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## Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients A Randomized Study

Ulrik Wisløff, PhD; Asbjørn Støylen, MD, PhD; Jan P. Loennechen, MD, PhD; Morten Bruvold, MSc; Øivind Rognmo, MSc; Per Magnus Haram, MD, PhD; Arnt Erik Tjønnå, MSc; Jan Helgerud, PhD; Stig A. Slørdahl, MD, PhD; Sang Jun Lee, PhD; Vibeke Videm, MD, PhD; Anja Bye, MSc; Godfrey L. Smith, PhD; Sonia M. Najjar, PhD; Øyvind Ellingsen, MD, PhD; Terje Skjærpe, MD, PhD

**Background**—Exercise training reduces the symptoms of chronic heart failure. Which exercise intensity yields maximal beneficial adaptations is controversial. Furthermore, the incidence of chronic heart failure increases with advanced age; it has been reported that 88% and 49% of patients with a first diagnosis of chronic heart failure are >65 and >80 years old, respectively. Despite this, most previous studies have excluded patients with an age >70 years. Our objective was to compare training programs with moderate versus high exercise intensity with regard to variables associated with cardiovascular function and prognosis in patients with postinfarction heart failure.

**Methods and Results**—Twenty-seven patients with stable postinfarction heart failure who were undergoing optimal medical treatment, including  $\beta$ -blockers and angiotensin-converting enzyme inhibitors (aged  $75.5 \pm 11.1$  years; left ventricular [LV] ejection fraction 29%;  $\dot{V}O_{2\text{peak}}$   $13 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) were randomized to either moderate continuous training (70% of highest measured heart rate, ie, peak heart rate) or aerobic interval training (95% of peak heart rate) 3 times per week for 12 weeks or to a control group that received standard advice regarding physical activity.  $\dot{V}O_{2\text{peak}}$  increased more with aerobic interval training than moderate continuous training (46% versus 14%,  $P < 0.001$ ) and was associated with reverse LV remodeling. LV end-diastolic and end-systolic volumes declined with aerobic interval training only, by 18% and 25%, respectively; LV ejection fraction increased 35%, and pro-brain natriuretic peptide decreased 40%. Improvement in brachial artery flow-mediated dilation (endothelial function) was greater with aerobic interval training, and mitochondrial function in lateral vastus muscle increased with aerobic interval training only. The MacNew global score for quality of life in cardiovascular disease increased in both exercise groups. No changes occurred in the control group.

**Conclusions**—Exercise intensity was an important factor for reversing LV remodeling and improving aerobic capacity, endothelial function, and quality of life in patients with postinfarction heart failure. These findings may have important implications for exercise training in rehabilitation programs and future studies. (*Circulation*. 2007;115:3086-3094.)

**Key Words:** endothelium ■ exercise ■ remodeling ■ heart failure

In recent years, there has been a growing consensus that exercise has beneficial effects in patients with cardiovascular disease, even for those with severely impaired cardiac function, and that physical inactivity accelerates the severity of heart failure.<sup>1,2</sup> Peak aerobic exercise capacity directly measured as peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ) was recently found to be the single best predictor of both cardiac and all-cause

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deaths among patients with established cardiovascular disease<sup>1,2</sup>; however, there is still controversy regarding the level and format of exercise that can yield optimal beneficial effects.<sup>3</sup> Several lines of evidence suggest greater aerobic and

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From the Department of Circulation and Medical Imaging (U.W., A.S., M.B., Ø.R., P.M.H., A.E.T., J.H., S.A.S., A.B., Ø.E.) and Department of Laboratory Medicine (V.V.), Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; Department of Cardiology (U.W., A.S., J.P.L., Ø.E., T.S.) and Department of Immunology and Transfusion Medicine (V.V.), St. Olav's Hospital, Trondheim, Norway; Institute of Biomedical and Life Sciences (G.L.S.), University of Glasgow, United Kingdom; and Department of Physiology, Pharmacology, Metabolism and Cardiovascular Sciences (S.J.L., S.M.N.), Medical University of Ohio, Toledo, Ohio.

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Correspondence to Ulrik Wisløff, PhD, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Olav Kyrres gt. 9, 7489 Trondheim, Norway. E-mail [ulrik.wisloff@ntnu.no](mailto:ulrik.wisloff@ntnu.no)

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cardiovascular adaptations after high-intensity exercise than with low and moderate levels in patients with coronary artery disease,<sup>4</sup> chronic heart failure,<sup>5,6</sup> or left ventricular (LV) dysfunction function<sup>7</sup> and in healthy subjects.<sup>8</sup> Exercise training at an intensity of  $\approx 90\%$  of  $\dot{V}O_{2\text{peak}}$  is in the upper range of current guidelines for humans.<sup>3</sup> This level of aerobic exercise can be achieved in an interval-training format in both humans and animal models. The rationale for interval training is that it allows for rest periods that make it possible for patients with heart failure to complete short work periods at a higher intensity (which challenges the heart's pumping ability) than would be possible during continuous exercise. Aerobic interval training (AIT) involving periods at  $90\%$  of  $\dot{V}O_{2\text{peak}}$  has been shown to rescue impaired cardiomyocyte contractility, attenuate myocardial hypertrophy, and reduce myocardial expression of atrial natriuretic peptide in a rat model of postinfarction heart failure.<sup>9</sup> The beneficial effects on cardiac remodeling and myocyte function were similar to those observed with the angiotensin II receptor blocker losartan,<sup>10</sup> which indicates that AIT might be a potent modifier of postinfarction heart failure. We therefore hypothesized that AIT is more effective than moderate continuous training (MCT) in enhancing cardiovascular fitness and reversing myocardial remodeling in patients undergoing optimal treatment for stable heart failure after a myocardial infarction.

