Published by Elsevier Science Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(02)02772-9

Exercise Training Improves Biventricular Oxidative Metabolism and Left Ventricular Efficiency in Patients With Dilated Cardiomyopathy

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OBJECTIVES The aim of this study was to determine the effect of exercise training on myocardial oxidative metabolism and efficiency in patients with idiopathic dilated cardiomyopathy (DCM) and mild heart failure (HF).

BACKGROUND Exercise training is known to improve exercise tolerance and quality of life in patients with chronic HF. However, little is known about how exercise training may influence myocardial energetics.

METHODS Twenty clinically stable patients with DCM (New York Heart Association classes I through III) were prospectively separated into a training group (five-month training program; n = 9) and a non-trained control group (n = 11). Oxidative metabolism in both the right and left ventricles (RV and LV) was measured using [^{11}C]acetate and positron emission tomography. Myocardial work power was measured using echocardiography. Myocardial efficiency for forward work was calculated as myocardial work power per mass/LV oxidative metabolism.

RESULTS Significant improvements were noted in exercise capacity (Vo_2) and ejection fraction in the training group, whereas no changes were observed in the non-trained group. Exercise training reduced both RV and LV oxidative metabolism and elicited a significant increase in LV forward work efficiency, although no significant changes were observed in the non-trained group.

CONCLUSIONS Exercise training improves exercise tolerance and LV function. This is accompanied by a decrease in biventricular oxidative metabolism and enhanced forward work efficiency. Therefore, exercise training elicits an energetically favorable improvement in myocardial function and exercise tolerance in patients with DCM. (J Am Coll Cardiol 2003;41:460–7)

Heart failure (HF) is a growing health problem in industrialized countries that will continue to worsen as the aged population increases. In HF patients, exercise training programs have proven to be safe and effective at improving many functional parameters such as exercise capacity (1–3), muscular strength (2,4,5), and health-related quality of life (1). The training benefits achieved in patients with HF have been primarily associated with peripheral vasculature adaptations, including improvements in peripheral endothelial function (6), increased proportion of type 1 skeletal muscle fibers (7), and enhanced skeletal muscle oxidative capacity (5,7). Studies have also investigated possible central changes

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with exercise training but have primarily focused on the functional parameters of the heart itself (3,8). The effect of exercise training on myocardial oxidative metabolism has not been previously investigated.

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Manuscript received May 31, 2002; revised manuscript received July 10, 2002, accepted August 26, 2002.

The use of positron emission tomography (PET) and [^{11}C]acetate is unique as it allows assessment of flux through the tricarboxylic acid cycle and thus provides an estimation of myocardial oxidative metabolism in both the right and left ventricles (RV and LV) simultaneously (9). The accuracy of using [^{11}C]acetate to measure myocardial oxygen uptake has been previously validated in animal studies (10,11) and also in patients with idiopathic dilated cardiomyopathy (DCM) (12). The use of [^{11}C]acetate in combination with non-invasive measures of ventricular function to estimate myocardial efficiency in patients with DCM has been successfully established (12–14).

The purpose of this study was to investigate the influence of long-term exercise training on myocardial energetics and efficiency in patients with idiopathic DCM and mild HF.

METHODS

Patient population. A total of 20 patients with idiopathic DCM and HF were enrolled in the study. All patients were clinically stable under active medical treatment (New York Heart Association [NYHA] class 1.47 ± 0.51) and did not have evidence of decompensated HF at the time of the study. All patients were receiving stable medical therapy, including beta-blockade, for at least three months before the start of the study (with a minor change in one patient two

Abbreviations and Acronyms

BP = blood pressure
DCM = dilated cardiomyopathy
HF = heart failure
HR = heart rate
k_{mono} = [^{11}C]acetate clearance rate
LV = left ventricle or ventricular
NYHA = New York Heart Association
PET = positron emission tomography
ROI = region of interest
RV = right ventricle or ventricular
V_{O_2} = oxygen uptake

weeks before the start of the study: atenolol from 12.5 to 25 mg/day). Exclusion criteria included a history of ischemic heart disease (as generally documented by angiography or stress nuclear imaging), diabetes mellitus, primary valvular disease, tobacco use, uncontrolled hypertension, and orthopedic limitations. The patients were separated into two groups based on living proximity to the exercise training site. This process was based solely on logistic factors and took place without the investigators' knowledge of the patient's functional capacity, medical status, or physical examination results. The training group (n = 9) participated in a five-month training program that included both endurance and strength training components. The non-training group (n = 11) served as a control group and continued medical therapy as advised by their physician.

The patient groups did not differ in terms of body size, peak oxygen uptake (V_{O_2}), ejection fraction, and NYHA functional class. Both patient groups also followed similar medication regimens (Table 1).

No significant changes in medication took place during the study. One patient from each group had atrial fibrillation. Four patients in the control group were withdrawn from the study: one patient had a biventricular pacemaker implanted; one was hospitalized for worsening HF, and thus medical therapy was changed; and two patients withdrew voluntarily. Thus, 16 patients completed the entire study: nine in the training group and seven in the control group.

