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

Kira Q. Stolen, MS,* Jukka Kemppainen, MD,* Heikki Ukkonen, MD,†‡ Kari K. Kalliokoski, PhD,* Matti Luotolahti, MD,† Pertti Lehikoinen, PhD,* Helena Hämaläinen, MD,§ Tiina Salo, MD,‡ K. E. Juhanai Airaksinen, MD,‡ Pirjo Nuutila, MD,*‡ Juhani Knuuti, MD*

*Turku, Finland

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 [11C]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 (VO2) 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.

The use of positron emission tomography (PET) and [11C]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 [11C]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 [11C]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

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 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.

From the *Turku PET Centre and †Departments of Clinical Physiology and ‡Medicine, University of Turku and Turku University Central Hospital, Turku; and the §Social Insurance Institution, Turku, Finland. This study was supported in part by the Ministry of Education, the Aarne Koskelo Foundation, the Research Foundation of Orion Corporation, and the Finnish Cardiovascular Foundation.

Manuscript received May 31, 2002; revised manuscript received July 10, 2002, accepted August 26, 2002.
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 (VO2), 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.

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 [15O]H2O, and hyperemic perfusion was assessed after dipyridamole administration. Myocardial oxidative metabolism was assessed using [11C]acetate.

**Cardiopulmonary exercise testing and training program.** All study subjects underwent a symptom-limited, incremental cycle ergometer test with continuous respiratory gas exchange analysis (Vmax; Sensormedics, Bilthoven, The Netherlands), and peak VO2 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 VO2 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—[15O]H2O and [11C]acetate—were produced as previously described (20,21). Subjects reported to the PET Centre in the fastest

---

**Abbreviations and Acronyms**

BP = blood pressure  
DCM = dilated cardiomyopathy  
HF = heart failure  
HR = heart rate  
kmono = [11C]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  
VO2 = oxygen uptake

---

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Training Group (n = 9)</th>
<th>Control Group (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>7/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 8.7</td>
</tr>
<tr>
<td>Peak oxygen uptake (ml/kg/per min)</td>
<td>19.4 ± 4.1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>33.3 ± 8.3</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>78% (7/9)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>78% (7/9)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>33% (3/9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>33% (3/9)</td>
</tr>
<tr>
<td>Angiotensin II blocker</td>
<td>11% (1/9)</td>
</tr>
</tbody>
</table>

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.
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$\textsubscript{2}$H$\textsubscript{2}$O 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 ($k_{\text{mono}}$) 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 monoequilibrium fitting of $k_{\text{mono}}$ 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 per gram/LV $k_{\text{mono}}$.

**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
sessions. The average exercise intensity was 72 ± 10% of initial peak VO₂, 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 VO₂ (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 in 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 [11C]acetate. This decrease occurred inde-
ependent 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...
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

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.
Exercise Improves Myocardial Oxidative Metabolism

Table 4. Myocardial Work and Efficiency

<table>
<thead>
<tr>
<th>Training Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV work power (mm Hg × l/per min)</td>
<td>757 ± 237</td>
</tr>
<tr>
<td>LV work power/gram (mm Hg × l/g × min)</td>
<td>1.88 ± 0.74</td>
</tr>
<tr>
<td>Forward work efficiency (mm Hg × l/g)</td>
<td>28.8 ± 9.8</td>
</tr>
</tbody>
</table>

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

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.

REFERENCES