## Methods

### Patients

We enrolled 27 consecutive patients (aged  $75.5 \pm 11.1$  years) with postinfarction heart failure from the Department of Cardiology, St. Olav's Hospital, Trondheim, Norway. None of the patients had a myocardial infarction in the 12 months preceding the study. Twelve patients were  $>80$  years of age, 9 were 70 to 80 years old, 4 were 60 to 70 years old, and 2 were 50 to 60 years of age. All exhibited an LV ejection fraction  $<40\%$  and were stable with optimal treatment that included  $\beta$ -blockers and angiotensin-converting enzyme (ACE) inhibitors. All patients had received  $\beta$ -blockers and ACE inhibitors for  $>12$  months. One patient had atrial fibrillation; the rest had sinus rhythm as evidenced by a-wave velocities. None of the patients had a pacemaker. As judged by the body mass index (Table 1), patients were noncachectic. Patients were randomly assigned to either high-intensity AIT (n=9), MCT (n=9), or a control group (n=9). Exclusion criteria included unstable angina pectoris, uncompensated heart failure, myocardial infarction during the past 4 weeks, complex ventricular arrhythmias, no use of  $\beta$ -blockers and ACE inhibitors, and orthopedic or neurological limitations to exercise. Medications (Table 1) did not change during the 12-week study period. The study was performed according to the Helsinki declaration and was approved by the regional medical research ethics committee. Written informed consent was obtained from all patients.

### Randomization Procedure

Subjects were randomized and stratified (by gender and age) to AIT, MCT, or control. The randomization code was developed with a computer random-number generator to select random permuted blocks.

### Exercise Testing

After a 10-minute warm-up, a  $\dot{V}O_{2\text{peak}}$  test (with MetaMax II, Cortex, Leipzig, Germany) was performed with an individualized treadmill ramp protocol with individualized constant band speed and increased inclination by 2% when oxygen uptake stabilized at each workload until  $\dot{V}O_{2\text{peak}}$  was reached. A leveling off of oxygen uptake despite

**TABLE 1. Patient Characteristics and Medication Use**

	Control	MCT	AIT
Male/female	6/3	7/2	7/2
Age, y	75.5 $\pm$ 13	74.4 $\pm$ 12	76.5 $\pm$ 9
Body mass index, kg/m <sup>2</sup>	25.5 $\pm$ 2	24.7 $\pm$ 3	24.5 $\pm$ 3
Systolic blood pressure, mm Hg	121 $\pm$ 7	124 $\pm$ 11	119 $\pm$ 9
Diastolic blood pressure, mm Hg	76 $\pm$ 11	73 $\pm$ 8	72 $\pm$ 10
Hemoglobin, g/dL	15.2 $\pm$ 1.3	14.4 $\pm$ 1.1	14.9 $\pm$ 1.1
Total cholesterol, mmol/L	5.9 $\pm$ 1.5	5.4 $\pm$ 1.2	5.5 $\pm$ 1.2
Serum creatinine, $\mu$ mol/L	118 $\pm$ 56	126 $\pm$ 42	108 $\pm$ 20
ACE inhibitor	9/9	9/9	9/9
$\beta$ -Blockers	9/9	9/9	9/9
Statins	9/9	9/9	9/9
Diuretics	5/9	4/9	5/9
Long-acting nitrates	4/9	5/9	4/9
Aspirin	3/9	3/9	4/9
Warfarin	6/9	6/9	5/9
Percutaneous coronary intervention*	2/9	2/9	1/9
Coronary artery bypass surgery*	...	1/9	...

Data are mean $\pm$ SD or number of patients.

\*Intervention performed  $>12$  months ago.

increased workload and a respiratory exchange ratio  $>1.05$  were used as criteria for maximal oxygen uptake. This was accomplished in 25 of 27 patients (at pretest and posttest), and results are by definition  $\dot{V}O_{2\text{peak}}$ . Work economy was determined as oxygen uptake at a standard submaximal workload; for each patient, we used the identical workload at posttest to measure work economy. Immediately after this workload, blood was drawn from a fingertip for measurement of lactate concentration. Ventilatory threshold was recorded as an indication of anaerobic threshold.

### Exercise Training

Patients randomized to AIT and MCT met for supervised training twice weekly and performed 1 weekly session at home. The control group met for supervised training once every 3 weeks. All training consisted of "uphill" treadmill walking as described previously.<sup>4</sup> The AIT group warmed up for 10 minutes at 50% to 60% of  $\dot{V}O_{2\text{peak}}$  ( $\approx 60\%$  to 70% of peak heart rate) before walking four 4-minute intervals at 90% to 95% of peak heart rate. Each interval was separated by 3-minute active pauses, walking at 50% to 70% of peak heart rate. The training session was terminated by a 3-minute cool-down at 50% to 70% of peak heart rate. Total exercise time was 38 minutes for the AIT group. Patients in the MCT group walked continuously at 70% to 75% of peak heart rate for 47 minutes each session to make sure the training protocols were isocaloric, as detailed previously.<sup>4</sup> All subjects used a heart rate monitor (Polar Electro, Kempele, Finland) to obtain the assigned exercise intensity. The Borg 6-to-20 scale was used to assess the rate of perceived exertion during and after each training session. The speed and inclination of the treadmill was adjusted continuously to ensure that every training session was carried out at the assigned heart rate throughout the training period. Blood lactate was measured after the first 3 and last 3 training sessions. Weekly home-based training consisted of outdoor uphill walking. Patients were instructed to perform the training program as in the laboratory; patients in the MCT group walked continuously for 47 minutes without breathing heavily, whereas AIT patients performed four 4-minute intervals with an exercise intensity that made them breathe heavily without becoming too stiff in their legs. Patients were instructed to immediately stop home-based training if they had chest pain or any other distressing symptoms and contact the emergency department at the hospital. Home-based training intensity was recorded twice by heart

rate monitors, placed so that the patients were unable to see their heart rate during the exercise. Recordings affirmed the correct exercise intensity during home training. The control group was told to follow advice from their family doctor with regard to physical activity; in addition, they met for 47 minutes of continuous treadmill walking at 70% of peak heart rate every 3 weeks.