Table 1. Patient Characteristics

	Training Group (n = 9)	Control Group (n = 7)
Gender (male/female)	7/2	7/0
Age (years)	55 ± 8	55 ± 8
BMI (kg/m^2)	27.8 ± 8.7	30.0 ± 3.4
Peak oxygen uptake (ml/kg/per min)	19.4 ± 4.1	20.6 ± 4.2
Ejection fraction (%)	33.3 ± 8.3	35.3 ± 7.4
NYHA functional class	1.6 ± 0.5	1.2 ± 0.4
Medications		
ACE inhibitors	78% (7/9)	86% (6/7)
Beta-blockers	78% (7/9)	100% (7/7)
Diuretics	33% (3/9)	14% (1/7)
Digoxin	33% (3/9)	29% (2/7)
Angiotensin II blocker	11% (1/9)	0

Data are presented as the mean value ± SD or percentage (n/N) of subjects.
ACE = angiotensin-converting enzyme; BMI = body mass index; NYHA = New York Heart Association.

The study protocol was approved by the local Ethical Committee and was carried out in accordance with institutional guidelines. The purpose and potential risks of the study were explained to all subjects, and all subjects gave written, informed consent.

Study design. All study procedures were completed under the same conditions and at the same time of day for both the baseline and follow-up tests. All patients were instructed to follow their normal medication regimen on the study days. The PET study day consisted of an echocardiographic study and two PET studies. Basal myocardial perfusion was assessed using [^{15}O]H_2O, and hyperemic perfusion was assessed after dipyridamole administration. Myocardial oxidative metabolism was assessed using [^{11}C]acetate.

Cardiopulmonary exercise testing and training program. All study subjects underwent a symptom-limited, incremental cycle ergometer test with continuous respiratory gas exchange analysis (V_{max}; Sensormedics, Bilthoven, The Netherlands), and peak V_{O_2} was measured. The training program consisted of an orientation period followed by three supervised exercise sessions per week for five months. All patients were continuously monitored by telemetry. Initial exercise intensity was 50% of peak V_{O_2} and progressively increased during the five-month period to reach a goal of 70% and a duration of 45 min. The resistance training component, added four weeks after the start of the training program, took place twice per week. It consisted of nine different exercises for the trunk and upper and lower extremities. All patients were asked to complete two home-exercise sessions per week in which they adjusted their exercise intensity according to a rating of perceived exertion and heart rate (HR) monitors (Pacer NV, Polar Electro Oy, Kempele, Finland).

Percent body fat was determined from skinfold measurements (15). All study patients also completed the "RAND 36-Item Health Survey" to assess health-related quality of life (16).

Echocardiographic evaluation. Measurements of LV function was assessed using two-dimensionally guided M-mode echocardiography (Acuson 128XP, Acuson Inc., Mountain View, California) to determine end-diastolic and end-systolic wall thicknesses, LV dimensions, and volumes. Left ventricular mass was calculated according to the Penn convention (17). Meridional LV wall stress was calculated according to Grossman et al. (18). Systemic vascular resistance was estimated as mean arterial pressure divided by cardiac output (19). External, or forward, LV work power was calculated as: systolic blood pressure (BP) × stroke volume × HR , and forward LV work power per gram of tissue was calculated as: forward LV work power/LV mass.

Measurement of myocardial perfusion and oxidative metabolism. The positron-emitting tracers—[^{15}O]H_2O and [^{11}C]acetate—were produced as previously described (20,21). Subjects reported to the PET Centre in the fasted

Table 2. Hemodynamic, Echocardiographic, and Functional Data

	Training Group			Control Group		
	Baseline	**Follow-Up**	**Change (%)**	**Baseline**	**Follow-Up**	**Change (%)**
Hemodynamic parameters						
Heart rate (beats/min)	69 ± 14	60 ± 9	−10.0	65 ± 8	65 ± 14	−1.0
SBP (mm Hg)	117 ± 20	120 ± 15	+3.2	133 ± 19	128 ± 12	−3.2
DBP (mm Hg)	63 ± 13*	70 ± 9	+14.3	78 ± 13*	82 ± 8	+6.0
RPP (mm Hg/min)	7, 941 ± 1, 411	7, 265 ± 1, 476	−7.7	8, 633 ± 1, 718	8, 335 ± 2, 291	−3.9
Echocardiographic parameters						
LV mass (g)	432 ± 132	428 ± 134	−0.5	323 ± 68	338 ± 61	+6.4
Wall stress (mm Hg)	779 ± 414	603 ± 319	−16.4	733 ± 435	614 ± 203	−8.3
LVEDD (mm)	74.1 ± 9.3	72.4 ± 10.9	−2.4	67.9 ± 6.3	67.6 ± 6.2	−0.5
LVESD (mm)	62.2 ± 10.2	58.8 ± 11.3†	−5.7	56.4 ± 7.2	55.1 ± 6.4	−2.1
SV (ml)	94 ± 21	104 ± 26†	+10.8	83 ± 17	87 ± 16	+6.0
SVR (dynes · s · cm^{-5})	999 ± 425	1, 091 ± 323	+22.2	1, 418 ± 382	1, 410 ± 230	+3.6
EF (%)	33.3 ± 8.3	38.6 ± 8.5‡	+16.9	35.3 ± 7.4	37.3 ± 5.9	+7.2
Functional capacity						
Peak VO_2 (ml/kg/per min)	19.4 ± 4.1	24.6 ± 5.2‡	+27.2	20.6 ± 4.2	21.2 ± 2.9	+4.2
Peak VO_2 (l/min)	1.7 ± 0.5	2.1 ± 0.7‡	+27.7	1.9 ± 0.5	2.0 ± 0.4	+5.9
Peak work load (W)	139 ± 40	161 ± 42‡	+16.9	147 ± 39	146 ± 29	+1.0
Exercise test time (min:s)	11:33 ± 3:56	14:34 ± 5:03‡	+27.8	12:13 ± 2:36	12:25 ± 1:31	+4.4
NYHA functional class	1.6 ± 0.5	1.2 ± 0.5	−18.5	1.2 ± 0.4	1.1 ± 0.4	−4.8

