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ORIGINAL RESEARCH ARTICLE

Effects of long-term endurance and resistance training on diastolic function, exercise capacity, and quality of life in asymptomatic diastolic dysfunction vs. heart failure with preserved ejection fraction

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Abstract

Background The long-term effects of exercise training (ET) in diastolic dysfunction (DD) and heart failure with preserved ejection fraction (HFpEF) are unknown. The present study compared the long-term effects of ET on exercise capacity, diastolic function, and quality of life (QoL) in patients with DD vs. HFpEF.

Methods A total of $n = 43$ patients with asymptomatic DD ($n = 19$) or HFpEF [DD and New York Heart Association (NYHA) ≥II, $n = 24$] and left ventricular ejection fraction ≥50% performed a combined endurance/resistance training over 6 months (2–3/week) on top of usual care. Cardiopulmonary exercise testing, echocardiography, and QoL were obtained at baseline and follow-up.

Results Patients were 62 ± 8 years old (37% female). In the HFpEF group, 67% of patients were in NYHA class II (33% in NYHA III). Exercise capacity (peak oxygen consumption, peak VO_2) differed at baseline (DD 29.2 ± 8.7 mL/min/kg vs. HFpEF 17.8 ± 4.6 mL/min/kg; $P = 0.004$). After 6 months, peak VO_2 increased significantly ($P < 0.044$) to 19.7 ± 5.8 mL/min/kg in the HFpEF group and also in the DD group (to 32.8 ± 8.5 mL/min/kg; $P < 0.002$) with no overall difference between the groups ($P = 0.217$). E/e′ ratio (left ventricular filling index) decreased from 12.2 ± 3.5 to 10.1 ± 3.0 ($P < 0.002$) in patients with HFpEF and also in patients with DD (10.7 ± 3.1 vs. 9.5 ± 2.3; $P = 0.03$; difference between groups $P = 0.210$). In contrast, left atrial volume index decreased in the HFpEF group ($P < 0.001$) but remained stable within the DD group (difference between groups $P = 0.015$). After 6 months, physical QoL (Minnesota living with heart failure Questionnaire, 36-item short form health survey), general health perception, and 9-item patient health questionnaire score only improved in HFpEF ($P < 0.05$). In contrast, vitality improved in both groups (difference between groups $P = 0.708$).

Conclusion A structured 6 months ET programme effectively improves exercise capacity and diastolic function in patients with DD and overt HFpEF. Therefore, controlled lifestyle modification with physical activity is effective both in DD and HFpEF.

Keywords Diastolic dysfunction; Heart failure with preserved ejection fraction; Exercise training

Introduction

The prevalence of diastolic dysfunction (DD) is common in elderly subjects and in patients with left ventricular hypertrophy, arterial hypertension, valvular disease, coronary artery disease, and/or diabetes mellitus. For the diagnosis of DD, evidence of slow left ventricular relaxation, abnormal left ventricular filling, reduced diastolic distensibility, or increased left ventricular stiffness is required.[1–3] Even in an asymptomatic stage, patients with DD are characterized by reduced exercise capacity and are at risk for the development of heart failure (HF).[1] However, despite impaired diastolic function that is also a diagnostic cornerstone for the classification of patients with HF with preserved ejection fraction (HFpEF), the diagnostic finding of DD does not surely imply the presence of HF symptoms.[4] HF is continuing to be a major health problem in our society,[5] and the prevalence of the subgroup with normal or preserved left ventricular ejection fraction (LVEF), termed HFpEF, accounts for more than 50% within the HF population.[6–8] Morbidity and mortality in patients suffering from HFpEF are comparable with HF with reduced ejection fraction (HFrEF).[6,9–11] However, although the therapy of HFrEF occurs on the basis of evidence, the management of HFpEF is still challenging, because large trials failed to improve morbidity and outcome in this condition.[4,12,13]

Exercise training (ET) has become an accepted additional therapeutic option for patients suffering from HFrEF. Numerous trials have determined that ET is associated with an improvement of exercise tolerance and quality of life (QoL),[14–20] and the large HF-ACTION study could show that ET positively affects morbidity and mortality in patients with adequate long-term adherence to the intervention.[21] In contrast, only a few single centre trials [14,22,23] and one multi-centre randomized controlled trial (RCT) [10] investigated an exercise intervention in patients with HFpEF and demonstrated an improvement of exercise capacity, diastolic function or musculoskeletal function, and QoL. In contrast, only a small number of single centre trials demonstrated an improvement of exercise capacity [24–26] and the potential to reverse a left ventricular DD [25] as a result of ET in patients suffering from asymptomatic DD.

The present ancillary sub-study of the Exercise Training in Diastolic Heart Failure – Pilot Study (Ex-DHF-P) was therefore conducted to compare the long-term effects of structured supervised long-term endurance and resistance training on top of usual care (UC) on exercise capacity, diastolic function, and QoL between patients with asymptomatic (DD) and symptomatic HFpEF.

Methods

We performed a prospective multi-centre controlled, parallel-group trial in patients suffering from DD or HFpEF, as an ancillary sub-study of the Ex-DHF-P trial, whose results were already published.[10] Structured long-term endurance and resistance training on top of UC was tested.

Patient population

Outpatients with New York Heart Association (NYHA) functional class I (DD), II, or III (HFpEF) at an age of ≥45 years were prospectively included if they had a preserved left ventricular systolic function (LVEF ≥50%), echocardiographically determined DD (grade ≥1), and sinus rhythm. Patients of the Ex-DHF-P study,[10] who were randomized to ET and agreed to perform 6 months of ET, were included as HFpEF group. Exclusion criteria were significant coronary artery disease (current angina pectoris or ischemia on stress test, untreated coronary stenosis >50%, and history of myocardial infarction or bypass surgery), diseases with significant impact on exercise performance, that is, musculoskeletal diseases, peripheral arterial obstructive disease, or pulmonary disease (vital capacity and/or forced expiratory volume in 1 s <80% of age-dependent predicted value), diseases limiting the validity of consent (psychiatric diseases, dementia, etc.), changes in concomitant cardiovascular medication within the last 2 weeks prior the randomization, and participation in another study within the last 30 days.

Patients were recruited at three university hospitals in Germany (Goettingen, Munich, and Berlin). The German Health Authorities and the Ethics Committees at each centre approved the study. Written informed consent was obtained from all patients before any study-related procedure was performed.

Exercise training and usual care

Patients with DD and HFpEF participated in a combined endurance and resistance training of 6 months in addition to UC. Throughout the first 3 months, ET was performed in a supervised method. During weeks 1 through 4, endurance training (two times per week) of increasing intensity and duration (from 10 to 20 min) was performed. Training intensity was adapted individually to a target heart rate of 50–60% of peak oxygen uptake (peak VO_2) during baseline spiroergometry. From week 5 onward, weekly training frequencies and

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duration were increased (three times per week, from 20 to 35 min), and workload was increased to a target heart rate of 60–70% of peak VO_2. Also starting at the fifth week, resistance training was added three times per week. Resistance training was performed for 15 repetitions per exercise per session at a workload corresponding to 60% of the one repetition maximum measured at the end of week 4. During weeks 8 and 12, weekly training duration of endurance training was increased (from 30 to 35 min), and workload was increased to a target heart rate of 65–70% of peak VO_2. Also starting at week 8, resistance training was performed for 2×15 repetitions per exercise per session (60% one repetition maximum).

Safety parameters (blood pressure and heart rate) and training intensity and attendance at training sessions were documented in a patient physical activity diary. All patients were on UC for DD and HFpEF and concomitant diseases, which remained unchanged during the trial.

