ORIGINAL RESEARCH ARTICLE

Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction

Anna Bobenko[1,2], Inke Bartels[3], Marlene Münch[4,5], Tobias Trippel[1,2], Ruhdja Lindhorst[1,2], Kathleen Nolte[3,6], Christoph Herrmann-Lingen[6,7], Martin Halle[8,9], André Duvinage[8], Hans-Dirk Düngen[1,2], Götz Gelbrich[4,5], Carsten Tschöpe[1,2,10], Gerd Hasenfuss[3,6], Rolf Wachter[3,6], Burkert Pieske[1,2,11] and Frank Edelmann[1,6]*

[1]Department of Cardiology, Charité—Universitätsmedizin Berlin, Berlin, Germany; [2]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [3]Clinic for Cardiology and Pneumology, University of Göttingen Medical Centre, Göttingen, Germany; [4]Institute for Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany; [5]Clinical Trial Centre, University Hospital Würzburg, Würzburg, Germany; [6]DZHK (German Centre for Cardiovascular Research), Partner Site Göttingen, Göttingen, Germany; [7]Department of Psychosomatic Medicine and Psychotherapy, University of Göttingen Medical Centre, Göttingen, Germany; [8]Department of Prevention, Rehabilitation, and Sports Medicine, Technische Universität München, Munich, Germany; [9]DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany; [10]BCRT (Berlin-Brandenburg Center for Regenerative Therapies), Berlin, Germany; [11]Department of Cardiology, Deutsches Herzzentrum Berlin (DHZB), Berlin, Germany

Abstract

Aims   Heart failure with preserved ejection fraction (HFpEF) remains a common condition with no pharmacological treatment. Physical activity (PA) improves symptoms and quality of life (QoL), but no clear recommendations exist on PA in HFpEF patients. We investigated the association of PA (amount/intensity) on clinical phenotype in HFpEF.

Methods and results   The Aldosterone in Diastolic Heart Failure trial investigated spironolactone vs. placebo in stable HFpEF patients. At baseline, all patients underwent detailed phenotypization including echocardiography, cardiopulmonary exercise testing, 6 minute walking test (6MWT), and QoL assessment (36-item Short-Form questionnaire). PA was assessed by a self-report questionnaire, classified in metabolic equivalents of task (MET) and analysed with regard to exercise capacity, diastolic function, and QoL. Four hundred twenty-two patients (52% women, age 67 ± 8 years, New York Heart Association II and III) were classified by weekly MET hours into a low (<70), middle (70–140), or high (>140) level of PA. Total PA correlated positively with 6MWT distance ($r = 0.17$; $P = 0.002$) and physical function of QoL ($r = 0.10$; $P = 0.05$), but not with peak oxygen uptake (peakVO$_2$). In contrast, both 6MWT distance and peakVO$_2$ were significantly higher in patients who performed high-intensity PA for >8 h/week ($P < 0.001$, $P = 0.02$, respectively). Time of high-intensity PA was related to higher 6MWT distance ($r = 0.21$, $P < 0.001$), peakVO$_2$, and better physical function of QoL (both $r = 0.13$, $P = 0.01$), whereas low-intensity PA did not show significant associations. Interestingly, PA was not related to any measure of diastolic function.

Conclusions   A higher amount of PA is related to higher submaximal exercise capacity and physical function of QoL. Regarding maximal exercise capacity, only high-intensity PA showed significant association in HFpEF patients.

Introduction

The epidemiological burden of heart failure (HF) has grown in the past decades.[1] The prevalence of HF with preserved ejection fraction (HFpEF) is high and increasing, making HFpEF a continuously growing public health problem.[1,2] Morbidity and mortality in HFpEF are quite similar to HF with reduced ejection fraction (HFrEF), but no effective pharmacological treatment has been identified so far[3–6] and a successful management of the disease remains elusive.[2] Therefore, an intensified search for prevention and treatment strategies in HFpEF is of global interest.

Although not yet separately demonstrated in patients with HFpEF, an active lifestyle and/or a structured training intervention prevents the development of HF[7–9] and is associated with considerable improvement of survival in patients at risk for HF and in symptomatic HFrEF.[10–12] In addition, several training interventions have shown significant improvement of exercise capacity and quality of life (QoL) in patients with HF.[10,13]

Overall, the amount of physical activity (PA), which is beneficial to prevent HF and its progression, has been investigated in epidemiological cohort studies. Higher fitness in early middle age is associated with a lower risk of HF and of HF hospitalization in later life.[14] However, the relationship between PA and HF and the optimal PA level to prevent HF are still discussed since data are conflicting.[9,11,15]

Intensity of PA is an important component for the improvement of cardiopulmonary function, metabolic control, and even intervention-related outcomes, but available data are conflicting.[16] In addition, data on PA in patients with clinically manifest HFpEF are scarce. Although several training interventions have shown promising results in improving exercise capacity and QoL in HFpEF,[17–19] there are no data available on the health-relevant extent of PA for this patient cohort. Previous trials comparing different training modalities in patients with HF and risk of HF did not identify a clear intensity mode for exercise.[20,21]

Therefore, the aim of this analysis was to identify associations between PA (volume, duration, and intensity) and clinical phenotype (including exercise capacity) in a large cohort of HFpEF patients. This may help identify the optimal amount and intensity of PA for high exercise capacity and form the basis for an optimal training intervention strategy in future intervention studies in patients with HFpEF.

