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Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial

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Abstract

Background: Despite suffering from poor prognosis, progressive exercise intolerance, and impaired quality of life (QoL), effective therapeutic strategies in heart failure with preserved ejection fraction (HFpEF) are sparse. Exercise training (ET) improves physical QoL in HFpEF, but the effects on other aspects of QoL are unknown.

Methods: The multicentre, prospective, randomized, controlled Exercise training in Diastolic Heart Failure Pilot study included 64 HFpEF patients (65 ± 7 years, 56% female). They were randomized to supervised endurance/resistance training in addition to usual care (ET, $n = 44$) or usual care alone (UC, $n = 20$). At baseline and after 3 months, QoL was assessed (36-item Short-form Health Survey (SF-36), Minnesota Living With Heart Failure Questionnaire (MLWHFQ), and Patient Health Questionnaire (PHQ-9).

Results: Exercise improved the following SF-36 dimensions: physical functioning ($p < 0.001$, $p = 0.001$ vs. UC), bodily pain ($p = 0.046$), general health perception ($p < 0.001$, $p = 0.016$ vs. UC), general mental health ($p = 0.002$), vitality ($p = 0.003$), social functioning ($p < 0.001$) physical ($p < 0.001$, $p = 0.001$ vs. UC), and mental component score ($p = 0.030$). ET did not improve role limitations due to physical and emotional problems. The MLWHFQ total scale ($p < 0.001$) and the MLWHFQ physical limitation scale ($p < 0.001$, $p = 0.04$ vs. UC) also improved with ET. The MLWHFQ emotional limitation scale did not change with ET. With ET, also the PHQ-9 total score improved significantly ($p = 0.004$, $p = 0.735$ vs. UC).

Conclusions: In patients with HFpEF, exercise training improved emotional status, physical and social dimensions of QoL as well as symptoms of depression from pre to post test. Physical dimensions of QoL and general health perception also improved significantly with exercise in comparison to usual care.

Keywords

Depression, diastolic heart failure, exercise training, heart failure with preserved ejection fraction, quality of life

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Introduction

In Western societies heart failure with preserved left ventricular ejection fraction (HFpEF) accounts for more than 50% of heart failure cases.[1,2] Over the past decades the prevalence of HFpEF was continuously increasing and in hospitalized patients morbidity and mortality appears to be as high as in heart failure with reduced ejection fraction (HFrEF).[3,4] Patients with HFpEF suffer from progressive exercise intolerance which heavily impacts physical activity of daily life and causes also an impairment of mental and social quality of life components.[5–8]

Exercise training (ET) has been established in HFrEF because a large number of trials showed that ET leads to an improvement in exercise intolerance and QoL.[9–15] Additionally, ET tended to affect morbidity and mortality positively, wherefore ET is now recommended in current guidelines for stable HFrEF patients.[16,17] While evidence-based guidelines are available for the therapy of HFrEF, the management of HFpEF is challenging because no single pharmacological therapy could demonstrate an improvement of exercise capacity, quality of life (QoL), or survival in HFpEF.[18] Only a few trials have investigated the effects of exercise training in HFpEF.[6,7,9,19,20] Consistently, these studies could also demonstrate that ET resulted in an improvement of exercise capacity and physical QoL. However, there is a complete lack of data from multicentre trials regarding the potential of ET to also positively affect other disease-specific or generic dimensions of QoL.

Therefore, the purpose of this present analysis, as a subanalysis of the Ex-DHF-Pilot trial (Exercise training in Diastolic Heart Failure),[6] was to investigate the clinical correlates of QoL and whether structured and supervised ET affects mental and social aspects of QoL, and also influences the existence and severity of depressive symptoms in patients with HFpEF.

Methods

We performed a prospective, multicentre, randomized, controlled trial including patients with HFpEF. Structured endurance/resistance ET on top of usual care (UC) was tested against UC alone. The methods and main results have been reported in detail and are only addressed briefly:[6]

Patients

Symptomatic (New York Heart Association, NYHA, functional class II/III) but stable patients (>45 years) were included if they had a preserved left ventricular ejection fraction (LVEF ≥50%), echocardiographically determined diastolic dysfunction (grade I or above), sinus rhythm, and one or more of the following cardiovascular risk factors: overweight, diabetes mellitus, hypertension, hyperlipidaemia, and smoking. Exclusion criteria have been published previously.[6] The Ethics Committees at each participating centre (three university hospitals) approved the study. Written informed consent was obtained from all patients before any study-related procedure was performed.

