Journal of the American College of Cardiology Vol. 58, No. 17, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.054

CME

Exercise Training Improves Exercise Capacity and Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction

Results of the Ex-DHF (Exercise training in Diastolic Heart Failure) Pilot Study

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to determine whether structured exercise training improves maximal exercise capacity, left ventricular diastolic function, and quality of life in patients with heart failure with preserved ejection fraction.

CME Editor Disclosure: *JACC* CME Editor Ajit Raisinghani, MD, FACC, reports that he has no financial relationships or interests to disclose.

Author Disclosures: This study was supported by the German Competence Network of Heart Failure, funded by the Federal Ministry of Education and Research, grant no. 01GI0205. The study group received NT-proBNP reagents from Roche Diagnostics free of charge. Dr. Hasenfuss is a consultant for Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz)

CME Term of Approval:

Issue date: October 18, 2011
Expiration date: October 17, 2012

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Manuscript received March 10, 2011; revised manuscript received June 21, 2011, accepted June 27, 2011.

Exercise Training Improves Exercise Capacity and Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction

Results of the Ex-DHF (Exercise training in Diastolic Heart Failure) Pilot Study

Objectives We sought to determine whether structured exercise training (ET) improves maximal exercise capacity, left ventricular diastolic function, and quality of life (QoL) in patients with heart failure with preserved ejection fraction (HFpEF).

Background Nearly one-half of patients with heart failure experience HFpEF, but effective therapeutic strategies are sparse.

Methods A total of 64 patients (age 65 ± 7 years, 56% female) with HFpEF were prospectively randomized (2:1) to supervised endurance/resistance training in addition to usual care (ET, n = 44) or to usual care alone (UC) (n = 20). The primary endpoint was the change in peak Vo_2 after 3 months. Secondary endpoints included effects on cardiac structure, diastolic function, and QoL.

Results Peak Vo_2 increased (16.1 ± 4.9 ml/min/kg to 18.7 ± 5.4 ml/min/kg; $p < 0.001$) with ET and remained unchanged (16.7 ± 4.7 ml/min/kg to 16.0 ± 6.0 ml/min/kg; p = NS) with UC. The mean benefit of ET was 3.3 ml/min/kg (95% confidence interval [CI]: 1.8 to 4.8, $p < 0.001$). E/e′ (mean difference of changes: −3.2, 95% CI: −4.3 to −2.1, $p < 0.001$) and left atrial volume index (milliliters per square meter) decreased with ET and remained unchanged with UC (−4.0, 95% CI: −5.9 to −2.2, $p < 0.001$). The physical functioning score (36-Item Short-Form Health Survey) improved with ET and remained unchanged with UC (15, 95% CI: 7 to 24, $p < 0.001$). The ET-induced decrease of E/e′ was associated with 38% gain in peak Vo_2 and 50% of the improvement in physical functioning score.

Conclusions Exercise training improves exercise capacity and physical dimensions of QoL in HFpEF. This benefit is associated with atrial reverse remodeling and improved left ventricular diastolic function. (Exercise Training in Diastolic Heart Failure–Pilot Study: A Prospective, Randomised, Controlled Study to Determine the Effects of Physical Training on Exercise Capacity and Quality of Life [Ex-DHF-P]; ISRCTN42524037) (J Am Coll Cardiol 2011;58: 1780–91) © 2011 by the American College of Cardiology Foundation

Epidemiological data indicate that the prevalence of heart failure with preserved ejection fraction (HFpEF) has significantly increased (1). Currently, over 50% of patients with symptomatic heart failure experience HFpEF (1,2). Morbidity and mortality is high and almost comparable to heart failure with reduced ejection fraction (HFrEF) (1,2). However, in HFpEF, no pharmacological therapy has shown to be effective in large clinical trials (3–6).

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In HFrEF, exercise training (ET) improves exercise capacity and reduces morbidity (7). As suggested by meta-analyses, the large HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial also demonstrated a modest outcome benefit with ET in HFrEF (8,9). Furthermore, conditions known to be significantly associated with HFpEF (e.g., endothelial dysfunction, systemic inflammation, metabolic syndrome) are substantially improved by ET (10–12). Limited data suggest an attenuation of the age-dependent decline in diastolic function with ET (13). However, no multicenter, prospective, randomized controlled trial (RCT) investigating also the effects of ET on diastolic function has been performed in HFpEF.

We conducted the multicenter, prospective RCT on exercise training in diastolic heart failure to investigate whether ET improves exercise performance, diastolic function, and quality of life (QoL) in patients with HFpEF.

Methods

We performed a prospective, multicenter, RCT in patients with HFpEF. Structured endurance/resistance ET on top of usual care (UC) was tested against UC alone.

Patient population. Symptomatic (New York Heart Association [NYHA] functional class II/III) outpatients older than 45 years of age were included if they had preserved left ventricular systolic function (left ventricular ejection fraction ≥50%), echocardiographically determined diastolic dysfunction (grade ≥1), sinus rhythm, and at least 1 of the following cardiovascular risk factors: overweight, diabetes mellitus, hypertension, hyperlipidemia, smoking. Exclusion criteria were hemodynamically relevant valvular disorders, pulmonary disease (vital capacity and/or forced expiratory volume in 1 s <80% of age-dependent predicted value), current angina pectoris, untreated coronary artery stenosis >50%, previous myocardial infarction, anemia (hemoglobin <12 g/dl), clinically relevant musculoskeletal disease, resting systolic blood pressure >150 mm Hg or diastolic blood pressure >100 mm Hg, clinically relevant arrhythmia,

Abbreviations and Acronyms

CI = confidence interval
ET = exercise training
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
IQR = interquartile range
LAVI = left atrial volume index
LVMI = left ventricular mass index
MLWHFQ = Minnesota Living With Heart Failure Questionnaire
NT-proBNP = N-terminal pro–B-type natriuretic peptide
NYHA = New York Heart Association
QoL = quality of life
RCT = randomized controlled trial
SF-36 = 36-Item Short-Form Health Survey
UC = usual care
Vo_2 = oxygen consumption

change in cardiovascular medication within the previous 4 weeks. Patients were recruited at 3 university hospitals in Germany. The German Health Authorities and the ethics committees at each center approved the study. Written informed consent was obtained from all patients before any study-related procedure was performed.