Methods

The Aldosterone in Diastolic Heart Failure (Aldo-DHF) trial was a multicentre, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2012 at 10 sites in Germany and Austria. The study design and main results have been previously published.[22,23] The trial included 422 ambulatory patients (mean age 67 ± 8 years; 52% female) with stable chronic HF (New York Heart Association class II or III), preserved left ventricular ejection fraction of 50% or greater, and evidence of diastolic dysfunction. Baseline data of Aldo-DHF were used for the present study.

Clinical data, diagnostic procedures, and patient questionnaires were collected using pre-defined standard operating procedures based on international guidelines.[24] Detailed echocardiography was done twice within 1 week to ensure stability of results. Diastolic function was assessed by echocardiography in accordance with American Society of Echocardiography guidelines, e.g. E/e′ and left atrial volume index (LAVI).[24] Exercise

performance was measured by 6 minute walk testing (6MWT) and cardiopulmonary exercise testing (CPET) [peak oxygen uptake (peakVO$_2$) and bicycle ergometer (starting at a workload of 20 W and a stepwise 20 W increment every 2 minutes)]. PA and QoL (including physical function) were assessed by the validated 36-item Short-Form (SF-36) questionnaire[25] and an *ad hoc* self-report questionnaire (Physical Activity Questionnaire on Amount and Intensity, PAQ-AI). The SF-36 (especially the physical function scale) correlates with accelerometry on physical performance measures.[26]

The PAQ-AI was adapted from the validated Freiburg Questionnaire of Physical Activity,[27] which assesses different types of activities and evaluates occupational, leisure time, and everyday life PA in hours per week. In contrast, the PAQ-AI assesses different intensities of activities and divides PA into three categories (light, moderate, and vigorous). For each category, mean metabolic equivalent of task (MET) values were calculated using the current Compendium of Physical Activities[28] with 1 MET set by convention to 3.5 mL O$_2$/kg/min and expressing the energy cost of PA. Therefore, total MET hours (METh) per week—representing total amount of PA per week—were calculated for each patient as follows:

$$\text{Total METh} = 4.6 \cdot h_{\text{light PA}} + 5.2 \cdot h_{\text{moderate PA}}$$
$$+ 7.3 \cdot h_{\text{vigorous PA}}.$$

Retest correlation of PAQ-AI was highly significant with 0.56 for 6 months and 0.50 for 12 months of follow-up data of the Aldo-DHF trial. PAQ-AI was used for evaluation of PA depending on amount and intensity.

Ethics

The Aldo-DHF complies with the Declaration of Helsinki and principles of good clinical practice. The protocol was approved by all responsible ethics committees. All participants gave written informed consent.

Statistics

Baseline characteristics were analysed using mean and standard deviation with Kruskal–Wallis for calculation of *P*-values (metric variables) and cross tabulation with χ^2 test for *P*-values (categorical variables). For analysis of N-terminal proBNP (NT-proBNP), median with quartiles and Kendall's tau for calculation of *P*-values were used. The effects of METh classes on dependent variables were tested using multifactorial ANOVA, adjusted for age and sex and shown as means and 95% confidence intervals for dependent variables with *P*-values. Correlations between time of exercise or total METh and clinical parameters were tested using Pearson's *r*. A one-way ANOVA was used to analyse means of dependent

variables across METh groups or high-intensity exercise groups. A P-value <0.05 (two-tailed) was considered statistically significant. SPSS software version 23.0 (IBM, Chicago, IL, USA) was used for the analyses.

Results

Baseline characteristics for the Aldo-DHF study have previously been published.[23] Additional baseline characteristics

are shown in *Table 1*. Age, sex, and body mass index (BMI) showed no specific trends across groups.

Patients were classified by tertile of METh/week values into patients of low, middle, and high levels of total PA. Significant differences among groups of total PA were noticed in the amount of high-intensity PA (defined as >6 MET). Of all patients with low-level PA, 73.2% performed high-intensity PA for <4 h/week and only 0.7% for >8 h/week ($P < 0.001$). In the group of patients with high-level PA, 72.4% performed high-intensity PA for >8 h/week and 13.8% for <4 or 4–8 h/week, respectively.