Randomization, intervention, and clinical assessment

Eligible patients were randomized in a 2:1 ratio to supervised ET on top of UC or to UC alone. As described previously, patients randomized to ET participated in a supervised, facility-based training programme consisting of endurance and resistance training (32 sessions, 3 months).[6] Weeks 1–4: aerobic endurance training (cycling, 2 times a week) of increasing intensity and duration (20–40 min). Training intensity was tailored individually to a target heart rate of 50–60% of peak oxygen uptake (VO_2) during baseline spiroergometry. Afterwards, workload was increased to a target heart rate of 70% of baseline peak VO_2 (3 times a week). Also starting at week 5, resistance training (bench press, leg press, leg curl, rowing machine, triceps dip, latissimus pull down) was added (2 times a week). Resistance training was performed for 15 repetitions per exercise per session at a work load corresponding to 60–65% of the 1 repetition maximum measured at the end of week 4. Safety parameters 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.

At baseline and follow up, all patients underwent a physical examination, symptom-limited cardiopulmonary exercise testing on bicycle ergometer, echocardiography, 6-minute walk testing, and blood sampling. Echocardiography was performed in accordance with guidelines of the American Society of Echocardiography and using a predefined standard operating procedure.[21] A reference centre performed staff training prior to and supervision during the trial. Diastolic dysfunction was determined as described previously.[22]

Quality of life

Quality of life (QoL) was assessed by the 36-item Short-form Health Survey (SF-36), the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), and the Patient Health Questionnaire depression scale (PHQ-9). Technical staff not involved in the training programme and blinded to patient assignment distributed the questionnaires to the patients.

36-item Short-form Health Survey (SF-36)

The 36-item short form was constructed to survey health status in the Medical Outcomes Study and was designed for use in clinical practice and research, health policy evaluations and general population surveys. It is including 36 items and exploring eight dimensions of QoL: (1) limitations in physical activities because of health problems (physical functioning); (2) limitation in social activities because of physical or emotional problems (social functioning); (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and wellbeing); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions. All scales were linearly transformed to 0–100 scoring, with 100 indicating the most favourable health state.[23]

Minnesota Living With Heart Failure Questionnaire (MLWHFQ)

The Minnesota Living With Heart Failure Questionnaire was developed by Rector et al.[24] as a disease-specific measure to systematically and comprehensively assess the patients' perception of the effects of heart failure and its treatment on their daily life. This disease-specific instrument for measuring the functional status of patients with heart failure is a 21-item, self-administered questionnaire that covers physical, socio-economic, and psychological impairment that patients often relate to their heart failure.[25] The 21 items can be used for computing two subscales – MLWHFQ physical limitations, MLWHFQ emotional limitations – and a MLWHFQ total score. The response scale for each question ranges from 0 (no) to 5 (very much).[24] The total scores could vary from 0 to 105 and higher scores of the MLWHFQ indicate lower quality of life.[25]

Patient Health Questionnaire depression module (PHQ-9)

The Patient Health Questionnaire (PHQ) was developed in 1999 by Spitzer et al. and is a self-administered version of the PRIME-MD interview.[26] The PHQ is based on DSM-IV criteria used in diagnosing depressive and other mental disorders commonly appearing in primary care. The PHQ-9 is the 9-item depression module of the full PHQ. It reflects the nine core symptoms of major depressive episodes according to DSM-IV and can be used both as a screening tool for probable depressive disorders and as a dimensional measure of depressive symptom severity. Major depression can be suspected if five or more of these nine depressive symptom criteria are present at least 'more than half the days' over the past 2 weeks, and one of the symptoms is anhedonia or depressed mood. Other depression is assumed if between 2 and four depressive symptoms are present at least 'more than half the days' over the past 2 weeks. Each of the nine items can be scored from 0 (not at all) to 3 (nearly every day.) Thereby the PHQ-9 score as a severity measure can range from 0 to 27 (1–4 minimal depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe, and 20–27 severe depression).[27]

Statistical analysis

Changes within groups during follow up were assessed by the t-test for paired variables. The 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. All analyses were performed as intention to treat analyses. A p-value ≤ 0.05 was considered statistically significant. Data are shown as mean $\pm$ SD or as median and IQR. The correlations between demographic and clinical variables are reported as Pearson correlation coefficients. SPSS 20.0 (SPSS, Chicago, IL, USA) was the software used for statistical analyses.

