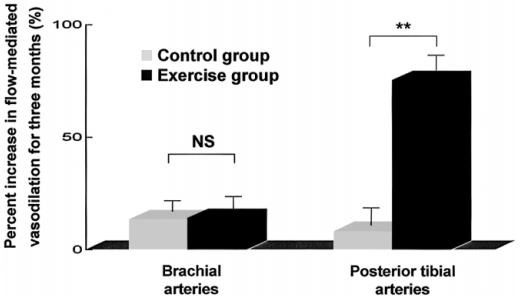

Fig 3. Percent increase in flow-mediated vasodilation (FMD) in the brachial and posterior tibial arteries after 3 months. The exercise group showed a greater increase in the posterior tibial arteries than did the control group, but not in the brachial arteries. ** p<0.01, NS, not significant.

Exercise Performance

The results of the 6-min walk test were compared between baseline and 3 months later in each group. In the control group, the distance walked did not change after 3 months (488±16 to 501±14 m, NS, Fig 2), whereas it had significantly increased in the exercise group (497±23 to 567±39 m, p<0.05, Fig 2).

Humoral Factors

There were no significant changes in any factors after 3 months in either group: norepinephrine, 654±90 to 792±180 pg/ml in the control group, 456±123 to 624±98 pg/ml in the exercise group; endothelin-1, 3.40±0.52 to 3.95±0.30 pg/ml in the control group, 2.92±0.22 to 2.79±0.32 pg/ml in the exercise group; interleukin-6, 3.56±0.94 to 2.73±0.69 pg/ml in the control group, 3.22±0.80 to 2.00±0.25 pg/ml in the exercise group; BNP, 383±89 to 383±130 pg/ml in the control group, 281±92 to 267±85 pg/ml in the exercise group.

Reactive Hyperemia

Reactive hyperemia was calculated as the percent increase in mean blood flow velocities after cuff deflation. In the control group, it did not change in either extremity after 3 months observation (Table 2). In the exercise group, reactive hyperemia in the lower extremities had a tendency to increase after 3 months training, but the change was not significant (Table 2).

Flow-Mediated Vasodilation

In each group, the value of FMD at baseline and after 3 months was compared. Control patients showed no improvement in either the brachial or posterior tibial arteries (Table 2). In the exercise group, FMD increased significantly in the posterior tibial arteries (p<0.01), but not in the brachial arteries (Table 2). In order to clarify the difference between the control and exercise group, we compared the percent increase in FMD for 3 months: ([FMD 3 months later]−[FMD at baseline]×[FMD at baseline] (100 (%). In the brachial arteries, the percent increase in FMD did not differ between the 2 groups (13.5±9.3% in the control group, 14.0±11.5% in the exercise group; NS) (Fig 3). In posterior tibial arteries, the percent increase in FMD was significantly greater in the exercise group than in the control group (8.27±10.0% in the control group, 75.3±9.6% in the exercise group; p<0.01) (Fig 3).

Discussion

We evaluated vascular endothelial function before and after cycle ergometer training in CHF patients. FMD improved in the trained lower limbs, but not in the untrained upper limbs. The control patients, who continued a sedentary lifestyle, showed no improvement in FMD in any of the extremities.

Flow-Mediated Vasodilation

Endothelium-dependent vasodilation has received attention as an indicator of endothelial function that can be measured in the clinical setting. Celermajer et al established a non-invasive evaluation of endothelium-dependent vasodilation using reactive hyperemia following cuff deflation[28] Reactive hyperemia enhances endothelial shear stress in

conduit arteries, which promotes the vasodilatory effects meditated by endothelial NO production?[29] In the present study, lower-limb dominant exercise training improved FMD in the lower extremities despite no significant increase in reactive hyperemia in those limbs. This finding may indicate that the improvement of FMD is mainly achieved by a rise in the endothelial response to shear stress, not by an increase in reactive hyperemia per se.