Table 1 Baseline characteristics

Variable	All subjects	Low MET value (<70 METh/week)	Middle MET value (>70 to 140 METh/week)	High MET value (>140 METh/week)	P-value
Number of subjects	379	142	121	116	
Demographics					
Age (years), mean (SD)	67.2 (7.4)	67.5 (7.5)	66.5 (7.9)	67.4 (6.9)	0.65
Female, no. (%)	196 (51.7)	77 (54.2)	58 (47.9)	61 (52.6)	0.58
Current smoking, no. (%)	24 (6.3)	8 (5.6)	10 (8.3)	6 (5.2)	0.57
Medical history					
Hospitalization for HF in past 12 months, mean (SD)[a]	0.5 (0.8)	0.4 (0.6)	0.5 (0.7)	0.6 (0.9)	0.49
Previous myocardial infarction, no. (%)[b]	63 (16.7)	22 (15.5)	26 (21.7)	15 (12.9)	0.18
Coronary heart disease, no. (%)	151 (39.8)	59 (41.5)	46 (38.0)	46 (39.7)	0.84
Hyperlipidaemia, no. (%)	229 (60.4)	89 (62.7)	76 (62.8)	64 (55.2)	0.38
Diabetes mellitus, no. (%)	59 (15.6)	23 (16.2)	22 (18.2)	14 (12.1)	0.42
Chronic obstructive pulmonary disease, no. (%)	13 (3.4)	4 (2.8)	6 (5.0)	3 (2.6)	0.53
Atrial fibrillation, no. (%)	63 (16.6)	25 (17.6)	20 (16.5)	18 (15.5)	0.90
Peripheral vascular disease, no. (%)	16 (4.2)	9 (6.3)	5 (4.1)	2 (1.7)	0.19
ICD, no. (%)	1 (0.3)	0 (0.0)	1 (0.8)	0 (0.0)	0.55
Pacemaker, no. (%)[a]	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.9)	0.32
Physical examination					
Body mass index (kg/m^2), mean (SD)	29.0 (3.5)	29.4 (3.9)	28.5 (3.3)	29.1 (3.3)	0.17
Systolic blood pressure (mmHg), mean (SD)[b]	135 (18)	134 (18)	135 (17)	138 (18)	0.10
Diastolic blood pressure (mmHg), mean (SD)[b]	79 (11)	78 (11)	80 (11)	80 (11)	0.24
Heart rate (1/min), mean (SD)[b]	66 (12)	67 (11)	67 (12)	66 (11)	0.74
Signs and symptoms of heart failure					
NYHA function class II, no. (%)	326 (86.0)	120 (84.5)	103 (85.1)	103 (88.8)	0.58
NYHA function class III, no. (%)	53 (14.0)	22 (15.5)	18 (14.9)	13 (11.2)	0.58
Peripheral oedema, no. (%)	153 (40.4)	64 (45.1)	36 (29.8)	53 (45.7)	0.02
Nocturia, no. (%)	310 (81.8)	121 (85.2)	99 (81.8)	90 (77.6)	0.29
Paroxysmal nocturnal dyspnoea, no. (%)	59 (15.6)	23 (16.2)	14 (11.6)	22 (19.0)	0.28
Nocturnal cough, no. (%)[b]	56 (14.8)	23 (16.2)	21 (17.4)	12 (10.4)	0.28
Fatigue, no. (%)	222 (58.6)	82 (57.7)	72 (59.5)	68 (58.6)	0.96
Laboratory measurements					
Sodium (mmol/L), mean (SD)[a]	140.27 (2.95)	140.03 (2.94)	140.04 (2.86)	140.79 (3.00)	0.02
Potassium (mmol/L), mean (SD)[a]	4.18 (0.39)	4.14 (0.40)	4.20 (0.38)	4.20 (0.41)	0.35
Haemoglobin (mmol/L), mean (SD)[c]	8.58 (0.77)	8.52 (0.74)	8.67 (0.81)	8.56 (0.76)	0.52
eGFR (mL/min/1.73 m^2), mean (SD)[c]	75.29 (18.72)	73.07 (18.09)	75.51 (19.21)	77.83 (18.81)	0.11
NT-proBNP (ng/L), median (IQR)[d]	169 (84–318)	190 (100–319)	133 (74–268)	174 (82–404)	0.60
High-intensity PA (>6 MET)					
<4 h/week, no. (%)	153 (40.4)	104 (73.2)	33 (27.3)	16 (13.8)	<0.001
4–8 h/week, no. (%)	111 (29.3)	37 (26.1)	58 (47.9)	16 (13.8)	
>8 h/week, no. (%)	115 (30.3)	1 (0.7)	30 (24.8)	84 (72.4)	

eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MET, metabolic equivalents of task; METh, MET hour; NT-proBNP, N-terminal proBNP; NYHA, New York Heart Association; PA, physical activity; SD, standard deviation. Patients are divided according to the amount of their total PA in metabolic equivalent of task hours per week.
[a]Number of subjects 377.
[b]Number of subjects 378.
[c]Number of subjects 376.
[d]Number of subjects 359.

We first analysed PA and clinical characteristics of HFpEF. Mean and standard deviation for groups of METh/week value are shown in *Table 2*. Patients of middle-level and high-level PA showed significantly higher SF-36 physical function scores (*P* = 0.04) and significantly greater 6MWT distances (*P* = 0.007) compared with those of low-level PA. However, there was no significant difference in the SF-36 physical function score or in the 6MWT distance between groups of middle and high levels of PA. Also, there was no significant difference in peakVO₂, E/e′, or LAVI between groups of different PA levels.

We further investigated the association of total PA (METh/week) and variables of CPET, 6MWT, blood testing, SF-36, and echocardiography (see *Table 3*). An increase in total PA is associated with higher maximum exercise level and duration, higher ventilatory efficacy [lower ratio of minute ventilation (VE) to carbon dioxide production (VCO₂), VE/VCO₂ slope], higher anaerobic threshold and higher oxygen uptake at the anaerobic threshold, higher 6MWT distance, and higher systolic blood pressure at rest and at maximum on 6MWT (*P* < 0.05). In addition, an increase in total PA is borderline significantly associated with higher SF-36 physical function scores (*P* = 0.05). Yet no significant associations between total PA and peakVO₂ or echocardiographic parameters of diastolic function were found, respectively. In addition, there was no significant association between total PA and NT-proBNP as indicators of functional HF severity.