Results

Study sample

Of 71 patients screened for eligibility, 64 patients were analysed (ET $n = 44$, UC $n = 20$).[6] There were no baseline differences between the groups in demographic data, risk factors, physical examination, and medical history. The patients were 65 ± 7 years old, and 56% of them were female. Body mass index was $31 \pm 5\,kg/m^2$, waist/hip ratio 0.93 ± 0.008, heart rate 66 ± 11 beats/min, systolic blood pressure 140 ± 19 mmHg, and diastolic blood pressure 82 ± 12 mmHg. The mean LVEF was $67 \pm 7\%$, a diastolic dysfunction grade I could be measured in 72%, and grade II in 28%. In echocardiography a mean E/e′ ratio of 12.8 ± 3.2 in the ET group and 13.5 ± 4.6 in the UC group and a mean left atrial volume index of $27.9 \pm 7.6\,ml/m^2$ in the ET group and

28.2 ± 8.8 in the UC group could be measured at baseline. The mean peak VO_2 was 16.1 ± 4.9 ml/kg/min in ET and 16.7 ± 4.7 ml/min/kg in UC. Cardiovascular medication was also not different between the training and the control group and consisted of angiotensin-converting enzyme inhibitors and/or angiotensin receptor antagonists (66%), beta-blockers (50%), and diuretics (45%).

Clinical and cardiac effects of exercise testing

The main results have been reported in detail and are only addressed briefly.[6] With ET symptoms, exercise capacity and diastolic function improved significantly. Mean increase of peak VO_2 was 2.6 ml/min/kg in the ET group (baseline 16.1 ± 4.9, follow up 18.7 ± 5.4, $p < 0.001$) compared to a decrease of −0.7 ml/min/kg in the UC group (baseline 16.7 ± 4.7, follow up 16.0 ± 6.0, $p = 0.34$). The changes of peak VO_2 during the trial were significant between the two groups ($p < 0.001$). At baseline, expiratory exchange ratio (RER) was not significantly different between groups (UC 1.18 ± 0.11, ET 1.20 ± 0.10, $p > 0.05$) and also changes of RER during the trial were not significantly different between the two groups (UC at follow up 1.12 ± 0.08, ET at follow up 1.15 ± 0.13, differences of change between groups $p = 0.52$). VE/VO_2 decreased significantly in the ET group (baseline 35.1 ± 4.9, follow up 32.3 ± 5.8, $p = 0.003$), as compared to the UC group (baseline 32.4 ± 4.8, follow up 31.5 ± 4.1, $p = 0.33$), differences of change between groups $p = 0.67$). The echocardiographic E/e′ ratio improved significantly in the ET group (baseline 12.8 ± 3.2, follow up 10.5 ± 2.5, $p < 0.001$) as compared to the UC group (baseline 13.5 ± 4.6, follow up 14.1 ± 3.9, $p = 0.26$), and the changes of E/e′ during the trial were significant between the ET and UC groups ($p < 0.001$). In contrast, E/A ratio did not change in the ET group (baseline 0.89 ± 0.34, follow up 0.88 ± 0.35, $p = 0.81$) and in the UC group (baseline 0.97 ± 0.22, follow up 0.99 ± 0.22, $p = 0.63$) with no difference between the groups ($p = 0.38$). Also deceleration time (ms) did not change in the ET group (baseline 225 ± 62, follow up 225 ± 42, $p > 0.99$) or in the UC group (baseline 212 ± 51, follow up 229 ± 44, $p = 0.10$) with no difference between the groups ($p = 0.41$).

Association of different measures of quality of life with maximal exercise capacity and diastolic function at baseline and during follow up

The association of different aspects of quality of life and parameters of functional capacity (peak VO_2) as well as diastolic function (E/e′) was examined at baseline and during follow up (Tables 1A and 1B). At baseline (Table 1A), significant positive correlations were found between peak VO_2 and the following aspects of SF-36: physical functioning, role limitations due to

Table 1A. Cross-sectional correlations between quality of life (QoL), peak VO_2 and E/é at baseline.

QoL measurements	Peak VO_2 correlation coefficient	p-value	E/é correlation coefficient	p-value
SF-36				
Physical functioning	**0.378**	**0.002**	−0.056	0.667
Role limitations due to physical problems	**0.330**	**0.011**	0.006	0.963
Bodily pain	0.202	0.115	−0.022	0.864
General health perceptions	**0.320**	**0.012**	0.030	0.817
Vitality	0.202	0.118	0.088	0.502
Social functioning	0.173	0.179	0.113	0.381
Role limitations due to emotional problems	0.223	0.090	0.100	0.452
General mental health	0.061	0.639	0.049	0.707
MLWHFQ				
Physical limitations	**−0.418**	**0.001**	0.036	0.781
Emotional limitations	−0.142	0.275	0.038	0.773
Total score	**−0.300**	**0.020**	0.050	0.703
PHQ-9				
Total score	−0.217	0.091	−0.078	0.548

SF-36, 36 item short form health survey; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; PHQ-9, Patient Health Questionnaire – Depression module; Peak VO2, peak oxygen consumption; E/é, ratio of early mitral inflow velocity to early tissue doppler velocity.

Table 1B. Correlations between changes of different quality of life (QoL) measures and changes of maximal exercise capacity and diastolic dysfunction during follow-up.