Clinical assessment

At baseline and at the 3 and 6 months follow-up, patients underwent physical examination, echocardiography, cardiopulmonary exercise testing, blood sampling, and 6-min walk test. QoL was measured by the 36-item short form health survey (SF-36), the Minnesota living with HF Questionnaire (MLWHFQ), and the patients health questionnaire—depression module (PHQ-9).

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 used continuously. Blood pressure was recorded at rest and every 2 min throughout exercise testing. Cardiopulmonary variables were acquired in 10-s intervals. Exercise was terminated when patients were physically exhausted (by a RER >1.0) or developed severe dyspnoe, dizziness, or peripheral muscle fatigue.

Echocardiographic parameters including tissue Doppler parameters and calculating left ventricular mass index (LVMI) and left atrial volume index (LAVI) were performed according to the recommendations of the American Society of Echocardiography.[27,28] A detailed standard operating procedure was used to ensure comparable results in all centres. A reference centre performed staff training prior to the trial and supervision and blinded core data evaluation during the trial.

Normal diastolic function was characterized by mitral valve early-to-late peak filling velocity ratio (E/A) ≥ 1 and at least two of the following criteria: pulmonary venous peak systolic-to-diastolic velocity ratio (S/D) ≥ 1, mitral valve peak early filling velocity to mitral annular velocity ratio (E/e′) <10, and preserved E/A ≥ 1 during performance of a Valsalva manoeuvre. Grade I DD was defined by a delayed relaxation pattern (E/A <1). Grade II DD was diagnosed if E/A ≥ 1 and <2 and at least two of the following conditions were met: S/D <1, E/e′ ≥ 10, and $E/A_{Valsalva}$ <1. Grade III DD was defined as E/A ≥ 2 and E/e′ ≥ 15. For determination of diastolic function and calculation of E/e′ ratio, the mitral annular velocity of the medial (septal) mitral annulus velocity was used.[29]

Endpoints of the study

Endpoints of the study were the change in maximum exercise capacity (peak VO_2) at 3 and 6 months compared with baseline in any group and also between the groups at different time points. Further endpoints included the change in echocardiographic parameters of systolic and diastolic function (E/e′, e′ medial, S/D, and LVEF) and of left ventricular and atrial remodelling (LVMI, LAVI, and left ventricular volume index). Furthermore, they included changes in additional parameters of exercise capacity (maximum workload, anaerobic threshold, and workload at anaerobic threshold, heart rate during exercise, and systolic blood pressure) and QOL (SF-36, MLWHFQ, and PHQ-9).

Statistical analysis

Data were shown as mean ± standard deviation. Differences between asymptomatic (NYHA I; DD) and symptomatic patients (NYHA II/III; HFpEF) at different time points were compared by using the *t*-test for continuous data and using the Fisher's exact test for dichotomous data or the χ^2 test for categorical data. Changes within groups from baseline to follow-up were assessed by the *t*-test for paired variables. Analysis of covariance with the follow-up measurement as dependent variable and baseline measurement as covariate was applied for all comparisons between the groups. Analyses were performed according to intent-to-treat principle. SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was the software used for statistical analyses.

Results

Study sample

A total of $n = 43$ patients with asymptomatic (NYHA I; $n = 19$; DD) or with symptomatic (NYHA II/III; $n = 24$; HFpEF) DD and preserved LVEF (>50%) were prospectively included to perform a combined endurance and resistance training over 6 months in addition to UC.

The baseline data were summarized in *Table 1*. At baseline age, female gender, body mass index, LVEF, blood pressure, heart rate, and medication were not different between patients

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Table 1 Demographic data, physical examination and medical history at baseline

Variable	All subjects ($n = 43$)	DD ($n = 19$)	HFpEF ($n = 24$)	Difference between groups (P-value)
Female	16 (37%)	7 (37%)	9 (38%)	0.965
Age (years)	62 ± 8	61 ± 8	62 ± 7	0.526
General examination				
Body mass index (kg/m^2)	31 ± 5	31 ± 5	31 ± 6	0.776
Waist/hip ratio	0.95 ± 0.07	0.95 ± 0.08	0.96 ± 0.06	0.755
Heart rate (beats/min)	67 ± 8	69 ± 7	65 ± 9	0.168
Systolic blood pressure (mmHg)	145 ± 16	143 ± 16	148 ± 15	0.304
Diastolic blood pressure (mmHg)	86 ± 9	89 ± 9	84 ± 9	0.084
Characterization of heart failure				
NYHA functional class of dyspnea				[a]
I	19 (44%)	19 (100%)	0 (0%)	
II	16 (37%)	0 (0%)	16 (67%)	
III	8 (19%)	0 (0%)	8 (33%)	
Orthopnea	7 (16%)	0 (0%)	7 (29%)	**0.012**
Paroxysmal nocturnal dyspnea	4 (9%)	0 (0%)	4 (17%)	0.118
Peripheral edema	11 (26%)	4 (21%)	7 (29%)	0.728
Nocturia	28 (65%)	14 (74%)	14 (58%)	0.349
Left ventricular ejection fraction (%)	67 ± 6	68 ± 5	67 ± 8	0.695
Medication				
ACE inhibitor and/or AT1 receptor antagonist	27 (63%)	13 (68%)	14 (58%)	0.542
Beta-blocker	15 (35%)	4 (21%)	11 (46%)	0.116
Diuretics	17 (40%)	8 (42%)	9 (38%)	1.000
Risk factors				
Overweight (body mass index >25 kg/m^2)	39 (91%)	18 (95%)	21 (88%)	0.618
Diabetes mellitus	1 (2%)	0 (0%)	1 (4%)	1.000
Hypertension	36 (84%)	17 (90%)	19 (79%)	0.437
Hyperlipidemia	23 (54%)	9 (47%)	14 (58%)	0.547
Ever smoked	24 (56%)	7 (37%)	17 (71%)	**0.034**
Number of present risk factors	2.9 ± 0.9	2.7 ± 0.9	3.0 ± 0.9	0.263

Values in bold have reached the significance level 0.05.
DD, diastolic dysfunction; HFpEF, heart failure with preserved ejection fraction; ACE, angiotensin-converting enzyme; AT, angiotensin; NYHA, New York Heart Association.
Values are *n*, frequency (%), or mean ± standard deviation.
[a]Existence of NYHA class II or III (HFpEF) was a definition criterion.

suffering from HFpEF and patients with asymptomatic DD. Overall, 69% of patients were in DD grade I, 31% in grade II or III. Furthermore, there were no relevant differences with statistical significance between DD and HFpEF group regarding cardiovascular risk factors.

A total of 37% ($n = 16$) of all patients were female, and the mean age was 62 ± 8 years. A total of 67% of patients suffering from HFpEF were in NYHA class II and 33% of them were in NYHA class III. Peak VO_2 was significantly different (DD: 29.2 ± 8.7 mL/kg/min vs. HFpEF: 17.8 ± 4.6; $P < 0.001$), and generally, patients with HFpEF were associated with much lower exercise capacity [maximum work load and exercise duration, anaerobic threshold ($ATVO_2$), and workload at $ATVO_2$, VE_{max}, all $P < 0.01$], lower e′ medial ($P = 0.005$), and higher values of LAVI ($P = 0.006$), compared with patients with DD. Patients with HFpEF also demonstrated impaired self-reported physical functioning (SF-36 physical functioning and MLWHFQ physical limitation scale, all $P \leq 0.01$), impaired MLWHFQ total scale ($P = 0.019$), and higher values of PHQ-9 ($P = 0.036$) than those with asymptomatic DD.

Clinical and cardiac effects of exercise training

Exercise training significantly improved exercise capacity, diastolic function, and QoL in patients with DD and HFpEF. The results are shown in detail in *Tables 2, 3*, and *4*.