We further assessed total PA, high-intensity PA, and clinical characteristics of HFpEF. Patients were additionally classified by tertile of weekly time of high-intensity PA into <4 h, 4–8 h, and >8 h of high-intensity PA per week. *Figure 1* shows mean for groups of total PA level (in METh/week) and for groups of high-intensity PA (in h/week). Patients with a low level of PA (<70 METh/week) showed significantly lower SF-36 physical function scores (*P* = 0.04) and significantly lower 6MWT distance (*P* = 0.007) than patients of middle and high levels of PA. In patients who performed high-intensity PA for >8 h/week, the SF-36 physical function score and 6MWT distance were both significantly higher than in those who performed it for 4–8 h/week or <4 h/week (*P* = 0.002 and *P* < 0.001, respectively). Also, the SF-36 physical function score was significantly lower in patients who performed high-intensity PA for <4 h/week than in

those who performed high-intensity PA for 4–8 h/week. In addition, patients who performed high-intensity PA for >8 h/week showed significantly higher peakVO₂ values than those who performed it for <4 h/week (*P* = 0.02), whereas no significant difference in peakVO₂ was observed among groups of total PA. The echocardiographic parameter of left ventricular filling E/e′ ratio was not significantly different among the groups of total PA and among groups of high-intensity PA.

We also investigated correlations between total PA, time of high-intensity PA, time of low-intensity PA, and clinical characteristics of HFpEF (see *Table 4*). A Pearson correlation analysis showed that the volume of PA is positively correlated with SF-36 physical function, although the significance is borderline (*r* = 0.10, *P* = 0.05), and with 6MWT distance (*r* = 0.17, *P* = 0.001) but has no significant correlation with peakVO₂. Time of high-intensity PA was positively correlated with 6MWT distance (*r* = 0.21, *P* < 0.001) and with peakVO₂ and SF-36 physical function (both *r* = 0.13, *P* = 0.01), whereas time of low-intensity PA did not show significant associations. Type and amount of PA were not significantly associated with any measure of diastolic function (E/e′ and LAVI).

Discussion

In this analysis, we describe two aspects regarding the association of PA and exercise capacity in HFpEF. The main finding of the study is that among all investigated parameters, only higher amounts of high-intensity PA were associated with higher values of maximal exercise capacity (measured by peakVO₂) in patients with HFpEF. Submaximal exercise capacity and physical function of QoL were positively correlated with total amount of PA (in METh/week) irrespective of intensity. Of interest, no association was identified between PA and echocardiographic parameters of diastolic function.

Study population

In Aldo-DHF, a total of 422 patients were included, 52% of which were female. This allowed a gender-independent

Table 2 Daily physical activity and clinical characteristics of heart failure with preserved ejection fraction: mean and standard deviation for groups of metabolic equivalents of task

Variable	Low MET value (<70 METh/week)	Middle MET value (>70 to 140 METh/week)	High MET value (>140 METh/week)	*P*-value
CPET peakVO₂ (ml/min/kg), mean (SD)	16.2 (3.6)	16.4 (3.6)	16.5 (3.4)	0.78
SF-36 physical function score, mean (SD)	59.6 (23.1)	63.3 (21.5)[a]	66.6 (20.7)[a]	0.04
6 min walking test distance (m), mean (SD)	512.5 (98.8)	541.5 (85.2)[a]	543.5 (64.0)[a]	0.007
Echocardiography E/e′ ratio, mean (SD)	13.1 (4.5)	12.4 (3.3)	13.1 (4.4)	0.39
Left atrial volume index (mL/m²)	28.1 (9.2)	27.5 (7.8)	29.2 (8.3)	0.30

CPET, cardiopulmonary exercise testing; MET, metabolic equivalents of task; METh, MET hour; peakVO₂, peak oxygen uptake; SD, standard deviation; SF-36, 36-item Short-Form questionnaire.
[a]Significant compared with low MET.

Table 3 Analysis of variance of metabolic equivalents of task effects on clinical characteristics of heart failure with preserved ejection fraction