### Endothelial Function

Endothelium-dependent and endothelium-independent dilation of the brachial artery was measured by ultrasound (14-MHz ultrasound Doppler probe, Vivid 7 system, GE Vingmed Ultrasound, Horten, Norway).<sup>11</sup> The guidelines for determining and analyzing flow-mediated dilation (FMD) described by Corretti et al<sup>12</sup> were adhered to strictly. The measurements were done on the brachial artery 4.5 cm above the antecubital fossa before inflation of a pneumatic cuff on the upper arm to 250 mm Hg for 5 minutes and at 1 minute after cuff release. FMD was expressed as percentage dilation from baseline diameter to that observed 1 minute after cuff release. Endothelium-independent dilation was measured by administering 500  $\mu$ g of nitroglycerin sublingually; no differences between groups were observed (data not shown).

### Echocardiography

Echocardiography was performed by 2 experienced cardiologists (A.S. and T.S.) blinded to the patients' group assignment. Subjects were examined at rest in the left lateral supine position with a Vingmed Vivid 7 scanner with B-mode ultrasound at a frame rate of 50 Hz. The following data were recorded: parasternal M-mode and long-axis B-mode; apical B-mode from 3 standard planes; pulsed Doppler flow recordings of LV outflow, mitral inflow, and apical M-mode; and pulsed tissue Doppler in the septal and lateral points in the 4-chamber plane and the anterior and posterior points in the 2-chamber plane. Systolic mitral annulus excursion and peak annulus velocities in systole, early diastole (Ea), and late diastole were measured as the average of the 4 points. Volumes were measured by the modified Simpson biplane method. Stroke volume was measured by 2D volumetry.

### Muscle Biopsy

Muscle biopsy samples were obtained from the vastus lateralis with a sterile 5-mm-diameter biopsy needle (Bergstrom) under local anesthesia. Muscle biopsy samples were homogenized in lysis buffer, and equal amounts of lysates were analyzed by SDS-PAGE and Western blot analysis with goat polyclonal antibodies against peroxisome proliferative activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), an indicator of mitochondrial biogenesis (Santa Cruz Biotechnology, Santa Cruz, Calif). Gels were reprobed with a monoclonal antibody against  $\alpha$ -actin for normalization (Sigma, St. Louis, Mo). Proteins were detected by chemiluminescence and quantified by densitometry.

### Sarcoplasmic Reticulum Ca<sup>2+</sup> ATPase-1 and -2 Transport Measurements

Reduced maximal rate of calcium (Ca<sup>2+</sup>) reuptake into sarcoplasmic reticulum has been inversely related to increased skeletal muscle fatigue in heart failure patients. To measure this, Ca<sup>2+</sup> (50  $\mu$ mol/L) was added to skinned fibers from the vastus lateralis muscle to induce a rapid increase in [Ca<sup>2+</sup>], and kinetics of the subsequent decline in Ca<sup>2+</sup> were analyzed with Fura-2 and an epifluorescence microscope (Diaphot-TMD, Nikon, Tokyo, Japan) to assess maximum sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA)-1 and -2 transport capacity.

### Blood Analyses

Citrated and EDTA plasma was obtained from venous blood by centrifugation at 3000 rpm for 10 minutes at 4°C. Aliquots of plasma were then stored at -80°C to allow batch analysis.

Serum triglycerides, glucose, high-density lipoprotein, low-density lipoprotein (LDL), total cholesterol, hemoglobin, high-sensitivity serum C-reactive protein, and creatinine were measured

with standard procedures at St. Olav's University Hospital, Trondheim, Norway. Oxidized LDL was measured in plasma with the Mercodia oxidized-LDL ELISA (Mercodia, Uppsala, Sweden). Total antioxidant status (TAS) was measured in plasma samples with the colorimetric TAS assay (Randox Laboratories Ltd, Crumlin, United Kingdom). The method is based on 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) incubation with metmyoglobin and H<sub>2</sub>O<sub>2</sub> to produce the radical cation ABTS<sup>+</sup>. The radical has a stable blue-green color that is measured at 600 nm. Antioxidants present in the added sample weaken the color intensity in proportion to their concentration. The assay was performed with an automated system (Cobas Mira Analyzer, Hoffmann-LaRoche, Basel, Switzerland). For calculation of total antioxidant status, the absorbance of the patient's plasma was related to the standard, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox, 1.76 mmol/L), according to the manufacturer's instructions (Randox Laboratories Ltd, Crumlin, UK). Commercial enzyme immunoassays were used to determine endothelin-1 (R&D Systems, Minneapolis, Minn), insulin-like growth factor 1 (R&D Systems), and pro-B-type natriuretic peptide levels (proBNP, Roche Diagnostics, Indianapolis, Ind).

### Quality of Life

Quality of life was measured by the MacNew Heart Disease Health-Related Quality of Life questionnaire (MacNew),<sup>13</sup> which has been shown to be well-suited for an older population. The self-administered MacNew questionnaire is designed to evaluate how daily activities and physical, emotional, and social functioning are affected by heart disease.<sup>13</sup>

### Statistical Analysis

Data are expressed as mean $\pm$ SD unless otherwise stated, with a significance level of  $P < 0.05$ . The Kruskal-Wallis test and post hoc test was used to evaluate unrelated observations between groups, whereas ANOVA with Scheffé post hoc analysis determined group differences between related observations.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

At baseline, there were no differences in medical treatment (Table 1) or physiological variables (Tables 2 through 4) among the 3 groups. Medical treatment did not change during the intervention period. During the experimental period, 1 of the patients in the moderate-intensity group died of cardiac causes, unrelated to exercise training, and data from 26 patients were available from postexercise tests. Patients in the AIT and MCT groups performed 92 $\pm$ 2% and 95 $\pm$ 3% of the scheduled training sessions, respectively. Measured exercise intensity, blood lactate, and Borg scale were different between the AIT and MCT groups during the training sessions, which confirms that the difference in exercise intensity between the groups was as intended (Table 2).