Randomization, intervention. Patients were randomized in a 2:1 ratio to ET or to UC. Blocked randomization lists were generated. The allocation sequence was implemented remotely via telefax by the Coordination Center for Clinical Trials Leipzig, Germany.

Patients randomized to ET participated in a supervised, facility-based training program consisting of endurance and resistance training (32 sessions). During weeks 1 through 4, aerobic endurance training (cycling 2×/week) of increasing intensity and duration (from 20 to 40 min) was performed. Training intensity was tailored individually to a target heart rate of 50% to 60% of peak oxygen uptake (peak Vo_2) during baseline spiroergometry. From week 5 onward, weekly training frequencies were increased (3×/week) and workload was increased to a target heart rate of 70% of baseline peak Vo_2. Also starting at the fifth week, resistance training (bench press, leg press, leg curl, rowing machine, triceps dip, latissimus pull down) was added twice per week. Resistance training was performed for 15 repetitions per exercise per session at a workload corresponding to 60% to 65% of the 1 repetition maximum measured at the end of week 4. Safety parameters such as blood pressure and heart rate as well as training intensity and attendance at training sessions were documented in a patient physical activity diary.

Patients randomized to the control group were instructed to continue and maintain their usual daily activities. All patients were on UC as recommended for HFpEF and concomitant diseases, which remained unchanged during the trial.

Clinical assessment. At baseline and follow-up, patients underwent physical examination, echocardiography, cardiopulmonary exercise testing, 6-min walk test, and blood sampling. QoL was assessed by the 36-Item Short Form Health Survey (SF-36) and the Minnesota Living With Heart Failure Questionnaire (MLWHFQ). Technical staff not involved in the training program and blinded to patient assignment distributed the questionnaires to the patients.

Patients performed symptom-limited cardiopulmonary exercise testing on a bicycle ergometer, beginning at a workload of 20 W and increasing stepwise at 20-W increments every 2 min. A 12-lead electrocardiogram was continuously recorded; blood pressure was measured every 2 min. Cardiopulmonary variables were calculated using printouts of 10-s–averaged values.

Methods against bias regarding the primary endpoint. None of the personnel involved in any exercise training procedure, or the physicians or investigators who were aware of treatment group assignment were present during cardiopulmonary exercise testing. Peak Vo_2 was defined as the highest Vo_2 value of the last 30 s before termination of exercise. A blinded investigator reviewed all measurements and confirmed correct peak Vo_2 determination. Ventilatory anaerobic threshold was determined as described by Beaver et al. (14) and using a blinded post-hoc analysis in a nonpaired fashion (15).

Echocardiography. Echocardiography, including tissue Doppler parameters and calculating left ventricular mass index (LVMI) and left atrial volume index (LAVI), was performed according to current guidelines of the American Society of Echocardiography (16). A standard operating procedure was used to ensure comparable results in all centers. A reference center performed staff training prior to the trial, and supervision and blinded core data evaluation during the trial (F.E. at Göttingen). Diastolic dysfunction was determined as described previously (17).

Biomarkers. Blood samples were taken in standardized conditions after a 20-min supine resting period. All samples were immediately centrifuged and stored at −80°C. N-terminal pro–B-type natriuretic peptide (NT-proBNP) was analyzed using a commercially available Elecsys proBNP sandwich immunoassay (Elecsys 2010 analyzer, Roche Diagnostics, Mannheim, Germany) and serum procollagen type I-NP (PINP) using a commercial radioimmunoassay kit (Orion Diagnostica, Espoo, Finland).

Endpoints of the study. The primary endpoint was the change in peak Vo_2 after 3 months follow-up. Secondary endpoints included echocardiographic parameters of left ventricular and atrial remodeling (LVMI, left ventricular end-diastolic volume index, LAVI), systolic and diastolic function (left ventricular ejection fraction, E/e′, e′, S/D, E/A); parameters of exercise capacity (maximum workload, Vo_2, and workload at the ventilatory anaerobic threshold, maximum ventilatory exchange, increase of heart rate during exercise); 6-min walk distance; QoL: SF-36 physical functioning scale and physical, emotional, and total scores of the MLWHFQ; and serum biomarkers (NT-proBNP, PINP).