Variable	Adjusted for age and sex	
	MET effect on variable (95% CI)	*P*-value
CPET		
Peak oxygen uptake (mL/min)	0.002 (−0.002 to 0.01)	0.37
Maximum level of watts (W)	0.03 (0.003 to 0.05)	0.03
Maximum exercise duration (s)	0.18 (0.04 to 0.31)	0.009
Anaerobic threshold (W)	0.04 (0.01 to 0.06)	0.003
Oxygen uptake at the anaerobic threshold (mL/min)	0.004 (0 to 0.01)	0.03
VE/VCO$_2$ slope	−0.01 (−0.01 to −0.001)	0.02
Respiratory minute volume (VE) (L)		
At rest	−0.001 (−0.004 to 0.001)	0.27
Maximum	−0.01 (−0.02 to 0.01)	0.26
Difference	−0.01 (−0.02 to 0.01)	0.35
Systolic blood pressure (mmHg)		
At rest	0.01 (−0.01 to 0.03)	0.48
Maximum	0.01 (−0.02 to 0.04)	0.36
Difference	0.01 (−0.02 to 0.04)	0.62
Diastolic blood pressure (mmHg)		
At rest	0.01 (−0.004 to 0.02)	0.20
Maximum	−0.002 (−0.02 to 0.02)	0.84
Difference	−0.01 (−0.03 to 0.01)	0.30
Heart rate (1/min)		
At rest	0.001 (−0.01 to 0.02)	0.91
Maximum	0.01 (−0.02 to 0.03)	0.59
Difference	0.01 (−0.01 to 0.02)	0.58
6 min walking test		
Distance (m)	0.14 (0.05 to 0.22)	0.002
Systolic blood pressure (mmHg)		
At rest	0.03 (0.01 to 0.05)	0.004
Maximum	0.04 (0.02 to 0.07)	<0.001
Difference	0.01 (−0.003 to 0.03)	0.11
Diastolic blood pressure (mmHg)		
At rest	0.01 (−0.002 to 0.02)	0.10
Maximum	0.01 (−0.004 to 0.02)	0.19
Difference	−0.001 (−0.01 to 0.01)	0.84
Heart rate (1/min)		
At rest	−0.01 (−0.02 to 0.004)	0.19
Maximum	−0.002 (−0.02 to 0.01)	0.83
Difference	0.01 (−0.004 to 0.02)	0.20
SF-36 scale		
Physical function	0.02 (−0.0003 to 0.05)	0.05
Laboratory measurements		
Log NT-proBNP (pg/mL)[a]	$6.00 * 10^{-5}$ (−$39.5 * 10^{-5}$ to 0.001)	0.80
Echocardiography		
E/e′ ratio	0.001 (−0.004 to 0.01)	0.76
Left atrial volume index (mL/m^2)	0.004 (−0.01 to 0.01)	0.36

CI, confidence interval; CPET, cardiopulmonary exercise testing; MET, metabolic equivalents of task; NT-proBNP, N-terminal proBNP; SF-36, 36-item Short-Form questionnaire; VE/VCO$_2$ slope, ratio of minute ventilation (VE) to carbon dioxide production (VCO$_2$).
[a]NT-proBNP shows right-skewed distribution in patients with HF and is therefore shown as log NT-proBNP.

analysis in a large number of patients, whereas previous studies on PA and exercise intervention showed a relatively small participant group.[17–19,29] Upon inclusion, all severe conditions other than HFpEF that could have been cause for reduced exercise capacity were excluded, e.g. significant arrhythmias or valve diseases, symptomatic coronary artery disease, anaemia, and severe pulmonary disease.[22] Exclusion criteria of the Aldo-DHF trial did not specifically consider orthopaedic limitations, but all patients had to perform CPET several times throughout the trial. Therefore, patients with severe orthopaedic limitations could not be included in the trial due to possible protocol violations.

Also, only 6.3% of all study participants reported current smoking. According to the microcensus of the Federal Statistical Office of Germany in 2009, the prevalence of smoking in Germany in the age class of 60–70 years was 20.6% for men and 13.6% for women.[30] The absence of severe disease other than chronic HF and underrepresentation of smokers in the study suggests a rather healthy and health-conscious, but still overweight, patient population (mean BMI 29 kg/m^2).

Median NT-proBNP plasma level in Aldo-DHF was 169 ng/L, which is lower than in other studies that analysed HFpEF patients, e.g. I-PRESERVE,[6] but higher than in healthy age-matched and sex-matched controls.[31] No association was