There was a significant increase in peak VO_2 in the HFpEF group from baseline to the 3 months follow-up. In the DD group, peak VO_2 did not change from baseline to the 3 months follow-up, but there was a significant increase between the 3 months and the 6 months follow-up. Generally, we observed a significant increase in peak VO_2 in both groups after 6 months (*Figure 1*).

Anaerobic threshold increased also in both groups: there was a significant increase in $ATVO_2$ in the HFpEF group from baseline to the 3 months follow-up. There was no increase in $ATVO_2$ in the DD group from baseline to the 3 months follow-up, but we observed a significant change in $ATVO_2$ between the 3 months and the 6 months follow-up and between baseline and the 6 months follow-

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Table 2 Cardiopulmonary exercise testing data during follow-up

Variable	HFpEF	DD	Difference between groups
Peak VO_2 (mL/min/kg)			
Baseline (mean ± SD)	17.8 ± 4.6	29.2 ± 8.7	***P* < 0.001**
3 months FU (mean ± SD)	20.6 ± 5.5	29.8 ± 8.3	
6 months FU (mean ± SD)	19.7 ± 5.8	32.8 ± 8.5	
Change			
BL to 3 months FU (mean (95% CI))	2.8 (1.5 to 4.0)	0.5 (−0.6 to 1.6)	
	***P* < 0.001**	*P* = 0.331	***P* = 0.009**
3 months FU to 6 months FU (mean (95% CI))	−0.9 (−2.9 to 1.1)	3.0 (0.7 to 5.3)	
	P = 0.360	***P* = 0.013**	***P* = 0.010**
BL to 6 months FU (mean (95% CI))	1.9 (0.1 to 3.7)	3.5 (1.5 to 5.5)	
	***P* = 0.044**	***P* = 0.002**	*P* = 0.217
Maximum workload (W)			
Baseline (mean ± SD)	135.2 ± 36	176.7 ± 45	***P* = 0.004**
3 months FU (mean ± SD)	149.5 ± 39	174.4 ± 44	
6 months FU (mean ± SD)	142.9 ± 35	184.4 ± 48	
Change			
BL to 3 months FU (mean (95% CI))	14.3 (5.6 to 23.0)	−2.2 (−11.8 to 7.4)	
	***P* = 0.003**	*P* = 0.631	***P* = 0.011**
3 months FU to 6 months FU (mean (95% CI))	−6.7 (−18.3 to 5.0)	10.0 (1.5 to 18.5)	
	P = 0.246	***P* = 0.024**	***P* = 0.021**
BL to 6 months FU (mean (95% CI))	7.6 (−7.5 to 22.7)	7.8 (−5.5 to 21.1)	
	P = 0.305	*P* = 0.233	*P* = 0.987
Maximum exercise time (s)			
Baseline (mean ± SD)	753 ± 216	1037 ± 290	***P* = 0.002**
3 months FU (mean ± SD)	823 ± 231	1021 ± 279	
6 months FU (mean ± SD)	809 ± 209	1088 ± 288	
Change			
BL to 3 months FU (mean (95% CI))	70 (30 to 109)	−16 (−73 to 41)	
	***P* = 0.002**	*P* = 0.556	**P = 0.014**
3 months FU to 6 months FU (mean (95% CI))	−14 (−82 to 53)	67 (22 to 112)	
	P = 0.664	***P* = 0.006**	***P* = 0.045**
BL to 6 months FU (mean (95% CI))	55 (−31 to 141)	51 (−29 to 130)	
	P = 0.195	*P* = 0.198	*P* = 0.934
Anaerobic threshold VO2 (ml/min/kg)			
Baseline (mean ± SD)	11.0 ± 3.1	23.3 ± 7.3	***P* < 0.001**
3 months FU (mean ± SD)	14.3 ± 4.3	22.7 ± 7.4	
6 months FU (mean ± SD)	12.8 ± 5.3	27.4 ± 7.9	
Change			
BL to 3 months FU (mean (95% CI))	3.3 (2.1 to 4.6)	−0.6 (−2.3 to 1.1)	
	***P* < 0.001**	*P* = 0.446	***P* < 0.001**
3 months FU to 6 months FU (mean (95% CI))	−1.5 (−3.8 to 0.7)	4.7 (1.5 to 7.9)	
	P = 0.171	***P* = 0.006**	***P* = 0.002**
BL to 6 months FU (mean (95% CI))	1.8 (−0.1 to 3.7)	4.1 (1.5 to 6.6)	
	P = 0.065	***P* = 0.004**	*P* = 0.142
Workload at anaerobic threshold (W)			
Baseline (mean ± SD)	73.8 ± 25.4	137.2 ± 47.9	***P* < 0.001**
3 months FU (mean ± SD)	93.0 ± 32.6	125.6 ± 42.0	
6 months FU (mean ± SD)	79.7 ± 32.3	155.4 ± 45.1	
Change			
BL to 3 months FU (mean (95% CI))	19.2 (10 to 28)	−11.6 (−23.7 to 0.5)	
	***P* < 0.001**	*P* = 0.059	***P* < 0.001**
3 months FU to 6 months FU (mean (95% CI))	−13.3 (−27 to 1)	29.9 (15.1 to 44.7)	
	P = 0.059	***P* = 0.001**	***P* < 0.001**
BL to 6 months FU (mean (95% CI))	5.9 (−7 to 19)	18.3 (3.7 to 32.9)	

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Table 2. (Continued)

Variable	HFpEF	DD	Difference between groups
	$P = 0.351$	$\mathbf{P = 0.017}$	$P = 0.191$
VE (maximal)			
Baseline (mean ± SD)	58.1 ± 14.3	85.1 ± 32.2	$\mathbf{P = 0.001}$
3 months FU (mean ± SD)	62.8 ± 14.1	96.7 ± 36.0	
6 months FU (mean ± SD)	58.7 ± 13.2	89.9 ± 25.3	
Change			
BL to 3 months FU (mean (95% CI))	4.7 (0.6 to 8.7)	11.7 (0.8 to 22.5)	
	$\mathbf{P = 0.025}$	$\mathbf{P = 0.036}$	$P = 0.216$
3 months FU to 6 months FU (mean (95% CI))	−4.1 (−9.7 to 1.4)	−6.8 (−18.8 to 5.1)	
	$P = 0.137$	$P = 0.244$	$P = 0.671$
BL to 6 months FU (mean (95% CI))	0.5 (−4.1 to 5.1)	4.8 (−3.3 to 13.0)	
	$P = 0.815$	$P = 0.228$	$P = 0.322$
VE/VCO_2 slope			
Baseline (mean ± SD)	28.5 ± 2.7	27.1 ± 4.0	$P = 0.212$
3 months FU (mean ± SD)	28.4 ± 3.6	26.1 ± 2.4	
6 months FU (mean ± SD)	28.0 ± 4.2	26.4 ± 3.6	
Change			
BL to 3 months FU (mean (95% CI))	−0.1 (−1.3 to 1.1)	−1.0 (−2.6 to 0.7)	
	$P = 0.862$	$P = 0.248$	$P = 0.389$
3 months FU to 6 months FU (mean (95% CI))	−0.4 (−2.3 to 1.5)	0.3 (−1.7 to 2.3)	
	$P = 0.663$	$P = 0.731$	$P = 0.580$
BL to 6 months FU (mean (95% CI))	−0.5 (−2.7 to 1.7)	−0.6 (−2.7 to 1.5)	
	$P = 0.633$	$P = 0.537$	$P = 0.932$
Heart rate (min) (beats/min)			
Baseline (mean ± SD)	70 ± 13	81 ± 9	$\mathbf{P = 0.003}$
3 months FU (mean ± SD)	72 ± 12	76 ± 8	
6 months FU (mean ± SD)	74 ± 9	73 ± 10	
Change			
BL to 3 months FU (mean (95% CI))	2 (−2 to 6)	−5 (−10 to −1)	
	$P = 0.281$	$\mathbf{P = 0.031}$	$\mathbf{P = 0.017}$
3 months FU to 6 months FU (mean (95% CI))	2 (−4 to 7)	−3 (−9 to 3)	
	$P = 0.569$	$P = 0.285$	$P = 0.241$
BL to 6 months FU (mean (95% CI))	4 (−1 to 9)	−8 (−14 to −2)	
	$P = 0.156$	$\mathbf{P = 0.009}$	$\mathbf{P = 0.003}$
Heart rate (maximal) (beats/min)			
Baseline (mean ± SD)	133 ± 19	149 ± 22	$\mathbf{P = 0.019}$
3 months FU (mean ± SD)	135 ± 19	153 ± 16	
6 months FU (mean ± SD)	133 ± 21	152 ± 19	
Change			
BL to 3 months FU (mean (95% CI))	3 (−4 to 9)	4 (−4 to 12)	
	$P = 0.411$	$P = 0.322$	$P = 0.767$
3 months FU to 6 months FU (mean (95% CI))	−3 (−10 to 5)	−1 (−6 to 5)	
	$P = 0.469$	$P = 0.733$	$P = 0.705$
BL to 6 months FU (mean (95% CI))	0 (−5 to 5)	3 (−6 to 12)	
	$P = 1.000$	$P = 0.480$	$P = 0.530$
Resting RR sys			
Baseline (mean ± SD)	131.6 ± 23.6	140.8 ± 20.1	$P = 0.196$
3 months FU (mean ± SD)	122.8 ± 17.2	134.2 ± 14.7	
6 months FU (mean ± SD)	115.4 ± 21.1	130.6 ± 20.4	
Change			
BL to 3 months FU (mean (95% CI))	−8.8 (−20.4 to 2.7)	−6.7 (−16.2 to 2.8)	
	$P = 0.127$	$P = 0.157$	$P = 0.766$
3 months FU to 6 months FU (mean (95% CI))	−7.4 (−18.1 to 3.3)	−3.6 (−10.8 to 3.6)	
	$P = 0.166$	$P = 0.303$	$P = 0.545$