### Clinical Follow-Up

Body mass index, blood pressure, hemoglobin, total cholesterol, and serum creatinine did not change (baseline values presented in Table 1). AIT subjects tended to have lower serum triglyceride (2.1 $\pm$ 1.2 mmol/L pretest versus 1.7 $\pm$ 0.7 mmol/L posttest,  $P=0.11$ ) and fasting glucose (7.0 $\pm$ 2.0 mmol/L pretest versus 6.1 $\pm$ 2.6 mmol/L posttest,  $P=0.10$ ) levels after training, in addition to a trend for increased high-density lipoprotein levels (1.2 $\pm$ 0.4 versus 1.3 $\pm$ 0.3 mmol/L,  $P=0.20$ ). The New York Heart Association functional class tended to be reduced in both

**TABLE 2. Aerobic Capacity and Exercise Data**

	Control		MCT		AIT	
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up
<b>Peak treadmill test</b>						
$\dot{V}O_{2peak}$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	13.2±1.9	13.4±2.0	13.0±1.1	14.9±0.9*	13.0±1.6	19.0±2.1*†
Peak heart rate, bpm	129±23	127±21	132±18	130±21	129±19	127±22
[La <sup>-</sup> ] <sub>b</sub> at $\dot{V}O_{2peak}$ , mmol/L	6.3±1.6	6.3±1.2	6.8±1.2	6.4±1.0	6.2±0.8	6.0±0.6
RER at $\dot{V}O_{2peak}$	1.10±0.04	1.11±0.04	1.10±0.04	1.09±0.05	1.08±0.05	1.11±0.04
<b>Anaerobic threshold</b>						
% Of peak oxygen uptake	64±6	65±4	61±3	68±4*‡	63±5	61±3
mL · kg <sup>-1</sup> · min <sup>-1</sup>	8.5±1.6	8.7±3.9	8.0±0.7	10.1±0.9*§	8.2±0.8	11.6±1.0*†
<b>Work economy</b>						
mL · kg <sup>-1</sup> · min <sup>-1</sup>	8.5±1.6	9.1±2.8	8.0±0.7	7.6±0.8§	8.2±0.8	7.0±0.6*†
Heart rate, bpm	84±9	88±8	82±6	81±9	84±9	76±5*†
[La <sup>-</sup> ] <sub>b</sub> , mmol/L	2.81±0.4	3.0±0.8	2.9±0.3	2.5±0.4	2.7±0.3	1.6±0.4*†
<b>Training data</b>						
Exercise intensity, km/h	3.3±1.0	3.3±1.0	3.0±0.8	4.0±0.5	3.1±0.2	4.6±0.6*†
Inclination of treadmill, %	2.3±1.5	2.3±1.5	2.3±0.6	4.7±1.5§	2.7±1.0	12.1±1.8*†
[La <sup>-</sup> ] <sub>b</sub> , mmol/L	2.4±0.3	2.6±0.9	2.3±0.4	2.4±0.6	5.0±0.5†	5.2±0.5†
% Of peak heart rate	71±2	69±3	74±2	73±2	92±2†	93±3†
Borg scale	12±1	12±1	12±1	12±1	17±1†	17±1†

[La<sup>-</sup>]<sub>b</sub> indicates blood lactate; RER, respiratory exchange ratio.

Data are mean±SD. Work economy was measured at the same speed/inclination for each individual before and after the experimental period.

\*Different from baseline, *P*<0.01; †different from control and MCT, *P*<0.05; ‡different from control and AIT, *P*<0.01; §significantly different from control, *P*<0.05.

training groups (*P*=0.21) and was 2.5±0.5 for all subjects combined at follow-up. No adverse effects of exercise training were detected.

**Exercise Capacity**

After 12 weeks of exercise training,  $\dot{V}O_{2peak}$  increased 46% and 14% in the AIT and MCT groups, respectively (*P*<0.001; Table 2; Figure 1). Anaerobic threshold increased more in relative terms (percent of  $\dot{V}O_{2peak}$ ) but not in absolute terms (mL · kg<sup>-1</sup> · min<sup>-1</sup>, and workload) in MCT compared with AIT (Table 2). AIT improved work economy as demonstrated by 15% reduced oxygen cost, an 8-bpm lower heart

rate, and 59% lower blood lactate at a given submaximal walking speed (Table 2). To extend the clinical usefulness of exercise training for those without access to heart rate monitors, patients were asked to indicate the level of effort during exercise on a Borg scale (Table 2), and a Borg scale score of 17±1 and 12±1 for AIT and MCT, respectively, was reported.