Figure 1 Mean for groups of total metabolic equivalents of task (MET) value (METh/week) and for groups of high-intensity physical activity (PA, in h/week): analysis of 36-item Short-Form questionnaire (SF-36) physical function score, 6 min walking test, peak oxygen uptake (peakVO$_2$), and echocardiographic parameter of left ventricular filling (E/e'); *Significant compared between two groups.
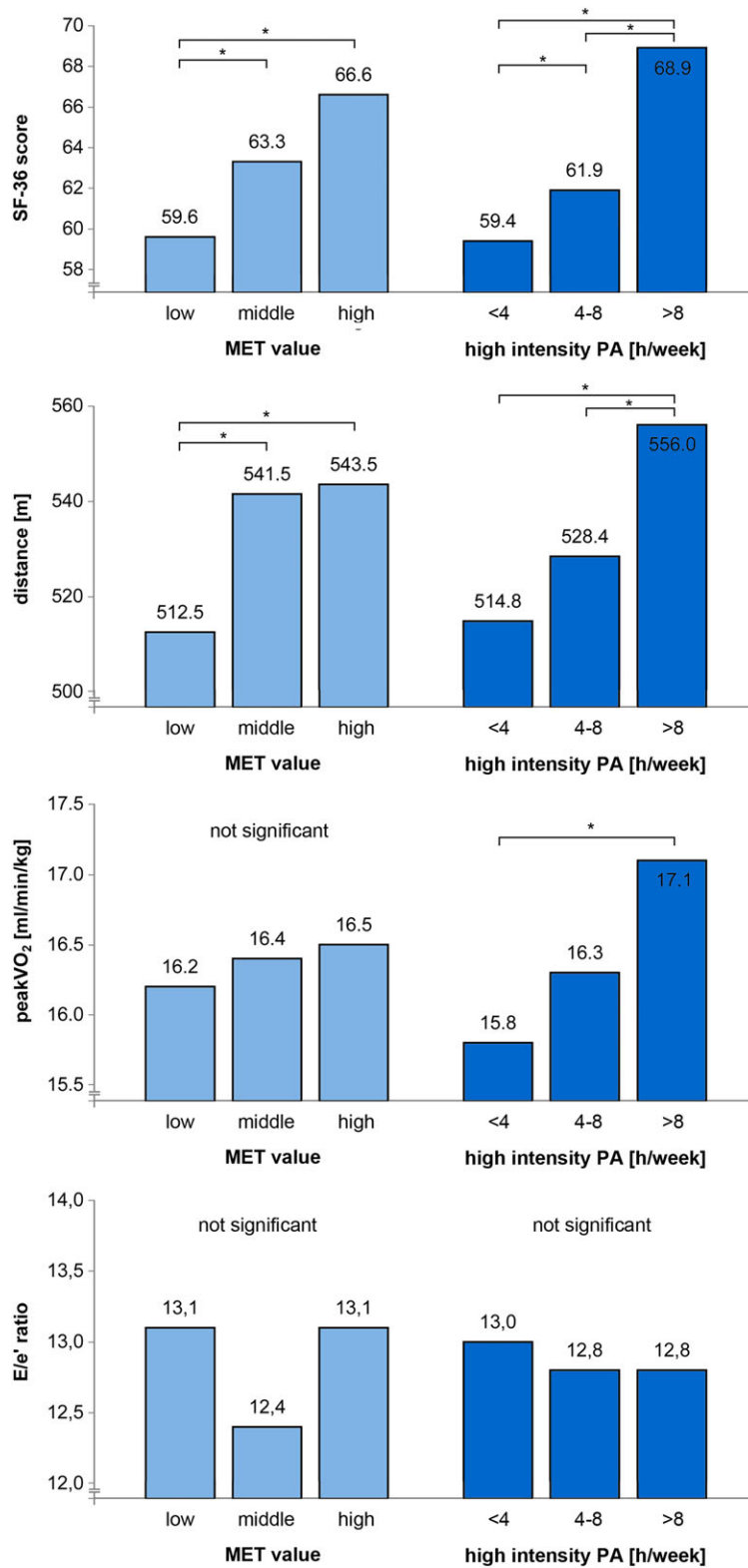
Table 4 Pearson correlation between clinical characteristics of heart failure with preserved ejection fraction and total metabolic equivalents of task or time of physical activity (high vs. low), respectively

Variable	Total MET (METh/week)		Time of high PA (h/week)		Time of low PA (h/week)	
	Correlation	P-value	Correlation	P-value	Correlation	P-value
CPET peakVO$_2$ (mL/min/kg)	0.06	0.29	0.13	0.01	−0.04	0.43
SF-36 physical function	0.10	0.05	0.13	0.01	0.04	0.40
6 min walking test distance (m)	0.17	0.001	0.21	<0.001	0.07	0.19
Echocardiography E/e′ ratio	0.004	0.94	0.02	0.66	−0.008	0.88
Left atrial volume index (mL/m^2)	0.04	0.49	0.08	0.13	−0.007	0.89

CPET, cardiopulmonary exercise testing; MET, metabolic equivalents of task; PA, physical activity; peakVO$_2$, peak oxygen uptake; SF-36, 36-item Short-Form questionnaire.

found between total amount of PA and NT-proBNP. Natriuretic peptide levels are low in obese patients.[32] BMI was high and comparable across all groups of total PA, which may explain the low values of natriuretic peptides. Since natriuretic peptides are valuable for identification of severe diastolic dysfunction, but not for mild or moderate diastolic dysfunction,[31,33] we may also conclude that the patients of our study did not present with severe diastolic dysfunction. This makes our results even more relevant since we analysed a study population with early-stage HFpEF where prevention strategies may still carry weight.

Physical activity and physical dimensions of quality of life

Previous studies have shown the harm of sedentary lifestyle and reduced physical fitness on the incidence of both HFrEF and HFpEF.[7,8,14] A clear dose dependency of PA on the risk of HF was shown,[8,11] and age-adjusted recommendations on the amount of PA were defined by the World Health Organization.[34] Furthermore, the positive effect of exercise training on the prognosis of HFrEF was shown in the large HF-ACTION trial.[10] In elderly HFpEF patients, regular exercise training was shown to improve self-rated physical dimensions of QoL, but not other aspects of QoL.[17–19,29] These data were consistent with our findings on the total amount of PA and SF-36 physical function score. Nevertheless, recommendations on the intensity of PA to prevent HFpEF and to improve QoL do not exist so far. Our study shows a clear dose dependency of high-intensity PA and physical dimensions of QoL in HFpEF, which was not found for total amount of PA (*Figure 1*).