*$p < 0.05$ between groups at baseline; †$p < 0.05$, ‡$p < 0.01$ vs. baseline. Data are presented as the mean value ± SD.
DBP = diastolic blood pressure; EF = ejection fraction; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NYHA = New York Heart Association; RPP = rate–pressure product; SBP = systolic blood pressure; SV = stroke volume; SVR = systemic vascular resistance; VO_2 = oxygen consumption.

state. After the echocardiographic study, the subjects were positioned supine in an eight-ring, 15-slice ECAT 931/08 tomograph (CTI, Knoxville, Tennessee). The $[^{15}O]H_2O$ studies were performed according to established protocols (22). Thereafter, an intravenous bolus of [^{11}C]acetate (724 ± 19 MBq) was administered simultaneously with the start of a 29-min (10 × 10, 1 × 60, 5 × 100, 5 × 120, 2 × 240 s) dynamic emission scan. Heart rate and BP were monitored throughout all procedures. All PET data were corrected for dead time, decay, and measured photon attenuation. Images were processed using the iterative reconstruction algorithm (23).

Calculation of myocardial perfusion, oxidative metabolism, and efficiency. Regions of interest (ROI) were drawn on an average of four transaxial mid-LV slices in each study. An average of the lateral and anterior wall ROIs was used to represent the LV. An additional ROI was drawn on the free wall of the RV for RV [^{11}C]acetate clearance rate (k_{mono}) determination in the [^{11}C]acetate study. For the myocardial perfusion analysis, ROIs were drawn on the rest images and then copied to the images obtained after dipyridamole administration. Regional myocardial perfusion was calculated using the single-compartment model (24). A LV cavity ROI was drawn and used as the input function for determination of the LV time–activity curve (25).

Myocardial perfusion reserve was defined as the ratio of perfusion after dipyridamole infusion to rest perfusion. Regional oxidative metabolism was derived by monoexponential fitting of k_{mono} after visual determination of the linear portion of the semi-logarithmic plot (26).

Myocardial efficiency (the relationship between forward work and oxygen consumption) was estimated as: forward LV work power per gram/LV k_{mono}.

Biochemical analysis. Plasma glucose concentrations were analyzed in duplicate by using the glucose oxidase method with an Analox GM7 or GM9 glucose analyzer (Analox Instruments Ltd., London, United Kingdom). Serum insulin was measured using an automated time-resolved immunofluorometric assay (Autodelfia, Wallac, Turku, Finland), and serum free fatty acid concentrations were measured using an enzymatic colorimetric method (Wako Chemicals Inc., Neuss, Germany). Plasma lactate concentrations were measured using a standard enzymatic method (Roche Diagnostics, Basel, Switzerland). Lipid concentrations were measured as previously described (22).

Statistical analysis. All data are expressed as the mean value ± SD. Intra-group comparisons (baseline vs. follow-up) were made using the Wilcoxon signed-rank test. Inter-group comparisons and relative changes in the training group compared with the control group were made using the Wilcoxon rank-sum test. All tests were two-sided, and a p value <0.05 was considered statistically significant. Correlation coefficients were calculated using the Spearman rank correlation coefficient. All statistical analyses were performed using the SAS statistical analysis system (SAS Institute Inc., Cary, North Carolina).