**PGC-1α and SERCA: Skeletal Muscle Molecular Mechanisms of Exercise Capacity**

Protein levels of PGC-1α, a critical factor coordinating the activation of metabolic genes required for substrate utilization

**TABLE 3. LV Volumes and Resting Hemodynamics**

	Control		MCT		AIT	
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up
LVDD, mm	67.2±8.1	67.8±12.5	69.1±8.6	68.2±6.5	66.7±6.8	59.0±6.8*†
LVSD, mm	56.2±9.2	56.7±13.7	56.6±8.8	53.9±7.4	53.9±6.7	46.1±8.2*†
LVEDV, mL	250.5±64.4	242.1±62.3	245.5±53.1	230.3±41.0	248.1±79.6	202.9±72.0*†
LVESV, mL	187.8±53.0	186.6±58.6	172.9±48.7	160.6±34.3	177.4±72.1	133.9±57.8*†
HR at rest, bpm	60±11	59±11	55±10	54±12	65±14	61±13
SV, mL	53.4±15.3	55.0±13.7	63.5±12.7	63.1±15.7	57.1±14.3	67.0±19.9*
CO, L/min	3.1±0.6	3.2±0.5	3.5±0.9	3.4±1.1	3.5±0.5	3.9±0.6*
EF, %	26.2±8.0	26.6±9.7	32.8±4.8	33.5±5.7	28.0±7.3	38.0±9.8*†

Data are mean±SD. LVDD indicates LV diastolic diameter; LVSD, LV systolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic diameter; HR, heart rate; SV, stroke volume; CO, cardiac output; and EF, ejection fraction.

\*Different from baseline, *P*<0.01; †different from controls and moderately trained, *P*<0.02.

**TABLE 4. Echocardiographic Resting LV Function**

	Control		MCT		AIT	
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up
<b>Systolic function</b>						
MAE, mm	8.0±2.1	8.1±2.5	8.8±1.8	8.6±2.0	7.4±2.4	9.6±2.8*‡
Sa, cm/s	4.73±1.23	4.79±1.34	4.80±1.10	5.16±0.96	4.79±1.32	5.86±1.53*‡
LVOT <sub>max</sub> , cm/s	78.7±16.1	77.6±9.7	78.7±9.1	78.1±7.3	81.8±11.5	97.7±10.5*‡
<b>Diastolic function</b>						
IVRT, ms	110.2±68.7	109.5±64.8	112.4±23.4	105.7±25.6	100.7±18.9	122.8±41.4†‡
E, m/s	0.6±0.1	0.5±0.2	0.7±0.3	0.6±0.1†	0.7±0.1	0.8±0.2
A, m/s	0.9±0.1	0.9±0.1	1.0±0.2	0.7±0.2*	0.9±0.1	0.9±0.3
E/A	0.7±0.2	0.6±0.2	0.8±0.1	0.8±0.3	0.7±0.1	0.9±0.2†§
Ea, cm/s	4.0±1.4	3.9±1.9	4.6±0.8	4.7±1.6	4.5±1.3	6.7±1.6*‡
Aa, cm/s	7.0±2.2	7.5±2.8	8.8±1.8	7.5±1.8	8.6±1.7	8.5±1.8
E/Ea	15.1±4.3	15.1±6.4	15.1±5.4	12.9±3.8†§	16.0±3.5	11.8±1.9*§

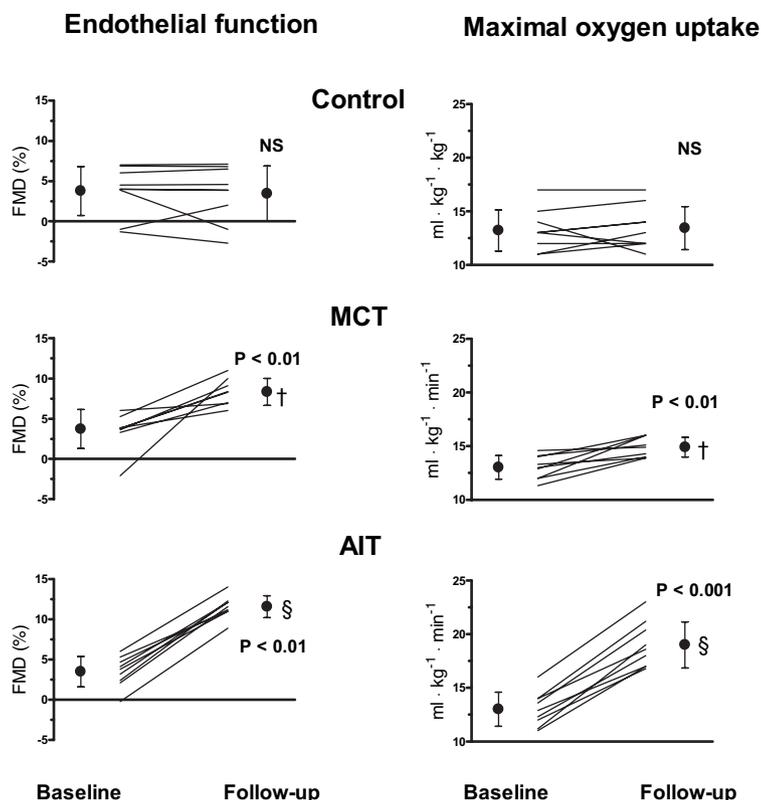
MAE indicates systolic mitral annulus excursion; Sa, peak mitral annulus velocity during systole by tissue Doppler; LVOT<sub>max</sub>, peak ejection velocity in LV outlet tract; IVRT, isovolumic relaxation time; E, peak mitral flow velocity during early filling; A, peak mitral flow velocity during atrial systole; E<sub>a</sub>, peak annulus velocity during early filling; and A<sub>a</sub>, peak annulus velocity during atrial systole.

\*Different from baseline,  $P<0.01$ ; †different from baseline,  $P<0.05$ ; ‡different from controls and MCT,  $P<0.02$ ; §different from control,  $P<0.05$ .