Physical activity and exercise capacity

CPET and 6MWT were used to determine maximal and submaximal exercise capacity. Peak exercise testing variables of CPET exhibit good reliability in HFpEF and are therefore also recommended for the diagnostic workup in HFpEF.[35] PeakVO$_2$, which is known to be lower in HF patients than in

healthy individuals,[36] is an established predictor of outcome as well as a recommended target for treatment in these patients.[37]

To our knowledge, this study shows for the first time that not the total amount of PA but specifically the amount of high-intensity PA is associated with maximal exercise capacity in HFpEF. This finding gives the rationale for ongoing studies to investigate which particular exercise training schedule is optimal for HFpEF patients.[38]

Andersen *et al*. reported that the greatest benefit of PA in HF patients has been observed in changing from sedentary behaviour to moderate levels of activity, meaning from 0 to 3 METhs/day.[11] Keteyian *et al*. reported a significantly higher cardiovascular event rate in HFrEF patients with PA of <4 METh/week.[15] Our data confirm this by showing significantly higher self-rated physical dimensions of QoL and submaximal exercise capacity in patients with middle MET values than in those with low MET value (see *Figure 1*).

Several studies showed that exercise training improves maximal exercise capacity.[17,18,39] Patients underwent supervised training to improve aerobic endurance, and exercise intensity was increased after several weeks. According to the World Health Organization, these training interventions cannot be considered as high-intensity exercise.[40] Also, although the studies' trainings were performed only two to three times per week, an increase in peakVO$_2$ was seen in patients of the intervention group. Those results may contradict ours. We must note that in those studies change in peakVO$_2$ was seen over a period of time within patients who underwent training, whereas our data reflect only one point in time.

Physical activity and echocardiographic parameters

Although patients with higher amounts of high-intensity PA showed better maximum and submaximal exercise capacity and experienced better physical function in QoL, no differences in echocardiographic parameters of diastolic function were found. Also, our results did not show any association between E/e′ and PA. This agrees with previous finding where throughout several exercise training trials in HFpEF,

the impact of exercise training on diastolic function still remains unclear.[18,19,39] Kitzman *et al.* did not see any change in echocardiographic parameters for diastolic function in patients undergoing exercise training,[18,39] whereas our previous Exercise Training in Diastolic Heart Failure (Ex-DHF) pilot trial described a significant decrease of E/e′ and LAVI in the training group compared to the control group.[19] However, in our Ex-DHF pilot study, we analysed the change of echocardiographic parameters for every study participant over a period of time, whereas the present analysis was performed inter-individually at one point in time. Therefore, E/e′ might be sufficient for long-term assessment of diastolic function within an individual, but unreliable when compared cross-sectionally among different individuals. A further search for new measurement of diastolic function should be considered.

Limitations

Several limitations should be mentioned. Firstly, this work constitutes a post hoc analysis and is therefore to be viewed as exploratory. Whether all statistically significant associations are of clinical importance should be assessed in the future. Nevertheless, it illuminates valuable findings that should be further analysed.

Since echocardiography and CPET were performed twice within 1 week and PA, exercise capacity and QoL were assessed once all data were collected at only one point in time. This snapshot of health and training status in HFpEF patients is valuable but requires careful consideration.

PA was assessed by SF-36 and PAQ-AI asking for PA during the past 4 weeks. Although the questionnaire is not validated yet, PAQ-AI was adapted from a well-validated questionnaire[27] and can provide a useful tool because (in contrast to its precursor) it assesses intensity of PA and enables calculation of MET values. Still, since it is based on self-report, it should be viewed with wariness. For further investigation, a more objective method for PA quantification, e.g. accelerometry, should be added, although SF-36 correlates with accelerometry data on PA.[26]

Also, it is unclear whether patients with high exercise capacity may be able to push themselves harder in their PA and therefore report higher amounts of high-intensity PA or whether the higher amount of high-intensity PA acts as a training effect and therefore leads to a higher exercise capacity.

HFpEF is more common in elderly women. In previous studies, the number of female participants was relatively high and representative of the usual patient population in HFpEF.[17–19,29] In our study, only half of all participants were female, which may be considered distorted. However, due to the large number of patients, we view both genders as well represented.

Conclusions

In patients with HFpEF, the total amount of PA is related to submaximal exercise capacity and physical dimensions of QoL, but not to maximal exercise capacity. In contrast, only high-intensity exercise is associated with maximal exercise capacity in HFpEF patients. Therefore, to improve maximal exercise capacity in HFpEF, high-intensity training in daily life should be compared with lower intensity of the same volume in future randomized exercise intervention trials in order to determine the optimal dose in primary and secondary preventions of HFpEF.

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Conflict of interest

None declared.

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References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259.
2. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology

and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2008; **117**: 2544–2565.

3. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.

4. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure. *Circulation* 2006; **114**: 397–403.

5. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. *Eur Heart J* 2006; **27**: 2338–2345.

6. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467.

7. Kraigher-Krainer E, Lyass A, Massaro JM, Lee DS, Ho JE, Levy D, Kannel WB, Vasan RS. Association of physical activity and heart failure with preserved vs. reduced ejection fraction in the elderly: the Framingham Heart Study. *Eur J Heart Fail* 2013; **15**: 742–746.

8. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, De Lemos JA, Berry JD. Dose–response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation* 2015; **132**: 1786–1794.

9. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, Berry JD. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol* 2017; **69**: 1129–1142.

10. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA. Efficacy and safety of exercise training in patients with chronic heart failure. *JAMA* 2009; **301**: 1439–1450.

11. Andersen K, Mariosa D, Adami H-O, Held C, Ingelsson E, Lagerros YT, Nyren O, Ye W, Bellocco R, Sundstrom J. Dose–response relationship of total and leisure time physical activity to risk of heart failure: a prospective cohort study. *Circ Heart Fail* 2014; **7**: 701–708.