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Table 2. (Continued)

Variable	HFpEF	DD	Difference between groups
BL to 6 months FU (mean (95% CI))	−16.2 (−30.7 to −1.7) **$P = 0.031$**	−10.3 (−20 to −0.6) **$P = 0.039$**	$P = 0.499$
Maximal RR sys			
Baseline (mean ± SD)	191.6 ± 19.6	221.1 ± 22.5	**$P < 0.001$**
3 months FU (mean ± SD)	190.3 ± 24.3	221.4 ± 22.5	
6 months FU (mean ± SD)	167.3 ± 33.6	218.9 ± 24.4	
Change			
BL to 3 months FU (mean (95% CI))	−1.3 (−10.6 to 8.0) $P = 0.776$	0.3 (−9.5 to 10.1) $P = 0.953$	$P = 0.809$
3 months FU to 6 months FU (mean (95% CI))	−23.0 (−39.2 to −6.8) **$P = 0.008$**	−2.5 (−12.2 to 7.2) $P = 0.594$	**$P = 0.036$**
BL to 6 months FU (mean (95% CI))	−24.3 (−38.8 to −9.8) **$P = 0.002$**	−2.2 (−13.7 to 9.3) $P = 0.689$	**$P = 0.017$**

Values in bold have reached the significance level 0.05.
HFpEF, heart failure with preserved ejection fraction; DD, diastolic dysfunction; FU, follow-up; BL, baseline; peak VO2, peak oxygen uptake; VE_{max}, maximal pulmonary ventilation; VE/VCO2 slope, ventilator equivalent ratio for carbon dioxide; RR, blood pressure; SD, standard deviation.

Table 3 Echocardiography data at baseline and 3 and 6 months follow-up

Variable	HFpEF	DD	Difference between groups
E/e′ ratio			
Baseline (mean ± SD)	12.2 ± 3.5	10.7 ± 3.1	$P = 0.129$
3 months FU (mean ± SD)	10.0 ± 2.4	9.4 ± 2.3	
6 months FU (mean ± SD)	10.1 ± 3.0	9.5 ± 2.3	
Change			
BL to 3 months FU (mean (95% CI))	−2.3 (−3.4 to −1.1) **$P < 0.001$**	−1.3 (−2.2 to −0.4) **$P = 0.009$**	$P = 0.184$
3 months FU to 6 months FU (mean (95% CI))	0.2 (−0.8 to 1.1) $P = 0.729$	0.2 (−0.6 to 1.0) $P = 0.638$	$P = 0.977$
BL to 6 months FU (mean (95% CI))	−2.1 (−3.3 to −0.9) **$P = 0.002$**	−1.1 (−2.1 to −0.1) **$P = 0.029$**	$P = 0.210$
e′ medial (cm/s)			
Baseline (mean ± SD)	5.9 ± 1.3	6.9 ± 1.0	**$P = 0.005$**
3 months FU (mean ± SD)	6.8 ± 1.4	7.2 ± 1.2	
6 months FU (mean ± SD)	6.8 ± 1.4	7.4 ± 1.5	
Change			
BL to 3 months FU (mean (95% CI))	0.9 (0.5 to 1.3) **$P < 0.001$**	0.3 (−0.1 to 0.8) $P = 0.113$	$P = 0.052$
3months FU to 6 months FU (mean (95% CI))	0.0 (−0.3 to 0.3) $P = 0.888$	0.2 (−0.3 to 0.7) $P = 0.389$	$P = 0.516$
BL to 6 months FU (mean (95% CI))	0.9 (0.4 to 1.4) **$P = 0.001$**	0.5 (0.1 to 1.0) **$P = 0.030$**	$P = 0.232$
S/D ratio			
Baseline (mean ± SD)	1.42 ± 0.47	1.34 ± 0.48	$P = 0.558$
3 months FU (mean ± SD)	1.34 ± 0.28	1.45 ± 0.68	
6 months FU (mean ± SD)	1.40 ± 0.30	1.35 ± 0.38	
Change			
BL to 3 months FU (mean (95% CI))	−0.09 (−0.29 to 0.11) $P = 0.375$	0.11 (−0.30 to 0.53) $P = 0.577$	$P = 0.373$
3 months FU to 6 months FU (mean (95% CI))	0.06 (−0.07 to 0.19) $P = 0.357$	−0.10 (−0.44 to 0.25) $P = 0.566$	$P = 0.385$
BL to 6 months FU (mean (95% CI))	−0.03 (−0.22 to 0.17)	0.02 (−0.20 to 0.23)	

(Continues)

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Table 3. (Continued)