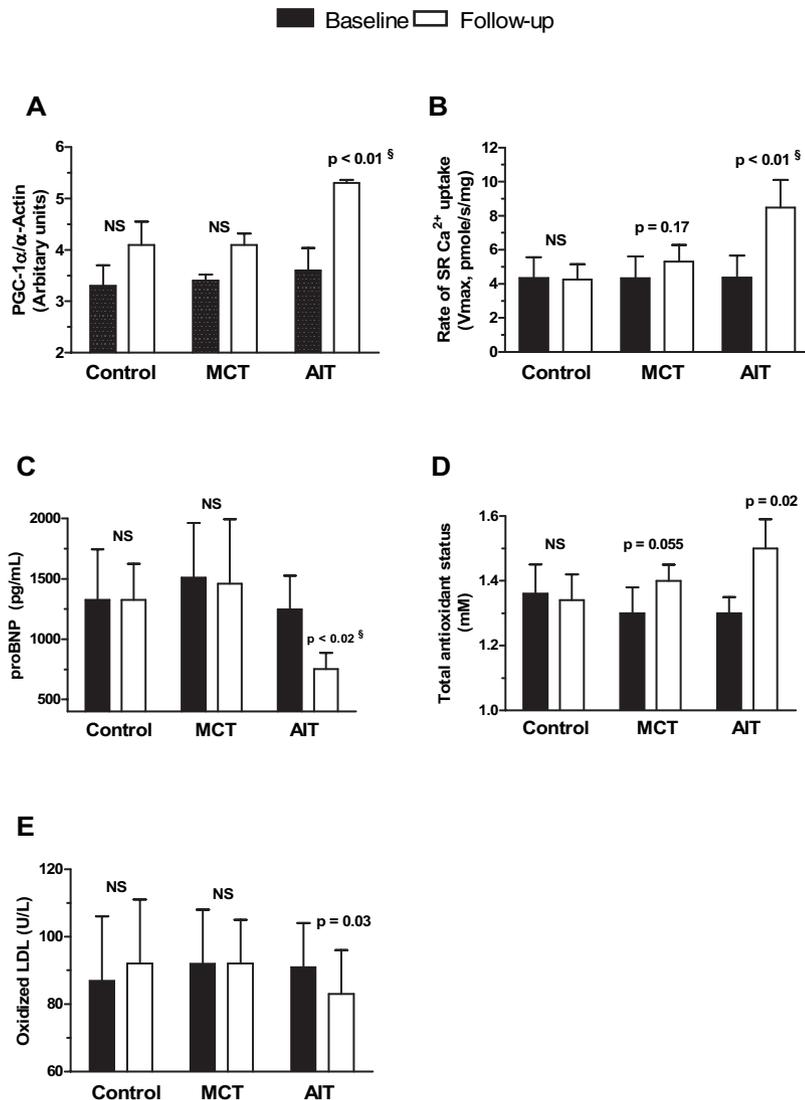
and mitochondrial biogenesis,<sup>14</sup> was increased by 47% in AIT subjects ( $P<0.01$ ; Figure 2A) and correlated with improved  $\dot{V}O_{2peak}$  ( $R=0.71$ ,  $P<0.01$ ). Maximal rate of  $Ca^{2+}$  reuptake into sarcoplasmic reticulum by SERCA in skeletal muscles increased by 60% ( $P<0.01$ ; Figure 2B) with AIT and correlated with the improvement in  $\dot{V}O_{2peak}$  ( $R=0.56$ ,  $P<0.05$ ).

### LV Remodeling

Twelve weeks of AIT induced reverse LV remodeling. LV diastolic and systolic diameters declined by 12% and 15% and estimated LV end-diastolic and end-systolic volumes by 18% and 25%, respectively (Table 3). proBNP, a marker of hypertrophy and severity of heart failure, declined by 40%



**Figure 1.** Left, Endothelial function measured as FMD. Right, Maximal oxygen uptake. Data are mean±SD. Lines represent individual values. Probability values inside figures indicate within-group differences. §Different from control and MCT,  $P<0.01$ ; †different from control,  $P<0.01$ .



**Figure 2.** A, PGC-1 $\alpha$  in vastus lateralis muscle. B, Rate of maximal Ca<sup>2+</sup> reuptake (V<sub>max</sub>) in the sarcoplasmic reticulum (SR) in permeabilized samples of vastus lateralis muscle. C, Plasma level of brain natriuretic peptide (proBNP). D, Total antioxidant status in plasma, ie, the individual's level of protection against attack by free oxygen radicals. Total antioxidant status was related to the standard (Trolox 1.76 mmol/L). E, Oxidized LDL in plasma. Data are mean $\pm$ SD. Probability values inside figures represent within-group differences. §Different from control and MCT groups,  $P < 0.01$ .

( $P < 0.02$ ) with AIT (Figure 2C). Endurance training did not influence wall thickness (data not shown).

### Systolic Function

All indexes of LV systolic performance in the present study suggest that AIT was highly effective in improving systolic function: LV ejection fraction increased by 10 percentage points, which corresponds to 35% in relative terms ( $P < 0.01$ ; Table 3), the systolic mitral annulus excursion by 30% ( $P < 0.01$ ; Table 4), and stroke volume by 17% ( $P < 0.01$ ; Table 3). Furthermore, peak systolic mitral annulus velocity measured by tissue Doppler imaging, which is an index of global contractility,<sup>15</sup> increased by 22% ( $P < 0.01$ ; Table 4). Peak ejection velocity, as measured by standard Doppler in the LV outlet tract, was increased by 19% ( $P < 0.05$ ; Table 4). No significant changes occurred in systolic function in the MCT or control groups.

### Diastolic Function

Ea is the most direct measure of ventricular relaxation and appears to be less sensitive to alterations in preload than the traditional Doppler E/A ratio. AIT, but not MCT, improved

Ea by 49% ( $P < 0.01$ ; Table 4) and the E/A ratio by 15% ( $P = 0.05$ ; Table 4). The ratio of transmitral flow velocity (E) versus annular velocity (Ea) has been proposed as the best indicator to assess LV filling pressure. It combines the influence of transmitral driving pressure and myocardial relaxation and appears to be less sensitive to alterations in preload than the standard Doppler E/A ratio. AIT and MCT reduced E/Ea by 26% ( $P = 0.001$ ) and 15% ( $P = 0.043$ ; AIT versus MCT,  $P < 0.05$ ; Table 4), respectively. Isovolumic relaxation time increased by 22% ( $P < 0.05$ ) in AIT, but no change was detected in the other groups (Table 4). Deceleration time of the mitral flow E wave did not change significantly in any of the groups.