RESULTS

Exercise training program. The duration of the intervention period was similar in both the trained (179 ± 6 days) and non-trained control groups (176 ± 8 days; $p = 0.37$). No adverse events took place during any of the training

Table 3. Anthropometric and Biochemical Data

	Training Group (n = 9)			Control Group (n = 7)		
	Baseline	Follow-Up	Change (%)	Baseline	Follow-Up	Change (%)
Weight (kg)	86.5 ± 27.8	87.7 ± 29.4	+1.2	93.5 ± 11.0	94.7 ± 10.8	+1.3
BMI (kg/m^2)	27.8 ± 8.7	28.2 ± 9.2	+1.2	30.0 ± 3.4	30.3 ± 3.5	+1.3
Body fat (%)	22.4 ± 4.7	21.3 ± 5.2*	−5.3	24.4 ± 3.8	24.4 ± 3.9	+0.1
fS-total cholesterol (mmol/l)	5.7 ± 0.8	5.8 ± 1.0	+1.8	5.1 ± 0.6	5.1 ± 0.7	+0.3
fS-HDL cholesterol (mmol/l)	1.4 ± 0.5	1.5 ± 0.5	+3.0	1.1 ± 0.1	1.0 ± 0.2	−5.5
fS-LDL cholesterol (mmol/l)	3.5 ± 1.0	3.7 ± 0.9	+9.5	3.5 ± 0.3	3.4 ± 0.6	−2.3
fS-trigylcerides (mmol/l)	1.8 ± 1.2	1.4 ± 0.6	−9.3	1.3 ± 1.0	1.4 ± 0.9	+23.7
fP-glucose (mmol/l)	5.8 ± 1.2	5.9 ± 1.0	+2.6	5.8 ± 0.4	5.5 ± 0.5	−5.1
fP-lactate (mmol/l)	1.2 ± 0.4	1.0 ± 0.3*	−16.0	1.3 ± 0.5	1.3 ± 0.3	+11.2
fS-FFA (mmol/l)	0.66 ± 0.32	0.56 ± 0.20	−8.3	0.57 ± 0.33	0.62 ± 0.39	+23.3
fS-insulin (mU/l)	8.1 ± 4.4	6.5 ± 2.1	−10.4	11.1 ± 6.4	12.6 ± 9.7	+8.0

*$p < 0.05$ vs. baseline. Data are presented as the mean value ± SD.
BMI = body mass index; HDL = high-density lipoprotein; FFA = free fatty acids; LDL = low-density lipoprotein; fP = fasting plasma; fS = fasting serum.

sessions. The average exercise intensity was 72 ± 10% of initial peak V_{O_2}, and the patients averaged 92 ± 35 min per week of home exercise. Attendance was 88 ± 12% for the 21-week training program (64 ± 4 sessions).

Functional capacity. Exercise training was associated with a 27% improvement ($p < 0.01$ vs. change in control group) in peak V_{O_2} (Table 2). Exercise training also improved the peak work load and duration of the exercise test ($p < 0.05$ for both vs. change in control group). No changes were observed in the control group. The NYHA functional class improved slightly but non-significantly in the training group ($p = 0.13$).

Hemodynamic and echocardiographic parameters. At baseline, the hemodynamic parameters were similar between the groups, except for diastolic BP, which was slightly lower in the training group (Table 2). Exercise training did not elicit a change in systolic BP, rate–pressure product, or systemic vascular resistance, but tended to decrease the resting HR ($p = 0.06$). Training increased the stroke volume ($p < 0.05$) and ejection fraction ($p < 0.01$) and reduced the LV end-systolic diameter ($p < 0.05$). Training also tended to reduce LV wall stress ($p = 0.10$). No changes were observed from baseline in any of the aforementioned parameters in the control group.

Anthropometric and biochemical assessments. Exercise training elicited a significant decrease (5%) in body fat percentage and fasting levels of plasma lactate in the training group ($p < 0.05$ vs. change in control group). No changes were noted in the other biochemical variables assessed, and no changes were observed in the control group (Table 3).

Health-related quality of life. Of the eight health concepts for quality of life, the training group had improvements from baseline in the areas of "general health," "pain," ($p < 0.05$ for both) and "vitality" ($p = 0.14$). The only change noted in the control group was in the area of "role limitations caused by physical health problems," where subjective scores slightly decreased ($p = 0.06$).

Myocardial perfusion. Exercise training elicited a reduction in basal myocardial perfusion ($p < 0.05$ vs. baseline; $p = 0.06$ vs. change in control group), although no change was noted in stimulated perfusion (Fig. 1A). Perfusion reserve also remained unchanged after the training period. No significant changes in basal or stimulated perfusion (Fig. 1B) or perfusion reserve were observed in the control group.

Myocardial oxidative metabolism, work, and efficiency. Exercise training elicited significant reductions (10%) in both RV and LV oxidative metabolism in the training group (Fig. 2A). No significant changes occurred in either RV or LV oxidative metabolism in the control group (Fig. 2B). The LV work parameters did not change with exercise training (Table 4). Myocardial forward work efficiency was improved by 24% ($p < 0.05$ vs. baseline; $p = 0.08$ vs. change in control group). In addition, the decrease in LV oxidative metabolism was comparable to the change in perfusion (10% and 12%, respectively). There were no observable changes from baseline in the aforementioned parameters in the non-trained group.

DISCUSSION

This study was designed to investigate the effects of exercise training on myocardial energetics and efficiency in patients with mild HF due to DCM. Exercise training elicited significant improvements in functional parameters characterized by increased exercise capacity and work load during the exercise test. The patients who participated in the training program also demonstrated significant changes in LV functional parameters, including an increase in ejection fraction and a decrease in end-systolic diameter. Most notably, exercise training significantly reduced biventricular oxidative metabolism and improved forward work efficiency, as compared with non-trained patients.