Variable	HFpEF	DD	Difference between groups
	$P = 0.777$	$P = 0.877$	$P = 0.758$
LVEF			
Baseline (mean ± SD)	67 ± 8	68 ± 5	$P = 0.695$
3 months FU (mean ± SD)	68 ± 6	67 ± 7	
6 months FU (mean ± SD)	68 ± 6	69 ± 5	
Change			
BL to 3 months FU (mean (95% CI))	1 (−4 to 5)	−1 (−4 to 2)	
	$P = 0.680$	$P = 0.544$	$P = 0.526$
3 months FU to 6 months FU (mean (95% CI))	0 (−4 to 4)	2 (−1 to 5)	
	$P = 0.981$	$P = 0.149$	$P = 0.355$
BL to 6 months FU (mean (95% CI))	1 (−3 to 4)	1 (−2 to 4)	
	$P = 0.610$	$P = 0.449$	$P = 0.901$
Left atrial volume index (ml/m^2)			
Baseline (mean ± SD)	30.0 ± 7.9	23.5 ± 6.2	**$P = 0.006$**
3 months FU (mean ± SD)	26.3 ± 6.7	23.2 ± 6.3	
6 months FU (mean ± SD)	25.1 ± 8.7	22.8 ± 5.8	
Change			
BL to 3 months FU (mean (95% CI))	−3.7 (−5.5 to −1.9)	−0.4 (−2.3 to 1.6)	
	$P < 0.001$	$P = 0.694$	**$P = 0.013$**
3 months FU to 6 months FU (mean (95% CI))	−1.2 (−3.5 to 1.0)	−0.3 (−2.7 to 2.0)	
	$P = 0.273$	$P = 0.764$	$P = 0.577$
BL to 6 months FU (mean (95% CI))	−4.9 (−6.7 to −3.2)	−0.7 (−4.0 to 2.5)	
	$P < 0.001$	$P = 0.651$	**$P = 0.015$**
Left ventricular volume index (ml/m^2)			
Baseline (mean ± SD)	41.7 ± 15.5	53.0 ± 23.9	$P = 0.100$
3 months FU (mean ± SD)	43.0 ± 13.8	48.7 ± 18.0	
6 months FU (mean ± SD)	39.7 ± 13.4	47.9 ± 22.6	
Change			
BL to 3 months FU (mean (95% CI))	1.3 (−4.7 to 7.4)	−4.3 (−12.1 to 3.4)	
	$P = 0.646$	$P = 0.252$	$P = 0.231$
3 months FU to 6 months FU (mean (95% CI))	−3.3 (−8 to 1.4)	−0.8 (−7.1 to 5.5)	
	$P = 0.159$	$P = 0.790$	$P = 0.511$
BL to 6 months FU (mean (95% CI))	−1.9 (−6 to 2.1)	−5.1 (−13.4 to 3.1)	
	$P = 0.333$	$P = 0.206$	$P = 0.470$
LVMI (g/m^2)			
Baseline (mean ± SD)	108.8 ± 21.2	118.3 ± 22.7	$P = 0.169$
3 months FU (mean ± SD)	113.1 ± 30.2	108.4 ± 22.1	
6 months FU (mean ± SD)	116.3 ± 29.0	116.9 ± 20.3	
Change			
BL to 3 months FU (mean (95% CI))	4.3 (−7.5 to 16.2)	−9.9 (−16.5 to −3.2)	
	$P = 0.455$	**$P = 0.006$**	$P = 0.037$
3 months FU to 6 months FU (mean (95% CI))	3.2 (−9.3 to 15.7)	8.5 (1.9 to 15.1)	
	$P = 0.603$	**$P = 0.015$**	$P = 0.440$
BL to 6 months FU (mean (95% CI))	7.5 (−4.6 to 19.6)	−1.4 (−10.4 to 7.7)	
	$P = 0.211$	$P = 0.755$	$P = 0.228$

Values in bold have reached the significance level 0.05.
HFpEF, heart failure with preserved ejection fraction; DD, diastolic dysfunction; FU, follow-up; BL, baseline; E/e′, mitral wave peak early filling velocity to (medial) mitral annular velocity ratio; e′ medial, mitral annular velocity of the medial mitral annulus; S/D ratio, pulmonary venous peak systolic-to-diastolic velocity ratio; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

up. Furthermore, we recognized a significant increase of VE_{max} after 3 months of ET in both groups.

The E/e′ ratio improved significantly in the HFpEF and the DD group between baseline and the 3 months follow-up and between baseline and the 6 months follow-up (*Figure 2*). There was also a significant increase of e′ medial in the HFpEF group from baseline to 3 months follow-up. In the DD group, there was only a trend towards higher values

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Table 4 Quality of life data during follow-up

Variable	HFpEF	DD	Difference between groups
MLWHFQ			
Total scale			
Baseline (mean ± SD)	22 ± 20	10 ± 9	***P* = 0.019**
3 months FU (mean ± SD)	16 ± 19	7 ± 9	
6 months FU (mean ± SD)	18 ± 19	7 ± 7	
Change			
BL to 3 months FU (mean (95% CI))	−6 (−10 to −1)	−3 (−6 to 1)	
	***P* = 0.020**	*P* = 0.166	*P* = 0.300
3 months FU to 6 months FU (mean (95% CI))	1 (−2 to 5)	0 (−3 to 3)	
	P = 0.457	*P* = 0.982	*P* = 0.575
BL to 6 months FU (mean (95% CI))	−4 (−8 to 0)	−3 (−5 to 1)	
	***P* = 0.040**	*P* = 0.101	*P* = 0.487
Physical limitation scale			
Baseline (mean ± SD)	12.8 ± 10.5	5.4 ± 5.7	***P* = 0.008**
3 months FU (mean ± SD)	8.8 ± 9.0	3.5 ± 3.8	
6 months FU (mean ± SD)	8.8 ± 9.4	3.5 ± 4.1	
Change			
BL to 3 months FU (mean (95% CI))	−4.0 (−6.7 to −1.4)	−1.9 (−3.8 to 0.0)	
	***P* = 0.005**	*P* = 0.054	*P* = 0.182
3 months FU to 6 months FU (mean (95% CI))	0.0 (−1.9 to 2.0)	0.0 (−1.6 to 1.6)	
	P = 0.966	*P* = 1.000	*P* = 0.973
BL to 6 months FU (mean (95% CI))	−4.0(−6.5 to −1.5)	−1.9 (−4.0 to 0.2)	
	***P* = 0.003**	***P* = 0.069**	*P* = 0.187
Emotional limitation scale			
Baseline (mean ± SD)	3.2 ± 5.2	2.4 ± 2.6	*P* = 0.540
3 months FU (mean ± SD)	3.2 ± 5.9	2.1 ± 3.1	
6 months FU (mean ± SD)	3.5 ± 5.3	1.8 ± 2.5	
Change			
BL to 3 months FU (mean (95% CI))	0.0 (−1.3 to 1.2)	−0.3 (−1.6 to 1.0)	
	P = 0.986	*P* = 0.636	*P* = 0.739
3 months FU to 6 months FU (mean (95% CI))	0.3 (−0.6 to 1.2)	−0.3 (−1.1 to 0.4)	
	P = 0.491	*P* = 0.380	*P* = 0.273
BL to 6 months FU (mean (95% CI))	0.3 (−0.7 to 1.3)	−0.6 (−1.9 to 0.6)	
	P = 0.567	*P* = 0.307	*P* = 0.246
SF 36			
Physical functioning			
Baseline (mean ± SD)	66 ± 24	82 ± 13	***P* = 0.010**
3 months FU (mean ± SD)	77 ± 22	88 ± 12	
6 months FU (mean ± SD)	77 ± 21	86 ± 15	
Change			
BL to 3 months FU (mean (95% CI))	11 (3 to 19)	5 (2 to 9)	
	***P* = 0.010**	***P* = 0.006**	*P* = 0.228
3 months FU to 6 months FU (mean (95% CI))	0 (−4 to 4)	−1 (−5 to 2)	
	P = 0.813	*P* = 0.438	*P* = 0.740
BL to 6 months FU (mean (95% CI))	11 (4 to 17)	4 (0 to 8)	
	***P* = 0.002**	*P* = 0.074	*P* = 0.086
Role limitations due to physical problems			
Baseline (mean ± SD)	69 ± 38	86 ± 22	*P* = 0.115
3 months FU (mean ± SD)	71 ± 43	91 ± 18	
6 months FU (mean ± SD)	74 ± 40	92 ± 15	

(Continues)

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Table 4. (Continued)