Statistical analysis. Changes within groups during follow-up were assessed by the *t* test for paired variables. Analysis of covariance (ANCOVA) with the follow-up measurement as dependent variable, baseline measurement as covariate, and treatment group as fixed factor was applied for all comparisons between the groups. Data were shown as mean ± SD. For skewed distributed laboratory data, pre-

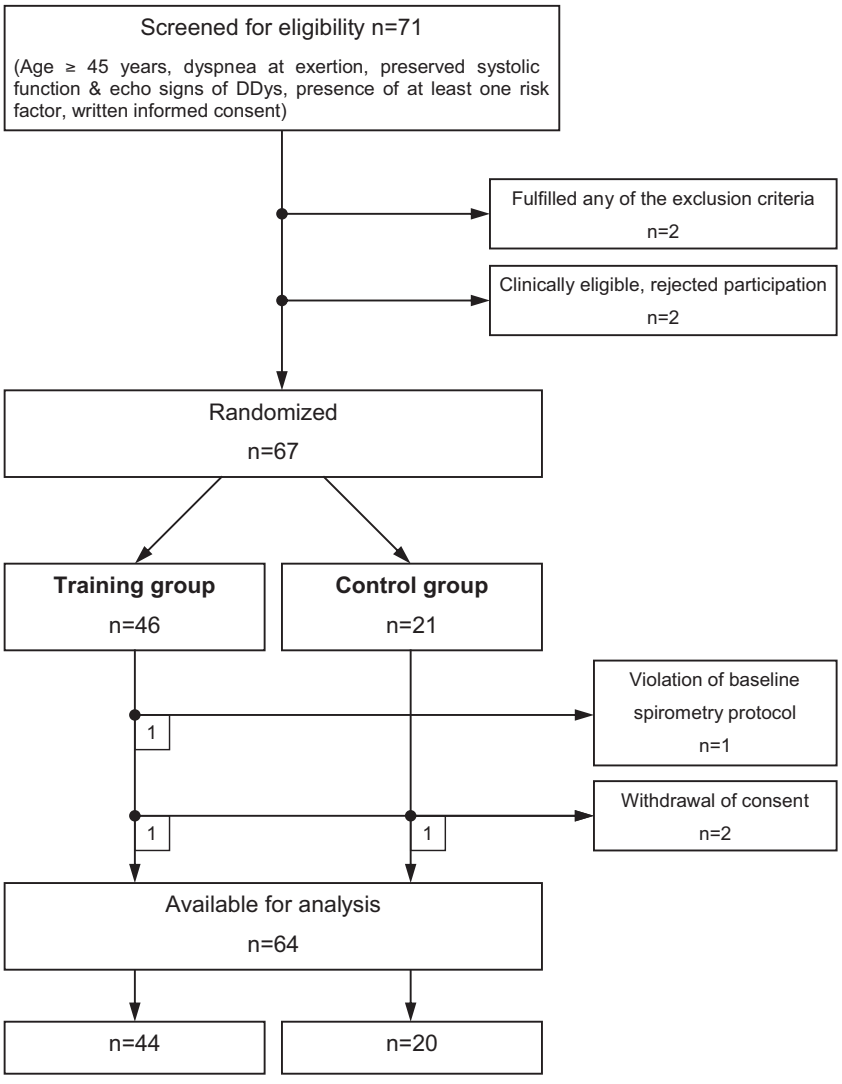

Figure 1 **Flow Chart of the Trial**

DDys = diastolic dysfunction.

sented at baseline and follow-up, data were shown by median and interquartile range (IQR). For NT-proBNP and PINP, *t* tests and ANCOVA were carried out on the logarithmic scale, and the results were transformed back by the exponential function, leading to estimates of ratios (instead of differences) for within-group changes and the between-group effect of intervention. Changes in NYHA functional class were compared by Fisher exact test. For explanatory purposes, post hoc analyses of the correlations between the changes of the main outcome measures were carried out. As well, possible correlations of training compliance and leisure activities with the outcomes were examined in the intervention group in an exploratory manner. Analyses were performed according to the intent-to-treat principle. SPSS version 15.0 (SPSS Inc., Chicago, Illinois) was the software used for statistical analyses.

Sample size. A mean improvement of peak Vo_2 of 3 ml/min/kg (standard deviation of changes within groups 5 ml/min/kg) in the training group and no change in the control group were expected. This pilot study was powered primarily to demonstrate a significant improvement of peak Vo_2 in the training group with type I and II error levels both equal to 0.05. Secondarily, the study was powered to show a trend in favor of ET versus UC with type I and II error levels both equal to 0.20. To meet both requirements, 2:1 randomization was the favorable solution, with 40 training patients and 20 controls available for evaluation.

Results

Study sample. Of 71 patients screened from January to August 2007, 67 were included and 64 were analyzed (Fig. 1).

Table 1 Demographic Data, Physical Examination, and Medical History at Baseline

Variable	All Subjects (n = 64)	Treatment Group: Training (n = 44)	Treatment Group: Control (n = 20)	Difference Between Groups (p Value)
Female	36 (56%)	24 (55%)	12 (60%)	0.79
Age, yrs	65 ± 7	64 ± 8	65 ± 6	0.51
General examination				
Body mass index, kg/m^2	31 ± 5	31 ± 6	31 ± 4	0.96
Waist/hip ratio	0.93 ± 0.08	0.93 ± 0.08	0.92 ± 0.08	0.63
Heart rate, beats/min	66 ± 11	67 ± 12	64 ± 9	0.46
Systolic blood pressure, mm Hg	140 ± 19	140 ± 18	141 ± 20	0.97
Diastolic blood pressure, mm Hg	82 ± 12	82 ± 10	82 ± 14	0.51
Characterization of heart failure				
NYHA functional class of dyspnea				0.15
II	54 (84%)	35 (80%)	19 (95%)	
III	10 (16%)	9 (20%)	1 (5%)	
Orthopnea	12 (19%)	8 (18%)	4 (20%)	1.00
Paroxysmal nocturnal dyspnea	8 (14%)	6 (14%)	2 (10%)	1.00
Peripheral edema	24 (38%)	17 (39%)	7 (35%)	1.00
Nocturia	39 (61%)	24 (55%)	15 (75%)	0.17
Grade of diastolic dysfunction				0.55
I	46 (72%)	33 (75%)	13 (65%)	
II	18 (28%)	11 (25%)	7 (35%)	
Left ventricular ejection fraction, %	67 ± 7	68 ± 7	67 ± 7	0.59
Medication				
ACE inhibitor and/or AT1 receptor antagonist	42 (66%)	31 (70%)	11 (55%)	0.26
Beta-blocker	32 (50%)	20 (45%)	12 (60%)	0.42
Diuretics	29 (45%)	21 (48%)	8 (40%)	0.60
Risk factors				
Overweight (body mass index >25 kg/m^2)	57 (89%)	38 (86%)	19 (95%)	0.42
Diabetes mellitus	9 (14%)	7 (16%)	2 (10%)	0.71
Hypertension	55 (86%)	38 (86%)	17 (85%)	1.00
Hyperlipidemia	30 (47%)	20 (46%)	10 (50%)	0.79
Ever smoked	36 (56%)	26 (59%)	10 (50%)	0.59
Number of present risk factors	2.9 ± 0.9	2.9 ± 0.9	2.9 ± 1.1	0.87