QoL measurements (change)	Peak VO_2 (change) correlation coefficient	p-value	E/é (change) correlation coefficient	p-value
SF 36				
Physical functioning	0.197	0.131	−**0.455**	<**0.001**
Role limitations due to physical problems	−0.094	0.487	−**0.267**	**0.045**
Bodily pain	−0.026	0.845	−0.056	0.667
General health perceptions	**0.296**	**0.022**	−0.167	0.201
Vitality	−0.020	0.878	−**0.279**	**0.031**
Social functioning	−0.134	0.303	−0.051	0.695
Role limitations due to emotional problems	−0.170	0.207	−0.071	0.598
General mental health	0.131	0.318	−**0.285**	**0.027**
MLWHFQ				
Physical limitations	−0.176	0.178	**0.289**	**0.025**
Emotional limitations	0.180	0.172	0.172	0.193
Total score	−0.123	0.354	**0.342**	**0.008**
PHQ-9				
Total score	0.233	0.071	0.062	0.634

SF-36, 36 item short form health survey; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; PHQ-9, Patient Health Questionnaire – Depression module; Peak VO2, peak oxygen consumption; E/é, ratio of early mitral inflow velocity to early tissue doppler velocity.

physical problems, and general health perception. Significant negative correlations were determined between peak VO_2 and the total scale of MLWHFQ and the MLWHFQ physical limitation subscale. There were no significant associations of peak VO_2 and mental or social dimensions of QoL. E/e′ was not significantly related to any aspect of QoL (Table 1A).

As shown in Table 1B, a closer correlation between the changes of QoL and the change of E/e′ than between the changes of QoL and the change of peak VO_2 could be determined: the change of E/e′ was significantly and negatively correlated with the change of the following SF-36 dimensions: physical functioning, role limitations due to physical problems, vitality, and general mental health. There was a significant positive correlation between the changes of E/e′ and the change of the total scale of MLWHFQ and MLWHFQ physical limitation scale. There was no correlation between the change of E/e′ and the change of mental and social dimensions of QoL. The change of peak VO_2 significantly correlated with a change of the general health perceptions on the SF-36, but not with the changes of other dimensions of the SF-36, MLWHQ, or PHQ-9.

Effect of exercise training on QoL aspects

After 3 months, various measures of QoL symptoms and depression improved with ET and remained unchanged with UC. The results of SF-36 physical functioning, MLWHFQ total scale, and MLWHFQ physical and emotional limitation scales have been described previously.[6] The results of all dimensions of QoL are shown in Table 2 and Figures 1–3.

By means of SF-36, an improvement of the following dimensions of QoL within the exercise group could be observed: physical component score, physical functioning, bodily pain, and general health perception. During ET, also some SF-36 social and mental dimensions improved significantly, in particular general mental health, vitality, social functioning, and mental component score. ET did not improve role limitations due to physical and emotional problems. The differences between the ET and UC groups only reached statistical significance in physical component score, physical functioning, and general health perceptions.

The MLWHFQ total scale and the MLWHFQ physical limitation scale also improved significantly with ET. The improvement of the MLWHFQ emotional limitation scale with ET was not significant. The differences between ET and UC reached statistical significance only for the MLWHFQ physical limitation scale and by tendency for the total score.

The PHQ-9 total score improved significantly with ET, whereas there was no significant change of the score in the control group. However, the differences between both groups did not reach statistical significance.

Table 2. Quality-of-life endpoint data at baseline and after 3 months.

Variable	Training	Control	Difference between groups
SF-36			
Physical functioning			
No. 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	0.304	0.001
Role limitations due to physical problems			
No. of responders	38	19	
Baseline	65 ± 40	78 ± 38	
Follow up	75 ± 39	71 ± 41	
Change	10 (−3 to 23)	−7 (−18 to 5)	11 (−7 to 30)
p-value	0.142	0.235	0.219
Bodily pain			
No. of responders	41	20	
Baseline	65 ± 28	67 ± 29	
Follow up	73 ± 29	66 ± 29	
Change	8 (0 to 16)	0 (−7 to 7)	8 (−4 to 20)
p-value	0.046	0.942	0.178
General health perceptions			
No. of responders	40	20	
Baseline	57 ± 18	60 ± 18	
Follow up	69 ± 17	63 ± 18	
Change	12 (8 to 17)	3 (0 to 7)	8 (2 to 15)
p-value	<0.001	0.071	0.016
Vitality			
No. of responders	40	20	
Baseline	52 ± 22	54 ± 17	
Follow up	60 ± 21	58 ± 21	
Change	9 (3 to 15)	3 (−2 to 9)	5 (−3 to 13)
p-value	0.003	0.213	0.242
Social functioning			
No. of responders	41	20	
Baseline	70 ± 29	84 ± 28	
Follow up	83 ± 25	92 ± 21	
Change	13 (6 to 19)	8 (−4 to 19)	−1 (−11 to 9)
p-value	<0.001	0.186	0.852
Role limitations due to emotional problems			
No. of responders	38	19	
Baseline	78 ± 35	93 ± 24	
Follow up	84 ± 32	93 ± 24	
Change	6 (−4 to 16)	0 (−5 to 5)	0 (−13 to 13)
p-value	0.228	1	0.997
General mental health			
No. of responders	40	20	
Baseline	67 ± 20	74 ± 12	
Follow up	74 ± 21	75 ± 19	

(continued)

Table 2. Continued.