LV oxidative metabolism and efficiency. The findings of the present study demonstrate that LV oxygen demand is decreased after training, as measured directly by the clearance kinetics of [^{11}C]acetate. This decrease occurred inde-

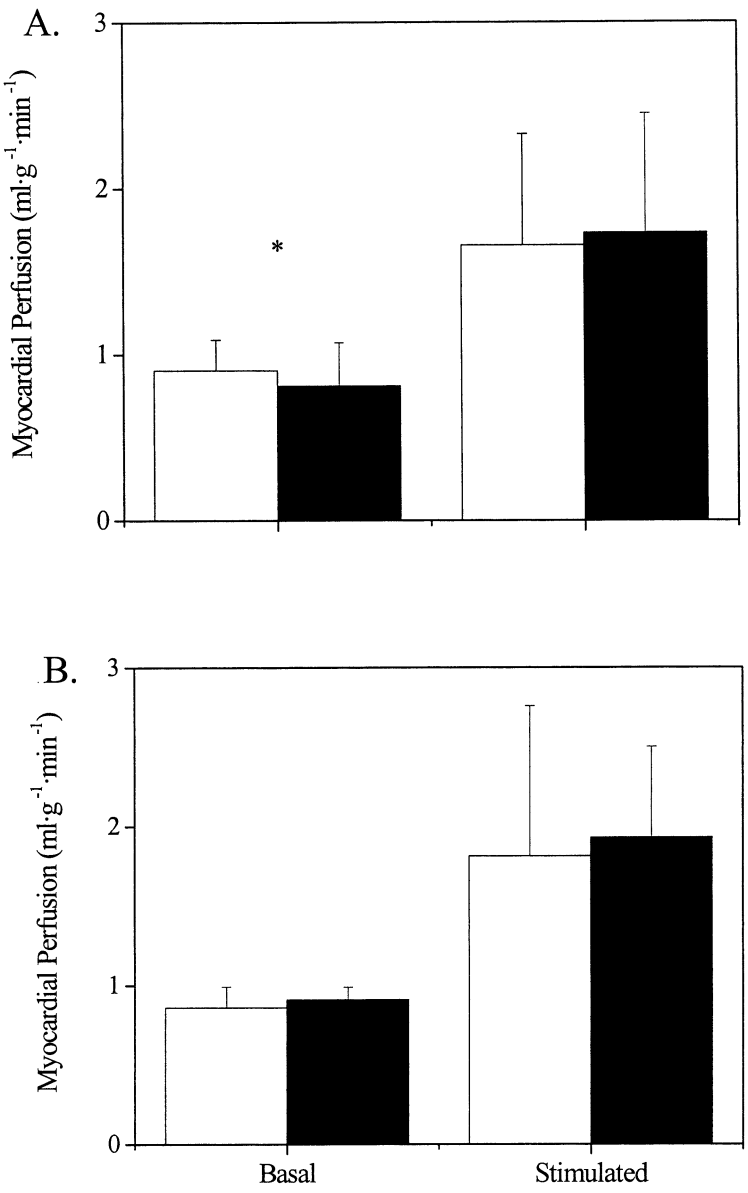

Figure 1. Basal myocardial perfusion and stimulated perfusion in the training group **(A)** and non-trained control group **(B)**. The **open bars** represent the baseline study, and the **solid bars** represent the follow-up study. *$p < 0.05$ vs. baseline.

pendent of a change in useful forward myocardial work, resulting in enhanced LV work efficiency; in other words, the oxygen cost of forward work was decreased.

Forward work efficiency accounts for ~12% to 20% of total LV oxygen consumption in the healthy heart (27). Most of the remaining available energy is converted to heat, and only a small portion is used for basal metabolism and other cellular processes. From the clinical point of view, forward work efficiency is important because the heart works to satisfy the body's needs (blood circulation), and the amount of energy used to achieve this is what is relevant.

LV function. The findings of improved LV function after exercise training in this study are in agreement with Hambrecht et al. (8) and Webb-Peploe et al. (28). However, in some previous studies, significant changes in ejection fraction were not detected after exercise training in patients with HF (3,29). The improvement in ejection fraction in the present study correlated nicely with the observed improvement in exercise capacity of the trained patients ($r = 0.72$, $p = 0.03$).