Although the evaluation of FMD following reactive hyperemia has become widely used for assessing endothelial function, the measurement technique has not been fully standardized?[30] In the present study, the duration of artery compression and the timing of vessel measurements were based on a previous report that had described the best settings in which maximum FMD should be expected?[31] In many previous studies, FMD has been evaluated in combination with endothelium-independent vasodilation using nitrates in attempts to clarify that FMD is an indicator of endothelial function. Many investigators have demonstrated that FMD is an endothelium-dependent phenomenon, chiefly induced by endothelial NO production?[29,32–34] In the present study, we evaluated FMD as an established index of endothelium-dependent vasodilation without the additional measure of using nitrates.

Evaluation of Exercise Capacity

We used the 6-min walk test as the evaluation of the change in exercise capacity. The test was first used in heart failure patients by Guyatt et al in 1985 and has subsequently gained acceptance as a measure for evaluating exercise capacity?[23] The test distance has been reported to correlate with peak oxygen consumption?[35,36] and to predict long-term mortality and morbidity in CHF patients?[37] Although some investigators are skeptical about its usefulness as a substitute for a cardiopulmonary exercise test?[38] the repeated measurements of peak oxygen consumption in a cardiopulmonary exercise test are somewhat laborious and pose risks to CHF patients, such as exercise-induced arrhythmias and myocardial ischemia. The walk test is considered to be a safe and simple method suitable for repeated testing in outpatients with CHF.

Training Program

In the present study, the lower limb dominant exercise training failed to improve the FMD in the untrained upper limbs, which does not agree with a previous study that demonstrated systemic vascular effects after cycle ergometer training in CHF patients?[21] We speculate that the discrepancy was chiefly caused by the difference in the training programs. The previous study involved six 10-min exercise sessions every day in hospitalized patients, so that the intensity of exercise training was equivalent to 70% peak oxygen consumption. In the present study, outpatients performed two 15-min exercise sessions for 2–3 days per week and the exercise intensity was regulated to maintain a ventilatory threshold level that corresponded to approximately 60–70% of maximum oxygen consumption. Therefore, our training program was not as frequent as in the previous study, although the exercise intensity was almost equivalent. Despite the increased attention given to exercise training in CHF patients, standard guidelines have not been fully established and even in recent studies, exercise intensities and frequencies vary from 50% to 80% of maximum oxygen consumption and 3–7 days per week, respectively?[39] The present study employed the same exercise program as we use in clinical practice for CHF patients. More frequent exercise training might have given a systemic vascular effect in addition to the predominantly local effect in the trained extremities.

Vascular Effects of Exercise Training

The reasons why exercise training corrects endothelial dysfunction in CHF patients remain controversial. Noris et al have reported that laminar shear stress up-regulates the mRNA concentration of NO synthase in cultured endothelial cells?[20] which indicates that exercise-induced blood flow acceleration may up-regulate endothelial NO-synthase activity dominantly in the trained extremities. On the other hand, some investigators have shown that exercise training corrects endothelial dysfunction systemically by the reduction of vasoconstrictive factors such as norepinephrine and endothelin-1?[21,24–26] Although those substances are known prognostic factors in CHF patients,?[40] it is still unclear whether the improvement in those factors contributes to the benefits of exercise training. For example, Hambrecht et al have demonstrated that exercise training corrects peripheral vascular resistance and exercise capacity, but the reduction in vascular resistance does not correlate to changes in plasma catecholamine concentrations?[6] In the present study, exercise training improved the distance covered in the 6-min walk and endothelial function in the trained extremities without changing the concentration of vasoconstrictive or pro-inflammatory humoral factors. Our finding suggests that the reduction in humoral factors, such as norepinephrine, endothelin-1, and interleukin-6, is not the main mechanism bt which physical training improves endothelial function and exercise capacity in CHF patients.

Clinical Implications

The present study results indicate that exercise-induced blood flow acceleration corrects endothelial dysfunction in CHF patients predominantly in the trained extremities. Therefore, to enhance the efficacy of physical training, a systemic exercise program is preferable to localized muscle training.

Study Limitation

The baseline characteristics were not entirely accordant between the 2 groups and so the difference in the age and exercise capacity might have influenced the outcome in the present study.

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