Variable	Training	Control	Difference between groups
Change	7 (3 to 11)	1 (−5 to 7)	5 (−3 to 12)
p-value	0.002	0.616	0.203
Physical component score			
No. of responders	37	19	
Baseline	43 ± 9	45 ± 10	
Follow up	47 ± 9	43 ± 10	
Change	5 (3 to 7)	−1 (−3 to 1)	6 (2 to 9)
p-value	<0.001	0.241	0.001
Mental component score			
No. of responders	37	19	
Baseline	48 ± 11	53 ± 8	
Follow up	51 ± 11	56 ± 7	
Change	3 (0 to 5)	3 (0 to 5)	−1 (−5 to 2)
p-value	0.030	0.23	0.462
MLWHFQ			
Physical limitation scale			
No. 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
Emotional limitation scale			
No. of responders	41	18	
Baseline	4 ± 6	3 ± 4	
Follow up	3 ± 5	2 ± 3	
Change	−1 (−2 to 1)	−1 (−2 to 0)	0 (−1 to 2)
p-value	0.291	0.168	0.566
Total scale			
No. 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
PHQ-9			
Total score			
No. of responders	41	20	
Baseline	7 ± 6	5 ± 5	
Follow up	5 ± 5	4 ± 5	
Change	−2 (−3 to −1)	−1 (−2 to 0)	0 (−2 to 1)
p-value	0.004	0.170	0.735

Values are *n*, mean ± standard deviation, or median (interquartile range); MLWHFQ, Minnesota Living With Heart Failure Questionnaire; PHQ-9, Patient Health Questionnaire depression module; SF-36, 36 item Short-form Health Survey.

Safety and compliance

The details have been reported previously:[6] there were no serious adverse events. In the ET group, 11 patients (25%) had adverse events during or immediately after exercise without clinical relevance, and only one of them discontinued participation in exercise sessions during week 9. In the ET group, 34% participated in >90%, 52% in 70 to 90%, and 14% in <70% of the exercise session.