Values are n, frequency (%), or mean ± SD.
ACE = angiotensin-converting enzyme; AT = angiotensin; NYHA = New York Heart Association.

One patient (ET) was excluded due to violation of the baseline spiroergometry protocol, and 1 patient in each group withdrew consent. Baseline data are summarized in Table 1.

Clinical and cardiac effects of exercise training. Cardiovascular medication was not different between the training and the control group (Table 1). During follow-up, minor modifications were noted, with no significant differences between the 2 groups. In any group, neither body mass index nor blood pressure changed significantly during follow-up (Table 2). ET significantly improved symptoms, exercise capacity, diastolic function, and QoL (Tables 2 and 3, Fig. 2). Mean increase of peak Vo_2 was +2.6 ml/min/kg in the training group compared with a slight decrease of −0.7 ml/min/kg in the control group. The net benefit of training was +3.3 ml/min/kg (95% confidence interval [CI]: 1.8 to 4.8, $p < 0.001$), translating into a number needed to treat of 3.5 (95% CI: 2.0 to 12.0, $p = 0.006$) to achieve an increase of at least 3 ml/min/kg at the individual level. At baseline, respiratory exchange ratio was not different between the groups (ET: 1.20 ± 0.10 vs. UC: 1.18 ± 0.11; $p > 0.05$) and did not change after follow-up (difference of changes between groups $p = 0.52$). The improvement in peak Vo_2 corresponded to an increase in the 6-min walking distance in the training group by 24 m ($p < 0.001$), although the difference between ET and UC remained statistically insignificant.

The E/e′ ratio improved significantly in the training group as compared with the control group. LAVI decreased significantly in the training group whereas no relevant change occurred in controls. LVEF and volumes as well as LVMI did not change in any group.

NT-proBNP levels were similar at baseline (ET: 157 ± 17 pg/ml; UC: 172 ± 110 pg/ml) and did not change throughout the study. There was a significant decrease of procollagen type I levels in ET patients as compared with UC (Table 2).

Compared with the control group, ET improved self-reported physical functioning (SF-36 and the MLWHFQ physical limitation scale). MLWHFQ emotional and total

Table 2 Spiroergometric Endpoint Data at Baseline and After 3 Months

Variable	Treatment Group		Difference Between Groups
	Training	Control	
Peak Vo_2, ml/min/kg primary			
Baseline	16.1 ± 4.9	16.7 ± 4.7	
Follow-up	18.7 ± 5.4	16.0 ± 6.0	
Change	2.6 (1.8 to 3.4)	−0.7 (−2.1 to 0.7)	3.3 (1.8 to 4.8)
p value	<0.001	0.34	<0.001
Maximum workload, W			
Baseline	117 ± 38	114 ± 35	
Follow-up	129 ± 41	111 ± 41	
Change	12 (7 to 17)	−3 (−11 to 5)	15 (6 to 24)
p value	<0.001	0.45	<0.001
Maximum exercise time, s			
Baseline	648 ± 224	630 ± 211	
Follow-up	700 ± 251	615 ± 245	
Change	52 (27 to 77)	−15 (−48 to 18)	66 (24 to107)
p value	<0.001	0.35	0.002
Anaerobic threshold Vo_2, ml/min/kg			
Baseline	10.2 ± 3.0	10.3 ± 2.5	
Follow-up	12.7 ± 3.6	10.0 ± 3.2	
Change	2.5 (1.9 to 3.1)	−0.3 (−1.3 to 0.6)	2.8 (1.7 to 4.0)
p value	<0.001	0.49	<0.001
Workload at anerobic threshold, W			
Baseline	63 ± 24	63 ± 21	
Follow-up	77 ± 30	61 ± 23	
Change	14 (9 to 19)	−2 (−8 to 4)	16 (8 to 25)
p value	<0.001	0.49	<0.001
Maximum ventilatory exchange, l/min			
Baseline	49.8 ± 17.1	47.8 ± 15.6	
Follow-up	52.7 ± 19.5	45.0 ± 19.2	
Change	2.9 (−0.4 to 6.2)	−2.8 (−7.9 to 2.2)	5.8 (−0.1 to 11.6)
p value	0.09	0.25	0.053
Δ Mean BP during exercise, mm Hg			
Baseline	29.0 ± 17.2	25.2 ± 19.9	
Follow-up	30.1 ± 15.1	25.4 ± 20.7	
Change	1.1 (−2.8 to 5.0)	0.2 (−6.0 to 6.3)	2.1 (−4.2 to 8.3)
p value	0.567	0.951	0.517
Δ Heart rate during exercise, beats/min			
Baseline	56 ± 20	52 ± 18	
Follow-up	58 ± 20	49 ± 16	
Change	2 (−2 to 6)	−3 (−8 to 2)	6 (−1 to 13)
p value	0.31	0.24	0.08

Data are mean ± SD or mean (95% confidence interval).
BP = blood pressure; Vo_2 = oxygen uptake; Δ = increase.

scales also improved significantly in the training group, but differences between groups did not reach statistical significance.