Mechanisms. One potential explanation for the downward shift in myocardial oxidative metabolism could be due to a shift in substrate preference to a more energy-efficient substrate. A switch in substrate utilization from fatty acids to glucose oxidation would be more energy efficient (30). However, the findings regarding substrate metabolism in the failing heart are controversial. Recent studies have shown an increase in the whole-body free fatty acid turnover rate and oxidation (31) and myocardial free fatty acid uptake (32) in HF patients. In contrast, some studies have found

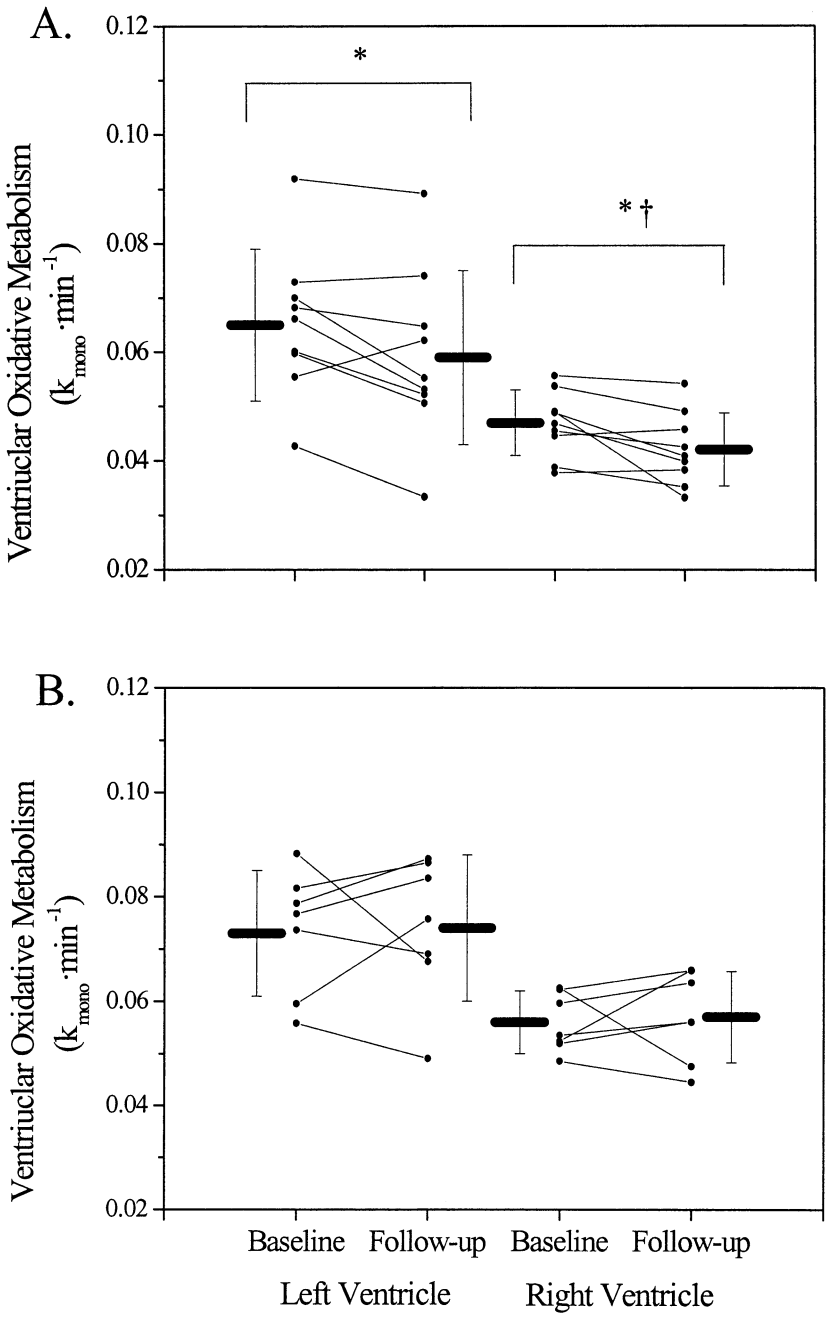

Figure 2. Biventricular oxidative metabolism during the baseline and follow-up studies in the training group **(A)** and control group **(B)**. *$p < 0.05$ vs. baseline. †$p < 0.05$ vs. change in control group.

that in the failing heart, substrate metabolism may revert to a more fetal condition, with enhanced glucose uptake and reduced fatty acid oxidation (33–35).

Two previous intervention studies investigating the effects of beta-blocker therapy in patients with HF demonstrated that beta-blocker therapy decreased LV oxidative metabolism by 24% (36) and also decreased myocardial free fatty acid uptake by 57% (37). It is important to note that the majority of the patients in the present study were already receiving stable beta-blocker therapy and continued the same medication regimen throughout the intervention period. Therefore, the myocardial energetic and metabolic shift demonstrated in the studies by Beanlands et al. (36) and Wallhaus et al. (37) most likely had already taken place. Thus, in the present study, the energy-sparing effect obtained from the training program is an additional benefit.