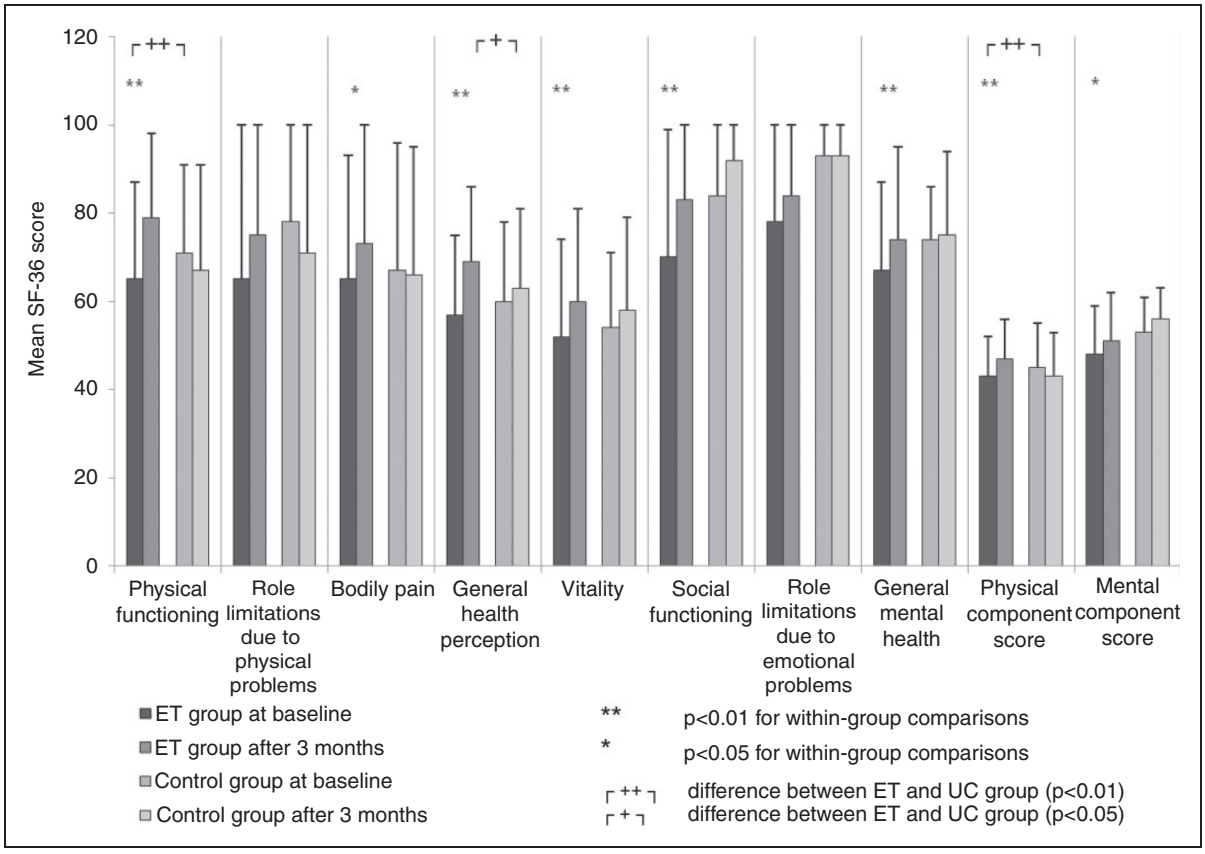

Figure 1. Subscores and component scores of the SF-36 in the exercise training (ET) and usual care (UC) groups at baseline and after 3 months.

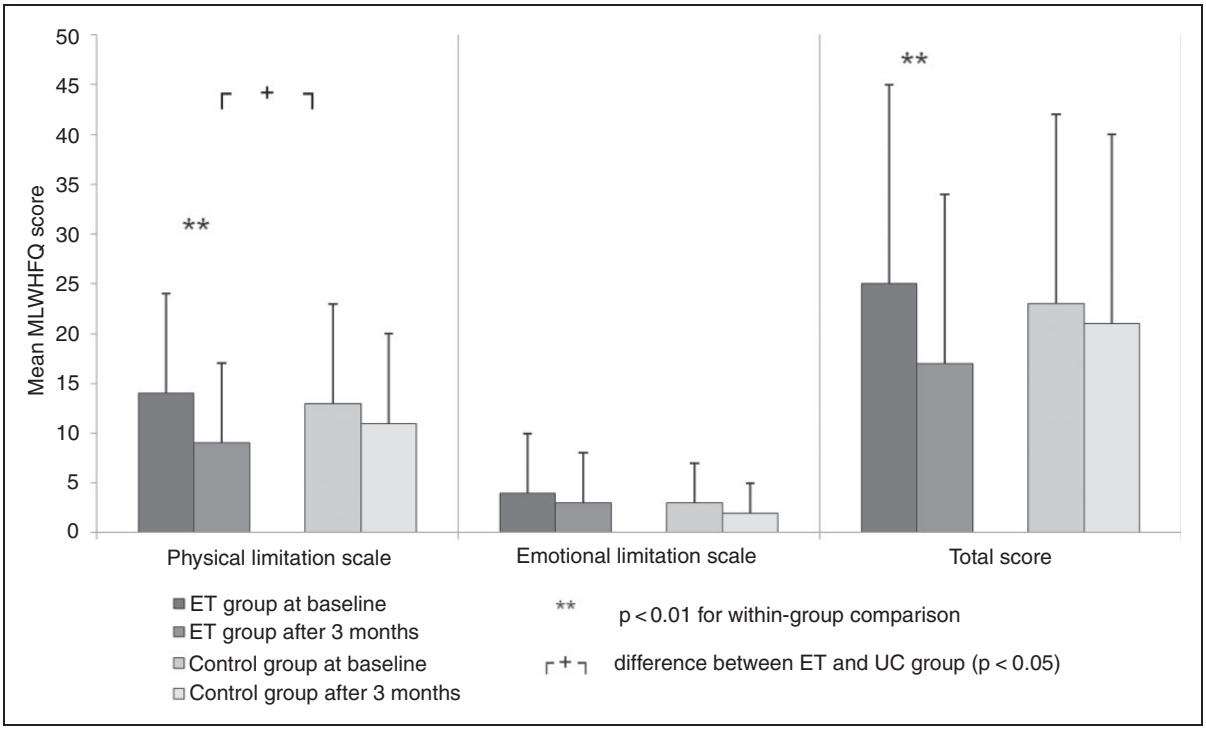

Figure 2. MLWHFQ subgroups in the exercise training (ET) and usual care (UC) groups at baseline and after 3 months.