12. Piepoli MF. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**: 189.

13. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, Schoene N, Schuler G. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA* 2000; **283**: 3095.

14. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, DeFina L, Willis B. Physical fitness and risk for heart failure and coronary artery disease. *Circ Heart Fail* 2013; **6**: 627–634.

15. Keteyian SJ, Leifer ES, Houston-Miller N, Kraus WE, Brawner CA, O'Connor CM, Whellan DJ, Cooper LS, Fleg JL, Kitzman DW, Cohen-Solal A, Blumenthal JA, Rendall DS, Piña IL. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol* 2012; **60**: 1899–1905.

16. Benda NM, Seeger JP, Stevens GG, Hijmans-Kersten BT, Van Dijk AP, Bellersen L, Lamfers EJ, Hopman MT, Thijssen DH. Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. *PLoS One* 2015; **10**: 1–16.

17. Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, Neelon V, McMurray R. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung* 2002; **33**: 210–218.

18. Kitzman DW, Brubaker PH, Morgan TM, Kathryn P, Little WC, Carolina N. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail* 2010; **3**: 659–667.

19. Edelmann F, Gelbrich G, Düngen H-D, Fröhling S, Wachter R, Stahrenberg R, Binder L, Töpper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Löffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2011; **58**: 1780–1791.

20. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen A-I, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017; **135**: 839–849.

21. Pattyn N, Vanhees L, Cornelissen VA, Coeckelberghs E, De Maeyer C, Goetschalckx K, Possemiers N, Wuyts K, Van Craenenbroeck EM, Beckers PJ. The long-term effects of a randomized trial comparing aerobic interval versus continuous training in coronary artery disease patients: 1-year data from the SAINTEX-CAD study. *Eur J Prev Cardiol* 2016; **23**: 1154–1164.

22. Edelmann F, Schmidt AG, Gelbrich G, Binder L, Herrmann-Lingen C, Halle M, Hasenfuss G, Wachter R, Pieske B. Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in PA. *Eur J Heart Fail* 2010; **12**: 874–882.

23. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen H-D, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013; **309**: 781.

24. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Ann Hunt S, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. *Circulation* 2003; **108**: 1146–1162.

25. Ware JE, Kosinski M, Dewey JE. *How to Score Version 2 of the SF-36 Health Survey (Standard and Acute Forms)*, 3rd ed. Lincoln, RI: QualityMetric; 2002.

26. Johansen KL, Painter P, Kent-Braun JA, Ng AV, Carey S, Da Silva M, Chertow GM. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int* 2001; **59**: 1121–1127.

27. Frey I, Berg A, Grathwohl D, Keul J. Freiburger Fragebogen zur körperlichen Aktivität-Entwicklung, Prüfung und Anwendung. *Sozial- und Präventivmedizin SPM* 1999; **44**: 55–64.

28. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-locke C, Greer JL, Vezina J, Whitt-glover MC, Leon AS. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011; **43**: 1575–1581.

29. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. *Congest Heart Fail* 2012; **18**: 295–301.

30. Mikrozensus - Fragen zur Gesundheit: Rauchgewohnheiten der Bevölkerung 2009, Wiesbaden, 2010.

31. Costello-Boerrigter LC, Boerrigter G, Redfield MM, Rodeheffer RJ, Urban LH, Mahoney DW, Jacobsen SJ, Heublein DM, Burnett JC. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community determinants and detection

of left ventricular dysfunction. *J Am Coll Cardiol* 2006; **47**: 345–353.

32. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PWF, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004; **109**: 594–600.

33. Lüers C, Trippel TD, Seeländer S, Wachter R, Hasenfuss G, Lindhorst R, Bobenko A, Nolte K, Pieske B, Edelmann F. Arterial stiffness and elevated left ventricular filling pressure in patients at risk for the development or a previous diagnosis of HF-A subgroup analysis from the DIAST-CHF study. *J Am Soc Hypertens* 2016; **49**: 1–11.

34. World Health Organization, WHO | Physical activity, WHO, 2017. http://www.who.int/mediacentre/factsheets/fs385/en/ (23 Jul 2016).

35. Scott JM, Haykowsky MJ, Eggebeen J, Morgan TM, Brubaker PH, Kitzman DW. Reliability of peak exercise testing in patients with heart failure with preserved ejection fraction. *Am J Cardiol* 2012; **110**: 1809–1813.

36. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, Levine BD. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011; **13**: 1296–1304.

37. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, Fowler MB. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. *Am Heart J* 2000; **139**: 78–84.

38. Suchy C, Massen L, Rognmo Ø, Van Craenenbroeck EM, Beckers P, Kraigher-Krainer E, Linke A, Adams V, Wisløff U, Pieske B, Halle M. Optimising exercise training in prevention and treatment of diastolic heart failure (OptimEx-CLIN): rationale and design of a prospective, randomised, controlled trial. *Eur J Prev Cardiol* 2014; **21**: 18–25.

39. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2013; **62**: 584–592.

40. World Health Organization, What is moderate-intensity and vigorous-intensity physical activity? WHO, 2014. http://www.who.int/dietphysicalactivity/physical_activity_intensity/en/ (29 Mar 2016).