Variable	HFpEF	DD	Difference between groups
Change			
BL to 3 months FU (mean (95% CI))	2 (−15 to 19)	5 (−8 to 18)	
	$P = 0.799$	$P = 0.456$	$P = 0.799$
3 months FU to 6 months FU (mean (95% CI))	3 (−6 to 13)	2 (−7 to 11)	
	$P = 0.503$	$P = 0.718$	$P = 0.804$
BL to 6 months FU (mean (95% CI))	5 (−12 to 22)	6 (−7 to 20)	
	$P = 0.534$	$P = 0.333$	$P = 0.920$
Bodily pain			
Baseline (mean ± SD)	62 ± 31	81 ± 26	**$P = 0.040$**
3 months FU (mean ± SD)	69 ± 32	80 ± 20	
6 months FU (mean ± SD)	70 ± 30	84 ± 23	
Change			
BL to 3 months FU (mean (95% CI))	6 (−3 to 16)	−1 (−13 to 10)	
	$P = 0.189$	$P = 0.842$	$P = 0.309$
3 months FU to 6 months FU (mean (95% CI))	2 (−8 to 11)	4 (−6 to 14)	
	$P = 0.732$	$P = 0.393$	$P = 0.710$
BL to 6 months FU (mean (95% CI))	8 (0 to 16)	3 (−14 to 20)	
	$P = 0.055$	$P = 0.721$	$P = 0.575$
General health perceptions			
Baseline (mean ± SD)	58 ± 20	61 ± 21	$P = 0.583$
3 months FU (mean ± SD)	68 ± 19	67 ± 21	
6 months FU (mean ± SD)	65 ± 18	64 ± 19	
Change			
BL to 3 months FU (mean (95% CI))	10 (5 to 16)	6 (−4 to 15)	
	$P = 0.001$	$P = 0.216$	$P = 0.361$
3 months FU to 6 months FU (mean (95% CI))	−4 (−8 to 0)	−3 (−10 to 4)	
	$P = 0.059$	$P = 0.404$	$P = 0.797$
BL to 6 months FU (mean (95% CI))	7 (2 to 12)	3 (−3 to 8)	
	$P = 0.012$	$P = 0.290$	$P = 0.287$
Vitality			
Baseline (mean ± SD)	53 ± 23	60 ± 17	$P = 0.279$
3 months FU (mean ± SD)	56 ± 23	64 ± 17	
6 months FU (mean ± SD)	60 ± 22	68 ± 14	
Change			
BL to 3 months FU (mean (95% CI))	3 (−3 to 10)	5 (−3 to 13)	
	$P = 0.301$	$P = 0.215$	$P = 0.764$
3 months FU to 6 months FU (mean (95% CI))	4 (0 to 8)	4 (−2 to 9)	
	$P = 0.039$	$P = 0.159$	$P = 0.983$
BL to 6 months FU (mean (95% CI))	7 (1 to 13)	9 (4 to 14)	
	$P = 0.018$	**$P = 0.002$**	$P = 0.708$
Social functioning			
Baseline (mean ± SD)	71 ± 29	86 ± 21	$P = 0.069$
3 months FU (mean ± SD)	81 ± 29	85 ± 16	
6 months FU (mean ± SD)	84 ± 27	91 ± 12	
Change			
BL to 3 months FU (mean (95% CI))	10 (2 to 18)	−1 (−9 to 8)	
	$P = 0.023$	$P = 0.871$	$P = 0.071$
3 months FU to 6 months FU (mean (95% CI))	3 (−4 to 9)	6 (0 to 12)	
	$P = 0.396$	**$P = 0.046$**	$P = 0.422$
BL to 6 months FU (mean (95% CI))	13 (5 to 20)	5 (−2 to 12)	
	$P = 0.003$	$P = 0.134$	$P = 0.163$
Role limitations due to emotional problems			
Baseline (mean ± SD)	72 ± 36	88 ± 30	$P = 0.153$

(Continues)

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Table 4. (Continued)

Variable	HFpEF	DD	Difference between groups
3 months FU (mean ± SD)	79 ± 38	90 ± 29	
6 months FU (mean ± SD)	79 ± 39	92 ± 15	
Change			
BL to 3 months FU (mean (95% CI))	7 (−8 to 22)	2 (−18 to 22)	
	$P = 0.347$	$P = 0.827$	$P = 0.684$
3 months FU to 6 months FU (mean (95% CI))	0 (−4 to 4)	2 (−14 to 19)	
	$P = 1.000$	$P = 0.791$	$P = 0.759$
BL to 6 months FU (mean (95% CI))	7 (−10 to 24)	4 (−9 to 17)	
	$P = 0.396$	$P = 0.497$	$P = 0.783$
General mental health			
Baseline (mean ± SD)	64 ± 20	74 ± 16	$P = 0.101$
3 months FU (mean ± SD)	68 ± 24	74 ± 15	
6 months FU (mean ± SD)	69 ± 22	76 ± 14	
Change			
BL to 3 months FU (mean (95% CI))	4 (−2 to 9)	0 (−5 to 5)	
	$P = 0.160$	$P = 1.000$	$P = 0.283$
3 months FU to 6 months FU (mean (95% CI))	1 (−4 to 6)	3 (0 to 6)	
	$P = 0.638$	$P = 0.055$	$P = 0.580$
BL to 6 months FU (mean (95% CI))	5 (−2 to −12)	3 (−2 to 7)	
	$P = 0.135$	$P = 0.190$	$P = 0.587$
PHQ-9			
Total score			
Baseline (mean ± SD)	7.2 ± 6.5	3.7 ± 2.6	$\mathbf{P = 0.036}$
3 months FU (mean ± SD)	5.7 ± 5.9	4.2 ± 3.5	
6 months FU (mean ± SD)	4.8 ± 4.7	3.7 ± 2.9	
Change			
BL to 3 months FU (mean (95% CI))			
	−1.5 (−3 to 0)	0.6 (−0.3 to 1.4)	$\mathbf{P = 0.018}$
3 months FU to 6 months FU (mean (95% CI))	$\mathbf{P = 0.048}$	$P = 0.197$	
	−0.8 (−1.8 to 0.1)	−0.6 (−1.4 to 0.3)	
BL to 6 months FU (mean (95% CI))	$P = 0.079$	$P = 0.197$	$P = 0.653$
	−2.3 (−4.0 to −0.6)	0 (−0.7 to 0.7)	
	$\mathbf{P = 0.009}$	$P = 1.000$	$P = \mathbf{0.023}$

Values in bold have reached the significance level 0.05.
HFpEF, heart failure with preserved ejection fraction; DD, diastolic dysfunction; FU, follow-up; BL, baseline; SF-36, 36-item short form health survey; MLWHFQ, Minnesota living with heart failure questionnaire; PHQ-9, patient health questionnaire—depression module.

of e′ medial from baseline to 3 months follow-up and from 3 to 6 months follow-up, but the differences remained statistically insignificant. Generally, e′ medial increased significantly in DD and HFpEF group after 6 months of ET.

Furthermore, LAVI decreased significantly in the HFpEF group from baseline to the 3 months follow-up and from baseline to the 6 months follow-up. No improvement of LAVI occurred in the DD group; however, these patients had LAVI values within the upper normal range at baseline (Lang *et al*. 2005) (*Figure 3*). LVEF and left ventricular volume index did not change in neither group. We could not observe any changes of LVMI from baseline to the 6 months follow-up in neither group.

Exercise training also improved physical, mental, and social dimensions of QoL (scores of MLWHFQ and SF-36) in patients with DD and in patients suffering from HFpEF. The MLWHFQ total scale and the MLWHFQ physical limitation scale improved significantly with ET in patients with HFpEF from baseline to the 3 months follow-up and from baseline to the 6 month follow-up. The improvement of MLWHFQ in patients with DD remained statistically insignificant. Furthermore, there was a significant increase of SF-36 physical functioning score in patients suffering from HFpEF from baseline to the 6 months follow-up and in patients with DD from baseline to the 3 months follow-up (*Figure 4*). Furthermore, the scores of SF-36 general health perceptions, vitality, and social functioning increased significantly in the HFpEF group after 6 months with ET. In the DD group, there was only a significant increase in SF-36 vitality scores from baseline to the 6 months follow-up and in SF-36 social functioning scores from the 3 months to the 6 months follow-up.