ET significantly improved NYHA functional class ($p = 0.009$ vs. controls). NYHA functional class improved in 14 patients in the training group (10 from NYHA functional class II to I, 4 from NYHA functional class III to II) but none of those in the control group.

Relationship between diastolic function, exercise performance, and physical functioning. The increase in peak Vo_2 was correlated with the improvement in E/e′ ($r = −0.37$, $p = 0.002$). According to the equation for the regression line (change in peak $Vo_2 = 1.00 − 0.42 \times$ change in E/e′ + error), the observed difference of change in E/e′ of −3.2 in the ET group as compared with UC determines an improvement of peak Vo_2 by 1.26 ml/min/kg. This corresponds to 38% of the total improvement in peak Vo_2 ($r = −0.37$, $p = 0.002$) (Fig. 3). The correlation of the change in physical functioning with the improvement of E/e′ was even more pronounced ($r = −0.46$, $p < 0.001$) (Fig. 3). The regression equation translates the difference in improvement of E/e′ into an improvement of the physical functioning score by nine points, corresponding to 50% of the entire effect of training on physical functioning.

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Table 3 Echocardiographic, Clinical, and QoL Endpoint Data at Baseline and After 3 Months

Variable	Treatment Group		Difference Between Groups
	Training	Control	
E/e′ ratio			
Baseline	12.8 ± 3.2	13.5 ± 4.6	
Follow-up	10.5 ± 2.5	14.1 ± 3.9	
Change	−2.3 (−3.0 to −1.6)	0.6 (−0.5 to 1.8)	−3.2 (−4.3 to −2.1)
p value	<0.001	0.26	<0.001
e′ medial, cm/s			
Baseline	5.4 ± 1.2	6.0 ± 1.5	
Follow-up	6.3 ± 1.3	5.5 ± 1.3	
Change	0.9 (0.6 to 1.1)	−0.5 (−0.8 to −0.1)	1.2 (0.8 to 1.7)
p value	<0.001	0.02	<0.001
S/D ratio			
Baseline	1.38 ± 0.32	1.37 ± 0.27	
Follow-up	1.40 ± 0.33	1.27 ± 0.29	
Change	0.02 (−0.08 to 0.11)	−0.10 (−0.22 to 0.03)	0.12 (−0.03 to 0.26)
p value	0.72	0.12	0.11
Left atrial volume index, ml/m^2			
Baseline	27.9 ± 7.6	28.2 ± 8.8	
Follow-up	24.3 ± 6.5	28.6 ± 9.2	
Change	−3.7 (−4.9 to −2.4)	0.3 (−0.7 to 1.4)	−4.0 (−5.9 to −2.2)
p value	<0.001	0.53	<0.001
Left ventricular ejection fraction, %			
Baseline	67 ± 7	66 ± 7	
Follow-up	66 ± 6	67 ± 8	
Change	−1 (−5 to 2)	1 (−4 to 6)	−1 (−5 to 3)
p value	0.33	0.75	0.54
Left ventricular volume index, ml/m^2			
Baseline	38.2 ± 9.8	38.7 ± 9.5	
Follow-up	39.1 ± 9.7	39.7 ± 10.6	
Change	0.9 (−0.9 to 2.8)	1.0 (−1.2 to 3.1)	−0.1 (−3.1 to 2.9)
p value	0.33	0.36	0.93
LVMI, g/m^2			
Baseline	116.8 ± 27.4	108.8 ± 28.9	
Follow-up	117.5 ± 38.4	113.2 ± 26.4	
Change	0.7 (−10.7 to 12.1)	4.4 (−7.1 to 15.9)	0 (−17.4 to 17.4)
p value	0.899	0.435	1.000
6-min walk distance, m			
Baseline	545 ± 86	551 ± 86	
Follow-up	569 ± 88	568 ± 80	
Change	24 (10 to 38)	17 (−3 to 38)	6 (−18 to 30)
p value	0.001	0.10	0.63
Procollagen type I, μg/l			
Baseline*	38 (25 to 51)	34 (24 to 41)	
Follow-up*	34 (25 to 42)	35 (30 to 46)	
Follow-up/baseline ratio	0.96 (0.93 to 0.99)	1.02 (0.96 to 1.08)	0.95 (0.91 to 1.00)
p value	0.01	0.55	0.049
SF-36 physical functioning scale			
Number of responders	40	20	
Baseline	65 ± 22	71 ± 20	
Follow-up	79 ± 19	67 ± 24	
Change	14 (8 to 19)	−4 (−11 to 4)	15 (7 to 24)
p value	<0.001	0.30	0.001

Continued on next page

Safety, compliance. There were no serious adverse events in any group. In the training group of 11 (25%) patients, adverse events during or immediately after exercise occurred without clinical relevance upon further investigation. Events with suspected cardiovascular background were brief episodes of palpitations (n = 2) or dyspnea (n = 3). Nine patients (including 2 with dyspnea) reported mild musculoskeletal discomfort during exercise, only 1 of them discontinued participation in exercise sessions during week 9. In the training group, n = 15 (34%) participated in >90%,