### Endothelial Function

Endothelial dysfunction contributes to exercise intolerance, impaired myocardial perfusion, and LV remodeling in chronic heart failure and serves as an independent prognostic marker for future cardiovascular events (e.g.<sup>16</sup>). We observed a close relationship between improved aerobic capacity and improved FMD ( $R = 0.69$ ,  $P < 0.05$ ) and a greater improvement in FMD by AIT than by MCT ( $P < 0.05$ ; Figure 1).

Central to the regulation of FMD is the bioavailability of nitric oxide (NO), and abnormalities in 1 or more pathways that ultimately regulate the availability of NO may lead to endothelial dysfunction. It is well established that increased oxidative stress and oxidized LDL reduce the bioavailability of NO, and in the present study, we observed that AIT patients increased their antioxidative status by 15% ( $P=0.02$ ), which indicates a lower level of reactive oxygen species and higher NO production. In line with this, enhanced FMD correlated with increased total antioxidant status in blood plasma ( $R=0.67$ ,  $P<0.01$ ; Figure 2D). Furthermore, AIT reduced the plasma levels of oxidized LDL by 9% (Figure 2E;  $R=0.59$ ,  $P=0.03$ ).

Endurance training did not change the plasma levels of insulin-like growth factor-1 or endothelin-1 (ET-1). After the exercise test, the median values were 2.9 (95% CI, 2.4 to 3.5) pg/mL and 61.3 (95% CI, 53.2 to 70.8) ng/mL, respectively. Finally, high-sensitivity C-reactive protein was similar between groups and was not changed by endurance training. The median high-sensitivity C-reactive protein value for all groups combined was 5.6 (95% CI, 3.8 to 12.8) mg/L.

### Quality of Life

The MacNew global score for quality of life in cardiovascular disease increased both after MCT ( $4.4\pm 0.4$  versus  $5.2\pm 0.2$ ,  $P<0.01$ ) and after AIT ( $4.41\pm 0.32$  versus  $5.73\pm 0.19$ ,  $P<0.001$ ; difference between groups  $P<0.02$ ). No change occurred in the control group ( $4.49\pm 0.24$  versus  $4.48\pm 0.36$ ).

## Discussion

The major finding of the present study was that AIT was superior to MCT in patients with postinfarction heart failure with regard to reversal of LV remodeling, aerobic capacity, endothelial function, and quality of life. Of particular interest is the old age of the majority of patients in the present study, who demonstrated robust training-induced adaptation, even in elderly heart failure patients. This is important information because chronic heart failure is a disease of the elderly; in fact, it has been reported that 88% and 49% of patients with a first diagnosis of chronic heart failure were  $>65$  and  $>80$  years old, respectively.<sup>17</sup> Despite this, most previous studies have excluded patients with an age  $>70$  years.

### Aerobic Capacity

The large increase in  $\dot{V}O_{2peak}$  in AIT may be explained in part by lower baseline values and a higher exercise intensity than in previous studies (eg, Dubach et al<sup>18</sup> and Gielen et al<sup>19</sup>), and one could speculate whether we underestimated  $\dot{V}O_{2peak}$  at before exercise but not afterward. However, this appears unlikely, because only 2 patients did not manage to satisfy the criteria defined for reaching true maximal oxygen uptake at both time points. Furthermore, high blood lactate concentrations and high respiratory exchange ratios suggest that the patients exercised at maximum effort at both occasions.

Two previous studies<sup>20,21</sup> involving patients with coronary artery disease have employed aerobic interval exercise with elements of the same high intensity as in the present study, both with a substantial increase of  $\dot{V}O_{2peak}$ . These studies showed that 12 months of exercise at 50% to 95% of  $\dot{V}O_{2peak}$

3 to 5 times per week induced an improvement in  $\dot{V}O_{2peak}$  of 37% to 42%. A longer training period, a large variation in exercise intensity, and varying numbers of training sessions per week makes comparison with the present study difficult; however, the previous studies demonstrated that high exercise intensity is associated with a large improvement of  $\dot{V}O_{2peak}$ . The main goal of the present study was to evaluate the effect of exercise when intensity was the only independent variable. The high-intensity exercise was chosen to be aerobic interval exercise at 90% to 95% of peak heart rate because this training method has been used by our research group in healthy individuals, yielding large improvements in  $\dot{V}O_{2peak}$  within a relatively short time period.<sup>22</sup> Informal comments from the patients in the exercise groups indicated that patients in the AIT group found it motivating to have a varied procedure to follow during each training, whereas those in the MCT group found it "quite boring" to walk continuously during the entire exercise period. In addition to improved  $\dot{V}O_{2peak}$ , improved anaerobic threshold and work economy increase the patient's ability to cope with the physical demands of daily activity.<sup>23</sup> The present study demonstrated that the anaerobic threshold increased more in AIT than MCT when expressed in absolute workloads. Interestingly, AIT but not MCT improved the patients' work economy (Table 2). The reason for these adaptations is not fully understood but probably reflects improved mitochondrial function (as indicated by an increased level of PGC-1 $\alpha$ ) and calcium cycling in skeletal muscle of AIT patients (as suggested by increased SERCA capacity).