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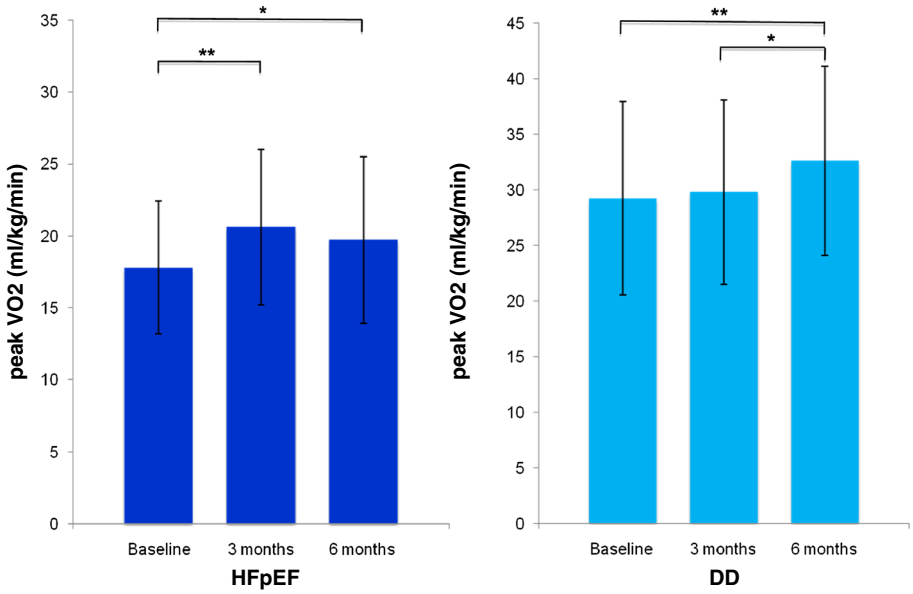

Figure 1 In both groups maximal exercise capacity (peak VO_2) was significantly improved after 6 months of exercise training (*$P < 0.05$; **$P < 0.01$).

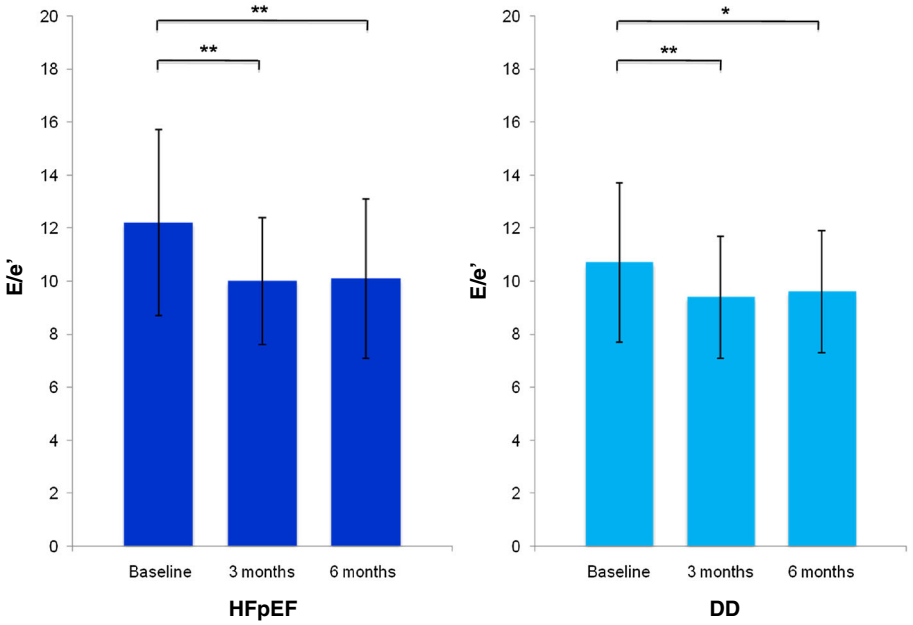

Figure 2 E/e′ decreased significantly in heart failure with preserved ejection fraction (HFpEF) and in diastolic dysfunction (DD)(*$P < 0.05$; **$P < 0.01$).

Also, the PHQ-9 total score improved with ET in patients suffering from HFpEF from baseline to the 3 months and from baseline to the 6 months follow-up significantly, whereas no relevant change occurred in the DD group.

Discussion

In the growing population of elderly people, DD is a frequent finding. Although a present DD does not necessarily imply the consecutive appearance of HF symptoms, DD is linked to the occurrence of HF, and the positive demonstration of DD in HFpEF is a cornerstone in the diagnosis of HFpEF.[3] Because morbidity and mortality in HFpEF are high and pharmacological treatment approaches did not show prognostic effectiveness, an early detection of DD and its treatment might be of favour.

The present study investigated for the first time the long-term effects of ET on exercise capacity, diastolic

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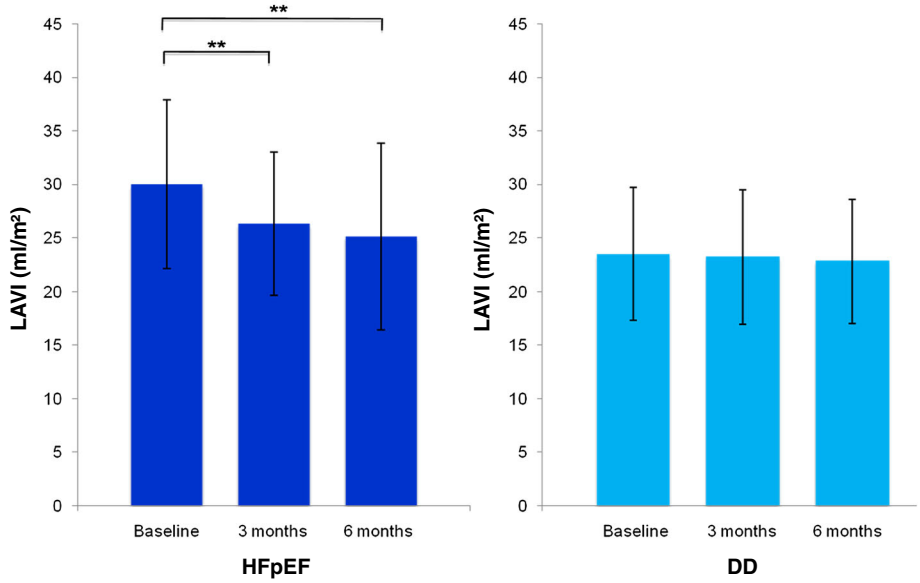

Figure 3 LAVI decreased significantly in heart failure with preserved ejection fraction (HFpEF) (**$P < 0.01$), but remained unchanged in diastolic dysfunction (DD).