Myocardial efficiency can also be enhanced by decreasing afterload (13). In the present study, afterload, as assessed by either cardiac work load, rate–pressure product, or systemic vascular resistance, did not change with exercise training. A decrease in sympathetic drive, which has been observed with exercise training (10) and is also suggested by the slight

Table 4. Myocardial Work and Efficiency

	Training Group			Control Group		
	Baseline	Follow-Up	Change (%)	Baseline	Follow-Up	Change (%)
LV work power (mm Hg × l/per min)	757 ± 237	818 ± 227	+9.7	773 ± 152	842 ± 201	+8.7
LV work power/gram (mm Hg × l/g × min)	1.88 ± 0.74	2.02 ± 0.62	+11.7	2.46 ± 0.55	2.54 ± 0.59	+4.0
Forward work efficiency (mm Hg × l/g)	28.8 ± 9.8	34.4 ± 7.9*	+24.3	33.6 ± 6.9	34.2 ± 5.4	+4.3

*$p < 0.05$ vs. baseline. Data are presented as the mean value ± SD.
LV = left ventricle.

decrease in resting HR in this study, could enhance myocardial efficiency as well, because increased adrenergic stimulation is an independent determinant of reduced efficiency in the failing heart (38).

RV parameters. The unique nature of this study is that it also provides data from the RV. Heart failure leads to significant changes in RV function and metabolism. Function of the RV has been associated with exercise capacity (39,40) and prognosis (39). We have previously shown that HF is associated with increased RV oxidative metabolism (41); however, no data are available on the effects of different treatments on RV parameters. In the present study, exercise training elicited a significant and similar degree of decrease (10%) in oxidative metabolism in both the RV and LV. It is likely that this change is linked to the improvement in LV function, resulting in reduced loading of the right side of the heart. However, we cannot exclude other potential mechanisms such as improvement in work efficiency or substrate metabolism. Because the measurement of work power in the RV requires invasive procedures, we could not include those measurements in the present protocol.

Study limitations. Owing to the limited number of patients available for this demanding study, a blinded randomization procedure could not take place. However, patients were separated into their respective group based solely on their proximity to the training site. Living in close proximity to the training site was mandatory in order to perform this intensive supervised training program. This process was unbiased, as it took place without the investigator's knowledge of the patient's present physical health status or functional capacity.

During all testing procedures, the patients were instructed to continue their normal medication regimen, and this may have influenced myocardial metabolism and energetics. Therefore, the extension of these results to untreated or unstable patients with HF may be limited. It is also important to note that the etiology of HF of the patients in this study was idiopathic DCM; thus, the results may not extrapolate to patients with ischemic cardiomyopathy.

Myocardial efficiency is dependent on the loading conditions of the heart. As stated previously, afterload was unchanged, but a direct measurement of preload was not possible in the present non-invasive study. However, end-diastolic LV diameter, a surrogate for preload, was not changed in this study. In addition, because all patients were clinically stable and did not have significant medication changes during the study or evidence of decompensation before the start of the study, it is unlikely that significant changes in preload occurred.

Conclusions. Exercise training in patients with idiopathic DCM and mild HF leads to a significant reduction in biventricular oxidative metabolism and a favorable improvement in forward work efficiency. This energy-sparing effect of exercise training in patients with DCM and mild HF underscores the importance of the inclusion of an exercise training as concomitant therapy for the treatment and prevention of chronic HF.

Acknowledgments

The authors extend a special thank you to Polar Electro Oy, Kempele, Finland, for providing the HR monitors for the home exercise program, as well as Tunturi Oy Ltd., Turku, Finland, for providing a treadmill during the exercise program. The personnel in the Department of Clinical Physiology, Social Insurance Institution of Finland and the Turku PET Centre are appreciated for their dedication to this study.

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REFERENCES

1. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173–82.
2. Delagardelle C, Feiereisen P, Krecke R, Essamri B, Beissel J. Objective effects of a 6 months' endurance and strength training program in outpatients with congestive heart failure. Med Sci Sports Exerc 1999;31:1102–7.
3. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation 1988;78:506–15.
4. Hare DL, Ryan TM, Selig SE, Pellizzer AM, Wrigley TV, Krum H. Resistance exercise training increases muscle strength, endurance, and blood flow in patients with chronic heart failure. Am J Cardiol 1999;83:1674–7.
5. Magnusson G, Gordon A, Kaijser L, et al. High intensity knee extensor training in patients with chronic heart failure: major skeletal muscle improvement. Eur Heart J 1996;17:1048–55.
6. Linke A, Schoene N, Gielen S, et al. Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. J Am Coll Cardiol 2001;37:392–7.
7. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. J Am Coll Cardiol 1997;29:1067–73.

8. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. JAMA 2000;283:3095–101.
9. Tamaki N, Magata Y, Takahashi N, et al. Oxidative metabolism in the myocardium in normal subjects during dobutamine infusion. Eur J Nucl Med 1993;20:231–7.
10. Armbrecht JJ, Buxton DB, Schelbert HR. Validation of [1–^{11}C]acetate as a tracer for non-invasive assessment of oxidative metabolism with positron emission tomography in normal, ischemic, postischemic, and hyperemic canine myocardium. Circulation 1990;81:1594–605.
11. Brown M, Marshall DR, Sobel BE, Bergmann SR. Delineation of myocardial oxygen utilization with carbon-11–labeled acetate. Circulation 1987;76:687–96.
12. Beanlands RS, Bach DS, Raylman R, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. J Am Coll Cardiol 1993;22:1389–98.
13. Beanlands RS, Armstrong WF, Hicks RJ, et al. The effects of afterload reduction on myocardial carbon 11–labeled acetate kinetics and noninvasively estimated mechanical efficiency in patients with dilated cardiomyopathy. J Nucl Cardiol 1994;1:3–16.
14. Bengel FM, Permanetter B, Ungerer M, Nekolla S, Schwaiger M. Non-invasive estimation of myocardial efficiency using positron emission tomography and carbon-11 acetate—comparison between the normal and failing human heart. Eur J Nucl Med 2000;27:319–26.
15. Jackson A, Pollock M. Practical assessment of body composition. Phys Sportsmed 1985;13:76–90.
16. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health survey 1.0. Health Econ 1993;2:217–27.
17. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613–8.
18. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.
19. Guyton AC. Overview of the circulation, and medical physics of pressure, flow and resistance. In: Wonsiewicz MJ, editor. Textbook of Medical Physiology. Philadelphia: W.B. Saunders, 1991:150–8.
20. Sipila HT, Clark JC, Peltola O, Teras M. An Automatic [^{15}O]H_2O production system for heart and brain studies (abstr). J Labelled Cpd Radiopharm 2001;44:S1066–8.
21. Pike VW, Eakins MN, Allan RM, Selwyn AP. Preparation of [1–^{11}C]acetate—an agent for the study of myocardial metabolism by positron emission tomography. Int J Appl Radiat Isot 1982;33:505–12.
22. Pitkanen OP, Raitakari OT, Niinikoski H, et al. Coronary flow reserve is impaired in young men with familial hypercholesterolemia. J Am Coll Cardiol 1996;28:1705–11.
23. Alenius S, Ruotsalainen U. Bayesian image reconstruction for emission tomography based on median root prior. Eur J Nucl Med 1997;24:258–65.
24. Iida H, Takahashi A, Tamura Y, Ono Y, Lammertsma AA. Myocardial blood flow: comparison of oxygen-15–water bolus injection, slow infusion and oxygen-15–carbon dioxide slow inhalation. J Nucl Med 1995;36:78–85.
25. Iida H, Rhodes CG, de Silva R, et al. Use of the left ventricular time–activity curve as a noninvasive input function in dynamic oxygen-15–water positron emission tomography. J Nucl Med 1992;33:1669–77.
26. Armbrecht JJ, Buxton DB, Brunken RC, Phelps ME, Schelbert HR. Regional myocardial oxygen consumption determined noninvasively in humans with [1–^{11}C]acetate and dynamic positron tomography. Circulation 1989;80:863–72.
27. Opie LH. The Heart Physiology, From Cell to Circulation, 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1998:369.
28. Webb-Peploe KM, Chua TP, Harrington D, Henein MY, Gibson DG, Coats AJ. Different response of patients with idiopathic and ischaemic dilated cardiomyopathy to exercise training. Int J Cardiol 2000;74:215–24.
29. Belardinelli R, Georgiou D, Cianci G, Berman N, Ginzton L, Purcaro A. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy: clinical and prognostic implications. Circulation 1995;91:2775–84.
30. Opie L. The Heart Physiology, From Cell to Circulation, 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1998:304.
31. Lommi J, Kupari M, Yki-Jarvinen H. Free fatty acid kinetics and oxidation in congestive heart failure. Am J Cardiol 1998;81:45–50.
32. Taylor M, Wallhaus TR, DeGrado TR, et al. An evaluation of myocardial fatty acid and glucose uptake using PET with (^{18}F)FDG in patients with congestive heart failure. J Nucl Med 2001;42:55–62.
33. Rosenblatt-Velin N, Montessuit C, Papageorgiou I, Terrand J, Lerch R. Postinfarction heart failure in rats is associated with upregulation of GLUT-1 and downregulation of genes of fatty acid metabolism. Cardiovasc Res 2001;52:407–16.
34. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation 1996;94:2837–42.
35. Takeyama D, Kagaya Y, Yamane Y, et al. Effects of chronic right ventricular pressure overload on myocardial glucose and free fatty acid metabolism in the conscious rat. Cardiovasc Res 1995;29:763–7.
36. Beanlands RS, Nahmias C, Gordon E, et al. The effects of β_1-blockade on oxidative metabolism and the metabolic cost of ventricular work in patients with left ventricular dysfunction: a double-blind, placebo-controlled, positron-emission tomography study. Circulation 2000;102:2070–5.
37. Wallhaus TR, Taylor M, DeGrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. Circulation 2001;103:2441–6.
38. Bengel FM, Permanetter B, Ungerer M, Nekolla SG, Schwaiger M. Alterations of the sympathetic nervous system and metabolic performance of the cardiomyopathic heart. Eur J Nucl Med Mol Imaging 2002;29:198–202.
39. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143–53.
40. Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic hemodynamics in determining exercise capacity of patients with chronic left ventricular failure. Am Heart J 1985;110:807–13.
41. Ukkonen H, Saraste M, Akkila J, et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther 2000;68:522–31.