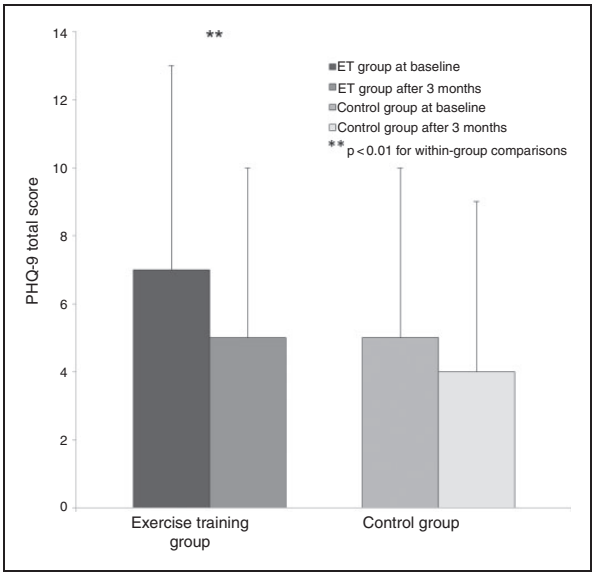

Figure 3. Results of PHQ-9 in the exercise training (ET) and usual care (UC) groups at baseline and after 3 months.

Discussion

Main findings

Exercise training over 3 months was an effective intervention in patients suffering from HFpEF: physical, mental, and social dimensions of QoL improved significantly. Furthermore, symptoms of depression were reduced with ET in patients with HFpEF.

Patient population

A total of 64 patients were analysed. The baseline variables of QoL are well comparable to former studies (as will be discussed). In the present study, 56% of the patients were women, and as patients suffering from HFpEF are predominantly women, our included patients well represented the general gender distribution within the HFpEF population. Of particular interest, the participants reported by Gary et al.[7,19] were only women, and Kitzman et al.[9] included 80% male patients.

Quality of life in HFpEF

Patients with HFpEF suffer from fatigue and dyspnoea on exertion.[8] Exercise intolerance is the leading symptom in HFpEF and results in recurrent presentations in the primary care setting. Exercise intolerance is also associated with reduced prognosis.[28] Concurrently, patients with HFpEF are also characterized by impaired physical, mental, and social dimensions of QoL and increased symptoms of depression.[5,6,29,30] The CHARM programme[31] observed an equally impaired QoL in HF patients with preserved and with reduced LVEF. Also, others found an impairment of QoL in patients with diastolic dysfunction similar to those with systolic dysfunction.[32,33] Kitzman et al.[30] demonstrated similar scores of SF-36 between HFpEF and HFrEF, but patients with HFpEF showed less severe impairments on the MLWHFQ than HFrEF patients. Therefore, current heart failure guidelines further recommend to improve exercise tolerance and QoL of life both in HFrEF and HFpEF.[17] Despite its high prevalence and prognostic relevance, HFpEF is a disease without evidence-based therapies for improving survival.[18] Also, single pharmacological approaches failed to show effectiveness regarding exercise capacity or QoL in HFpEF.[18,34,35] In patients with HFrEF exercise training significantly improved exercise tolerance and QoL, but there are only a few prior single-centre trials that investigated the influence of ET on QoL also in patients with HFpEF.[7,9,19,36]

Impact of ET on QoL in HFpEF

In a single-centre, single-blind trial, Kitzman et al.[9] compared 16 weeks of ET with attention control in 46 elderly patients with HFpEF. They reported an improvement of exercise capacity which was accompanied by an improvement only in the physical limitation scale of the MLWHFQ. The investigators could not find a change in the emotional limitation scale and the MLWHFQ total score. They also used the SF-36 and CES-D (Center for Epidemiological Studies Depression Survey), but no differences between the groups could be demonstrated during follow up.[9] Since the intervention scheme and duration of the trial was comparable with our study, sample size, older age of participants, gender distribution, and the single centre trial design might have impacted on these results. Gary et al.[7] compared a 12-week home-based, combined walking and education programme with education in 32 women suffering from HFpEF; they reported a significant improvement of QoL in the intervention group compared with the control group as measured by the MLWHFQ and the Geriatric Depressions Scale (GDS). Another study[19] tested the effect of 12 weeks of a home-based walking intervention compared with education only on sleep patterns, depressive symptoms, physical function, and QoL with 23 older women suffering from diastolic heart failure. The investigators detected a significant increase of total sleep time, an improvement of the heart failure-related QoL measured by the MLWHFQ, and a trend for decreased depressive symptoms measured by the GDS in the intervention group. They also reported a