Table 3 Continued

Variable	Treatment Group		Difference Between Groups
	Training	Control	
MLWHFQ physical limitation scale			
Number of responders	41	19	
Baseline	14 ± 10	13 ± 10	
Follow-up	9 ± 8	11 ± 9	
Change	−5 (−7 to −3)	−2 (−4 to 0)	−3 (−5 to 0)
p value	<0.001	0.08	0.04
MLWHFQ total scale			
Number of responders	41	19	
Baseline	25 ± 20	23 ± 19	
Follow-up	17 ± 17	21 ± 19	
Change	−8 (−12 to −4)	−2 (−6 to 1)	−5 (−11 to 1)
p value	<0.001	0.19	0.07

Data are n, mean ± SD, or mean (95% CI), except where noted. *Data are median (interquartile range).
CI = confidence interval; IQR = interquartile range; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; SF-36 = 36-Item Short-Form Health Survey.

n = 23 (52%) in 70% to 90%, and n = 6 (14%) in <70% of the exercise sessions. Twenty-three training patients (52%) and 10 controls (50%, p > 0.05) reported high levels (more than 2 h daily) of leisure-time physical activities.

Discussion

This is the first multicenter, prospective RCT that investigated the effects of supervised, structured ET on exercise capacity, diastolic function, and QoL in patients with HFpEF. Endurance/resistance ET over 3 months was a feasible, safe, and effective intervention: ET improved functional capacity and QoL, and this was associated with improved diastolic function.

Despite its high prevalence and prognostic relevance, HFpEF is a disease without evidence-based therapies (1–6,18). ET has been found to improve exercise capacity in HFrEF, mediated by cardiac and extracardiac mechanisms (7,10–12,19). Of particular interest, ET was able to reduce diastolic stiffness in patients with HFrEF (19). These observations, together with promising, albeit preliminary, observations of beneficial effects of ET in HFpEF, gave the rationale for the Ex-DHF pilot study (20,21).

A few smaller, single-center studies have also investigated ET in HFpEF. However, Gary et al. (20) and Smart et al. (21) either did not provide a control group, the effects of exercise training were investigated only when linked to an educational program, or diastolic function was not measured. Kitzman et al. (22) reported the first single-center, single-blind RCT on ET in older patients with HFpEF. Although diastolic function was measured, the presence of diastolic dysfunction was not required as a specific inclusion criterion, and diastolic function was not determined using novel tissue Doppler techniques. In Ex-DHF, diastolic function was investigated as a main outcome measure during follow-up. And, in contrast to previous large trials, all patients were diagnosed through positive demonstration of diastolic dysfunction and strict exclusion of other potential causes for impaired exercise capacity (3–6,21–23). However, although 55% of all included patients fulfilled the very stringent diagnostic criteria defined by the European Society of Cardiology that were published after finalization of our study protocol, we are aware that we also included patients better defined as having mild HFpEF (18,24).

The training program was adopted from successfully conducted studies in HFrEF, where ET improved relevant clinical endpoints (7). Furthermore, the use of a standardized patient diary enabled us to exclude changes in leisure-time physical activity as a potential confounder for the observed beneficial effects of ET. ET was a safe and well-tolerated intervention; only a few minor and conceivable training-related events were reported. Compliance to intervention was high (81%), and only 3 of 67 patients did not complete the study. This rate is substantially lower than in previous reports and has led to increased power to detect beneficial effects regarding diastolic function and exercise capacity (20,21). However, it must be acknowledged that the low rate of adverse events might to some extent be explained by the strict exclusion of serious concomitant diseases. Compliance would likely be lower in unselected patients than within the settings of a voluntary clinical trial. Furthermore, our study population suffered also from mild HFpEF; therefore our observations cannot be extrapolated easily to patients with advanced HFpEF.

Impaired relaxation and diastolic left ventricular filling is the pathophysiological hallmark of HFpEF. Echocardiography including tissue Doppler assessment allows a detailed characterization of diastolic function and estimation of filling pressures (25–27). Morphological parameters, such as left atrial volume, are now additionally used for noninvasive