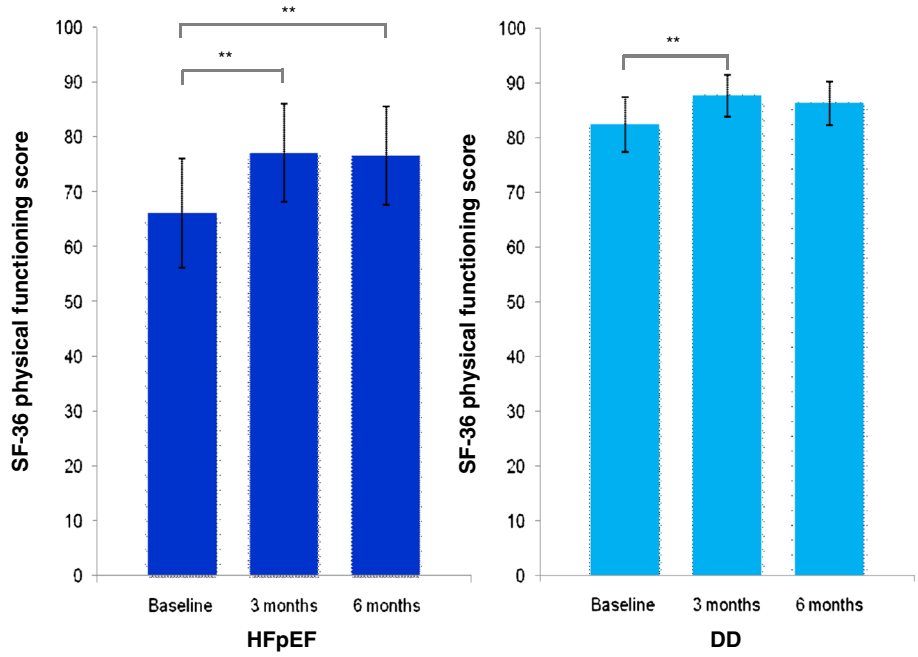

Figure 4 Change of quality of life (SF-36 physical functioning) after exercise training (changes within groups: *$P < 0.05$, **$P < 0.01$).

function, and QoL in patients with asymptomatic DD compared with patients with HFpEF. The training programme was adopted from successfully conducted studies in HFrEF, where ET improved relevant clinical endpoints.[18] Of particular interest and in contrast to other reports, all patients completed the study that is underpinning the long-term feasibility of our training programme. As a result of the ET programme, diastolic function and exercise capacity improved in both patients with DD and patients with HFpEF. However, although the HFpEF group already showed significant increases of peak VO_2 and $ATVO_2$ from baseline to the 3 months follow-up, we could first detect a significant increase of peak VO_2 and $ATVO_2$ in DD group after the 3 months to the 6 months follow-up. This suggests that lower baseline exercise capacity is related to a quicker response to ET. Also, a differential

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contribution of peripheral and central factors to exercise limitation at different stages of DD and HFpEF might contribute to the observed time displacement of peak VO_2 increase or diastolic function improvement after ET in our study.[10,30]

A large number of studies were performed about ET in patients suffering from HFrEF. They could demonstrate an improvement of exercise capacity and of systolic LV function and morphological parameters.[14–21] Interestingly, also first reports about the beneficial effects of ET also on LV diastolic function were derived from studies performed in HFrEF. Belardinelli *et al.* [31] established improved left ventricular diastolic filling patterns in 55 consecutive patients suffering from HFrEF after 2 months of supervised ET.[31] Additionally, the recent Leipzig exercise intervention in chronic heart failure and aging study demonstrated an improvement of left ventricular diastolic function in HFrEF patients regardless of age as a result of 4 weeks supervised endurance training.[32]

There is also increasing evidence from studies investigating ET in patients with HFpEF or with asymptomatic DD. Gary *et al.* [22] and Gary and Lee [23] tested the effect of 12 weeks ET in older women suffering from HFpEF. Home-based walking improved functional capacity[22] and QoL.[22,23] However, diastolic function was not measured. The single centre, single-blind randomized controlled trial of Kitzman *et al.* [14] investigated 16 weeks supervised aerobic ET compared with attention control in 46 elderly outpatients with isolated HFpEF and could demonstrate a significant improvement of exercise performance in the ET group. Although diastolic function was measured, the presence of DD was not required as an inclusion criterion, and the authors did not find significant changes in any resting Doppler echocardiography measure.[14] Haykowsky *et al.*[30] compared 4 months ET with attention control in elderly stable compensated HFpEF patients. After ET, they demonstrated a significant improvement of peak VO_2, but changes in DD were not reported. Therefore, our findings are in line with all studies reporting an improvement of exercise performance and add evidence regarding the beneficial long-term effects and the positive impact of ET also on DD.

The effect of ET on diastolic function and exercise capacity in patients with preexisting asymptomatic DD has only been examined in a few trials.[33,34,24–26] Overall, ET improved exercise tolerance in patients with DD, but the effects of ET on diastolic function were described inconsistently. Yu *et al.* [33] examined the effect of 8 weeks cardiac rehabilitation and prevention programme compared with conventional therapy on left ventricular diastolic function in patients with coronary heart disease. They could show a significant improvement of LV diastolic parameters towards less severe delayed relaxation in the CRPP group, especially in those patients with abnormal relaxation patterns or recent acute myocardial infarction. CRPP prevented the progression of resting LV DD.[33] Another study investigated the effect of 12 months ET in 48 men with newly onset of type 2 diabetes mellitus. Although peak VO_2 increased significantly, myocardial diastolic tissue velocities did not change.[34] In a small nonrandomized pre–post-study, Smart *et al.* observed the influence of 16 weeks ET on diastolic function, exercise capacity, and QoL in 18 patients with DD and in 22 patients with systolic dysfunction (SD). They demonstrated a similar improvement of peak VO_2 and QoL in patients with DD and those with SD after ET, but they reported no significant effect of ET on left ventricular DD.[24] Also, Korzeniowska-Kubacka *et al.* [26] performed a single centre, nonrandomized study of 48 post-myocardial infarction men with preserved LV function and mild DD ($E/e' > 8$) could find significantly increased maximal oxygen consumption after 4.5 months of ET. Diastolic function did not change significantly after the training programme (TDI values of the E′, A′, E/e′, and E/A′ ratios of all parts of the mitral annulus); only the deceleration time was significantly shorter in the training group. However, the improvement of exercise capacity was greater in patients with a more preserved diastolic function.[26] Only one small study of 23 sedentary patients with type 2 diabetes mellitus and DD established an improvement of left ventricular diastolic function after 3 months of ET programme compared with a control group. Their results demonstrated that, along with an improvement of VO_{2max}, aerobic ET could potentially reverse left ventricular DD in patients with well-controlled uncomplicated type 2 diabetes mellitus.[25] These findings were only in part supported by studies performed in obese persons with DD.[35,36] In summary, the evidence regarding the effects of ET on DD is conflicting, and our study adds evidence that ET in both DD and HFpEF can improve diastolic function properties of the left ventricle. Because the impairment of diastolic function is related to the inability to increase cardiac output during exercise, such improvement might be related to the observed exercise capacity.[37] In fact, in the Ex-DHF-P study, more than one third of the improvement of peak VO_2 was directly explained by the improvement of diastolic function.[10] Improved diastolic function might therefore indicate an improvement of exercise capacity and of subjective well-being and mental and physical aspects of QoL.

Study limitations

We investigated a small number of middle-aged patients; therefore, no assumption could be made about the effects of ET in older and more affected patients. The strict exclusion of relevant co-morbidities may contribute to a limited generalizability of our findings. Although the follow-up period of 6 months is longer than reported in the majority of

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former ET trials in DD and HFpEF, no general assumptions about long-term effects can be derived from our trial. Because all of included patients took part in supervised endurance and resistance training sessions on top of UC, no control group with UC alone could be reported.

The associations between changes in outcome parameters, body weight, blood pressure, and other peripheral parameters remain to be addressed. As reported by others, also the potential important contribution of peripheral factors to changes in exercise capacity needs to be investigated in further studies.

Conclusion

A structured long-term combined endurance and resistance ET programme is feasible and effectively improves exercise capacity and diastolic function in patients with DD and manifest HFpEF. Therefore, controlled lifestyle modification with physical activity should be considered as therapeutic option both in DD and HF with preserved ejection.

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Declaration of interest

None declared.

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