trend for an improvement of subjective physical function in the intervention group measured by the Duke Activity Status Index (DASI).[19] In both trials, an improvement of QoL measured by the MLWHFQ could be shown; however, the improvement was only defined on the basis of the MLWHFQ total score, and subscales were not reported. Different gender distribution, sample size, single-centre design, and type of intervention are limiting the comparability of these studies with our study. Smart et al.[36] investigated the role of 16 weeks of ET in heart failure patients with systolic dysfunction (HFrEF) compared with patients suffering from diastolic dysfunction (HFpEF). To evaluate the QoL the MLWHFQ, the Hare-Davis Cardiac Depression Scale and the SF-36 was used. In the HFpEF group only the MLWHFQ-emotional limitation scale and depression-scores significantly improved after 16 weeks ET. In contrast, the MLWHFQ total score and the SF-36 did not change in HFpEF. However, this trial was a pre–post study without randomization and nor any control group. Furthermore, there was no blinding of the observers assessing the exercise and QoL outcomes and 30% of HFpEF patients were lost to follow up.[36] Palau et al.[37] investigated a 12-week programme of inspiratory muscle training (IMT) in 26 patients with advanced HFpEF. Exercise capacity and QoL improved markedly with IMT, but the discrepancy of this type of intervention limits the comparability with our study.

Exercise intolerance is one of the major limiting factors of QoL of patients with HFpEF. An impairment of diastolic function is associated with limited exercise capacity and results in reduction of physical components of health and QoL.[5] Physical dimensions of QoL in our intervention group was related to the improvement of diastolic dysfunction (E/e′) and peak VO_2.[6] Furthermore, we found a significant improvement of mental and social dimensions of QoL after ET. These results could be explained by a trend toward increased physical function and exercise tolerance with ET which seem to translate into better general wellbeing. Patients who feel fitter with exercise training may realize the great progress in their functional ability and have the sense of control over their illness. Additionally, regular ET possibly may have promoted more active coping and positive affect. Prior studies have also shown that active behavioural coping contributes to less fatigue and more vigour, which has been shown to be a central factor in improving QoL.[19]

Impact of ET on depression

Depression among patients with heart failure is common and may be underrecognized and undertreated in cardiac populations such as HFpEF. A prior meta-analysis showed an aggregated estimate of 27.8%, with higher prevalence rates associated with a higher NYHA functional class.[38] Blumenthal et al.[39] reported that exercise or pharmacological treatment with sertraline resulted in greater reductions of depressive symptoms compared with placebo in patients with coronary heart disease. Interestingly, this effect was mainly driven by the exercise group. So far, investigations about the presence and severity of depression in patients suffering from HFpEF and about the influence of ET are scarce, and the effects on depression reported from previous exercise intervention trials in HFpEF are conflicting.[7,9,19,36] In the present analysis, we could assert that, on average, our patient cohort suffered from mild to moderate symptoms of depression and we could observe a significant decrease of symptoms of depression, measured by an improvement of the PHQ-9 total score. Of note, this was independent of a prior diagnosis of depression. Various mechanisms might be responsible for this improvement, but the present study can only give limited insights into pathophysiology. Prior studies about HFrEF determined that depression and heart failure share several biological mechanisms, and they suggested a link between depression, inflammation, and the progression of heart failure.[38]

Association between QoL, peak VO_2, and E/e′

Cross-sectional higher peak VO_2 was related to different better QoL measures, particularly physical dimensions. That means patients with a better objective functional capacity feel less limited in their physical capacity. However, the change of diastolic function during 3 months follow up was significantly correlated with changes of QoL measures. In particular, improvements in E/e′ and patient-reported physical dimensions of QoL were significantly correlated, which suggests that an improvement of diastolic dysfunction might be felt as relief by the patients. However, others demonstrated that rather peripheral than central mechanisms are responsible for the ET-induced improvement.[40] Whether the reduction of heart failure symptoms, the decrease of fatigue or more active and optimistic behaviour than before is responsible, needs to be addressed in future studies.

Limitations

We investigated a multicentre trial with a relatively small number of middle-aged patients in short-term follow up. Therefore, future studies with an adequately powered sample size, a broader population with a wider range of stages of HFpEF, and long-term follow up are necessary.

We could observe an improvement of various parameters of QoL during ET, but only a part of these parameters could show a significant difference to the control group. These results could be a statistical phenomenon, because the control group is considerably smaller than the ET group and therefore an identical effect in the control group had a lower chance to reach statistical significance than in the ET group. We could detect that the pre–post differences were descriptive greater in nearly all scales of the ET group than in the control group. There is a need for trials with a larger sample size to evaluate between-group differences during follow up.

Furthermore, the obvious lack of standardization of the use of QoL instruments in clinical trials further limits the interpretative power and comparability of these trials.

Conclusion

Structured supervised exercise training performed in HFpEF positively affects general health perceptions, improves patients' emotional status and social dimensions of QoL, and reduces symptoms of depression. ET should be considered for improving QoL in patients with HFpEF.

Conflict of interest

None declared.

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