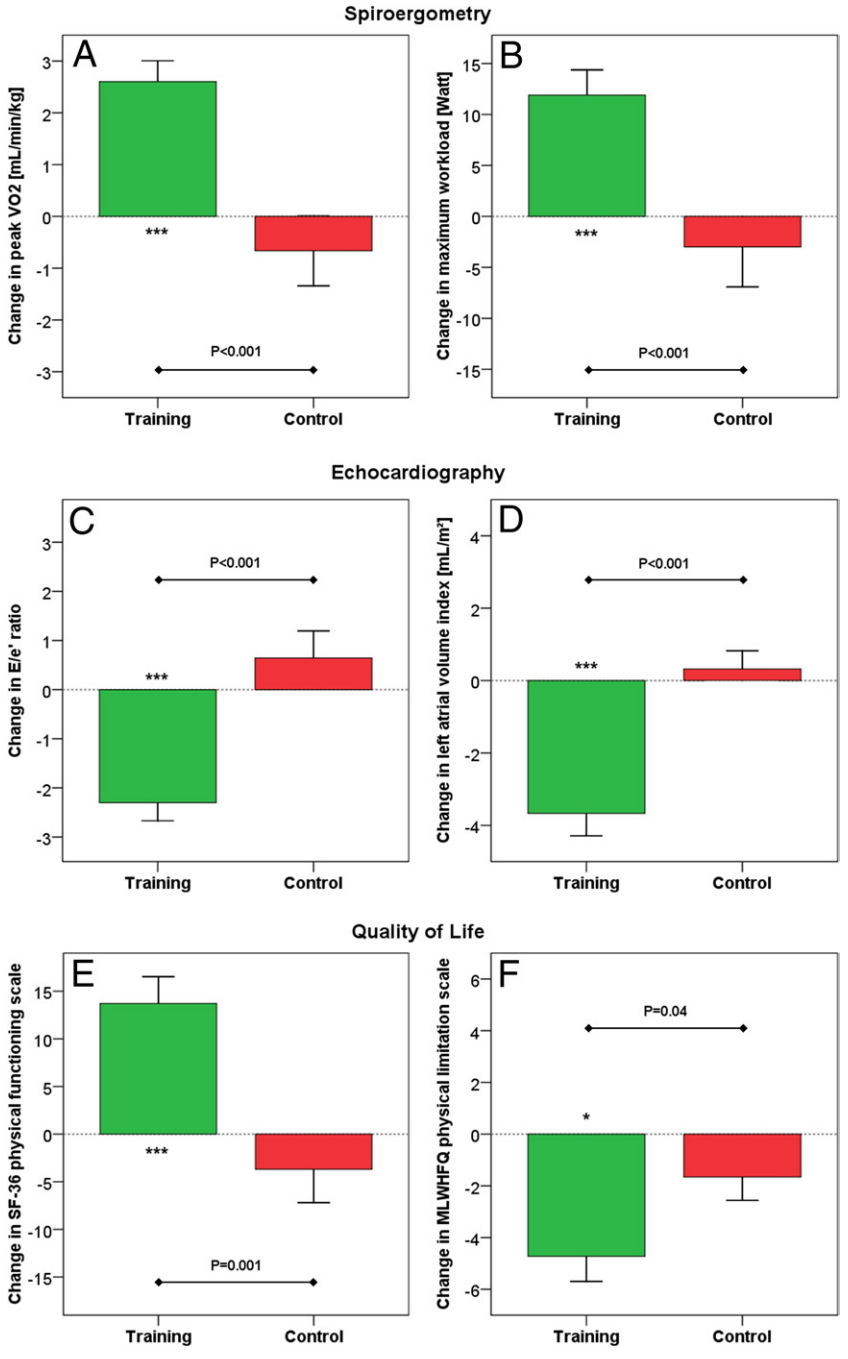

Figure 2 **Changes of the Primary and Main Secondary Endpoints**

Changes from baseline to follow-up of spiroergometric **(A and B)**, echocardiographic **(C and D)**, and QoL **(E and F)** outcome parameters (***p $<$ 0.001 for change within-group). Vo_2 = oxygen consumption.

characterization of HFpEF (28). Both diastolic function parameters and LAVI serve as prognostic indicators (28,29). Furthermore, the severity of diastolic dysfunction is related to functional capacity in HFpEF (30,31). It therefore appears to be reasonable that the improvement of diastolic properties should be a treatment target in HFpEF. In Ex-DHF, ET significantly improved E/e′ and left atrial volume index, suggesting an improvement in left ventricular filling pressures (27). Therefore, our data indicate that an exercise intervention in patients with HFpEF has the potential to improve diastolic function and induce reverse atrial remodeling. Of note, because blood pressure and body mass index did not change in either group, changes in blood pressure and body mass index are unlikely to be a major

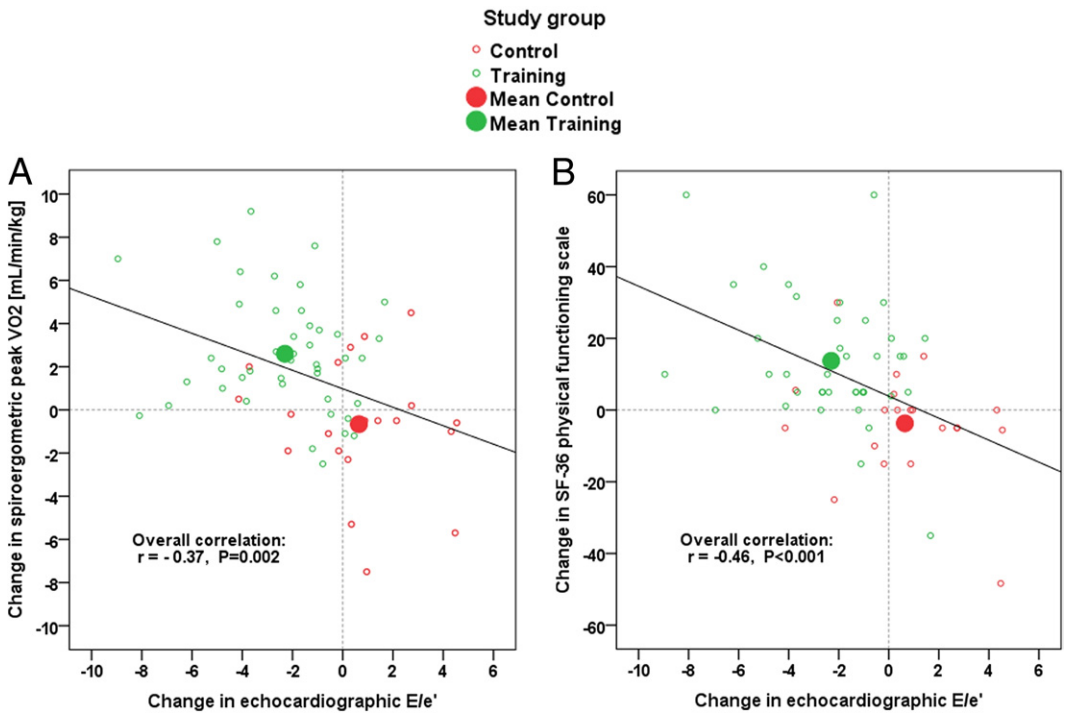

Figure 3 **Association of Changes of Diastolic Function With Changes of Objective and Subjective Measures of Exercise Performance**