### Reversed LV Remodeling

Lower plasma proBNP levels clearly demonstrate the effectiveness of AIT in modifying postinfarction remodeling. Accordingly, AIT reduced LV end-diastolic and end-systolic volumes by 18% and 25%, respectively, similar to the effect of 3 months of cardiac resynchronization therapy.<sup>24</sup> It has been shown that treatment with ACE inhibitors halts the progression of remodeling,<sup>25</sup> whereas combined treatment with ACE inhibitors and  $\beta$ -blockers in patients with chronic heart failure increases ejection fraction  $\approx 12\%$ <sup>26</sup> similar to the findings with AIT in the present study. These observations indicate that AIT utilizes a potential for further reversal of remodeling, because it was added on top of medication. Moreover, myocardial contractile function also markedly improved in AIT patients in terms of ejection fraction, stroke volume, mitral annular excursion, ejection velocity, and systolic mitral annular velocity measured by tissue Doppler imaging.

Ea, which is the most direct measure of LV relaxation and is less sensitive to load than flow indices,<sup>27</sup> was improved in the AIT group only. Mitral flow is a function of both left atrial pressure and LV relaxation, and the ratio of transmitral flow velocity (E) versus annular velocity (Ea) has been proposed as an indicator of LV filling pressure.<sup>28</sup> E/Ea decreased substantially in the AIT group, which indicates a decrease in filling pressure toward normal. This is consistent with the increase in isovolumic relaxation time. MCT had no significant effect on LV systolic or diastolic performance, measured by tissue Doppler imaging, other than causing a

minor improvement in the E/Ea ratio; however, the decreased E/Ea ratio in MCT was due to a small decrease in transmitral flow velocity alone and was not accompanied by supporting evidence showing an increase in E/A or isovolumic relaxation time, and it might, therefore, represent a dubious result.

### Endothelial Function

It is well established that endurance training improves coronary endothelium-dependent vasodilation in patients with coronary artery disease.<sup>29</sup> It is therefore reasonable to speculate that this also occurred in the present study and contributed to the antiremodeling effect of AIT in the LV.

Both the level of reactive oxygen species and the amount of oxidized LDL are known to directly influence NO bioavailability, and a normal endothelial function is dependent on the balance of oxidant and antioxidant mechanisms. During oxidative stress, superoxide anions ( $O_2^-$ ) decrease the function of endothelial NO synthase and reduce the half-life of NO by increasing the production of peroxynitrite from NO and  $O_2^-$ , whereas in the normal state, the  $O_2^-$  is quenched by superoxide dismutase. AIT improved FMD more than MCT, and the reason for this may be the increased bioavailability of NO in AIT patients. In line with this notion, we found that AIT increased the antioxidant status in blood plasma, which indicates reduced oxidative stress. These results are in agreement with a recent study by Linke et al<sup>30</sup> demonstrating antioxidative effects of exercise training in skeletal muscle of patients with chronic heart failure. Because AIT reduced the amount of reactive oxygen species, it was not surprising that oxidized LDL was lower in AIT. Why AIT was more effective is unknown, but it appears reasonable to speculate that higher shear stress during the exercise bouts of AIT patients triggers larger responses at the cellular and molecular level. Despite the decreased level of reactive oxygen species and improved NO-mediated endothelial function, we did not observe any change in the levels of endothelin-1 and insulin-like growth factor-1 in blood, which indicates that endurance training acts through other pathways or may act locally to improve endothelial function.

### Quality of Life

The physiological improvements were paralleled by better quality of life. Interestingly, quality of life improved more markedly in AIT subjects than in the other groups, which suggests that more intensive physical training is more rewarding. This observation is in line with a study by Klocek et al.<sup>31</sup> The mechanism of the superior effect of intensive physical training on the quality of life is not presently known, but it is reasonable to suggest that it is due to greater physiological adaptation and thereby improved capacity for activity in AIT subjects.

### Study Limitations

The number of patients in the present study was small, and subjects were predominantly males, which precludes any inference about the safety of this training technique. The study should therefore be regarded as a "proof-of-concept" study. It is not known whether the present training protocol will yield similar adaptations in heart failure due to causes

other than myocardial infarction. A recent study by Rognmo et al<sup>4</sup> showed that a similar interval program was more than twice as effective in improving  $\dot{V}O_{2peak}$  compared with moderate-intensity exercise in patients with coronary artery disease. However, the present data are provocative and should encourage the creation of larger multicenter studies using the same training technique and addressing the safety issue.

### Conclusions

The present study demonstrates that high-intensity training relative to the individual's maximal oxygen uptake is feasible even in elderly patients with chronic heart failure and severely impaired cardiovascular function. It also shows that the intensity of exercise may be an important factor for reversing LV remodeling, improving aerobic capacity, and improving quality of life in patients with postinfarction heart failure. These findings may have important implications for exercise training in rehabilitation programs and future studies. It is our view that the time has come to perform multicenter studies comparing exercise at moderate versus high relative intensities for stable cardiovascular patients, including those with postinfarction heart failure. We suggest that training programs based on these principles may yield more favorable results than those with low to moderate exercise intensities.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

In recent years, there has been a growing consensus that physical inactivity accelerates the severity of heart failure and that the level of aerobic fitness predicts survival in a cardiovascular disease population, even when other traditional risk factors are present or in the setting of established  $\beta$ -blockade. However, there is still controversy regarding the level and format of exercise that can yield optimal beneficial effects. In the present study, we sought to find out whether exercise intensity was of importance for improving aerobic fitness and cardiac function in patients with postinfarction heart failure. Patients aged  $75.5 \pm 11.1$  years either performed high-intensity aerobic interval training or moderate continuous exercise or received standard advice regarding physical activity. The protocols were made isocaloric so that only exercise intensity differed between the 2 intervention groups. The present study demonstrates that high-intensity training relative to the individual's aerobic fitness capacity is feasible even in elderly patients with chronic heart failure who have severely impaired cardiovascular function. It also shows that the intensity of exercise is an important factor for reversing left ventricular remodeling, improving aerobic capacity, and improving quality of life in patients with postinfarction heart failure.