Overall, change in E/e′ was significantly correlated with changes in peak oxygen consumption (Vo_2) **(left)** and in SF-36 physical functioning scale **(right)**. Patients who underwent ET significantly improved in peak Vo_2, 36-Item Short-Form Health Survey physical functioning scale, and E/e′ (**green data point**, shift to the **upper left quadrant**), whereas patients in the control group remained unchanged during follow-up **(red data point)**.

mechanism for the improvement of diastolic function (32,33).

Patients with HFpEF experience reduced exercise capacity, which is associated with a poor prognosis and impaired QoL (20–22,29,30,34,35). ET improved exercise capacity in our training cohort, and this effect was at least as large as reported in HFrEF (7,21). It is known that aerobic capacity is partially determined by patient motivation. However, with respect to respiratory exchange ratio values, it is unlikely that patient effort would have biased our results. Since reduced exercise tolerance is known to be a powerful prognostic indicator, the increase in peak Vo_2 may reflect the potential of ET for an improvement of clinical outcome in HFpEF (34). However, considering the results of HF-ACTION in HFrEF, the hypothesis that ET has prognostic impact has yet to be proven (8,9). QoL was also reduced in our patient cohort as described in previous studies (20–22). Similar to peak Vo_2, the extent of improvement in all physical dimensions is comparable to results in HFrEF, strengthening the validity of our results (20,22).

The increase in peak Vo_2 with exercise was associated with improved diastolic function. There may be a major concern whether superior outcome in the training group might predominantly be attributable to the knowledge of treatment allocation (single-blind), leading to bias in the execution of the exercise test and in reporting, driven by the expectations and wishes of both patients and examiners. However, this argument does not apply to E/e′ because of blinded core evaluation. In addition, improvements in E/e′ and patient-reported physical functioning were significantly correlated (and patients were unaware of their change in E/e′) (Fig. 3). Most importantly, this correlation was still significant after controlling within the randomized groups ($r = -0.31$, $p = 0.02$), that is, among patients who received the same treatment. These findings cannot be explained by the group assignment open to the patient; they rather strongly support the hypothesis that reduction of E/e′ is a relevant clinical improvement associated with increased physical functioning. Taken together, we were able to demonstrate that improved diastolic function had a share in improvement of functional capacity and subjective well-being.

Increased collagen turnover is associated with increased ventricular stiffness and HFpEF (36). In our study, ET was associated with a significant reduction in procollagen type I plasma levels. Although such an observed effect on 1 single parameter of the complex collagen turnover may be misleading, it is reasonable to speculate that the improvement in diastolic function may be associated with reduced collagen turnover.

NT-proBNP levels were at the upper limit of normal in our patients. Even when most of the patients enrolled meet the criteria for the diagnosis of HFpEF defined by the European Society of Cardiology, levels of NT-proBNP were still below the levels that were reported in acutely decompensated HFpEF (37). Our finding of NT-proBNP values at the upper limit of normal despite symptomatic HFpEF with proven diastolic dysfunction is also not unexpected, since the major stimulus for release of BNP and its biologically inactive cleavage product NT-proBNP is ventricular wall stress. However, wall stress may be normal in patients with HFpEF and small, but hypertrophied, ventricles (38). Furthermore, NT-proBNP levels have been described to be heavily influenced by comorbidities that were excluded in our study population (39). The fact that NT-proBNP levels did not reflect the improvement in physical function that has been described also in HFrEF, supports the recommended approach to use natriuretic peptides for a diagnosis of HFpEF only in conjunction with other parameters (18,39,40). Furthermore, it generates the hypothesis that NT-proBNP may not be an ideal stand-alone surrogate marker to evaluate the success of interventions in HFpEF.

Study limitations. Although we provided blinded analyses of the main outcome measures, the nature of ET interventions prohibits pure blinding. The lack of periodic contact with rehabilitation staff in the control group could have resulted in potential bias since the frequent contact with rehabilitation staff may explain some of the improvement seen in the intervention group. We investigated a relatively small number of younger and middle-aged patients in short-term follow-up. Therefore, no assumptions about the effects of ET in older, more affected patients can be made. Although we cannot ascertain the extent of the contribution of deconditioning and body weight to symptom burden in our cohort, a relevant association between changes in body weight and outcome parameters can be excluded. The potential contribution of peripheral factors to changes in exercise capacity needs to be investigated in future studies. Furthermore, the long-term feasibility and tolerability of ET, the optimal type of training, as well as the optimal training frequency and intensity, need to be investigated in the future also in broader populations with a wider range of stages of HFpEF.

Conclusions

We have shown that a short-term supervised endurance/resistance exercise program is feasible, safe, and effective in patients with HFpEF. ET improves functional capacity, diastolic function, and QoL in patients with HFpEF. ET may therefore be considered as having potential as an effective therapy in patients with HFpEF. Its long-term effects and prognostic relevance should be evaluated in future trials.

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Key Words: diastolic dysfunction ■ exercise training ■ heart failure with preserved ejection fraction ■ therapy.

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