Participation in an Exercise-Based Cardiac Rehabilitation Program and Functional Improvement of Heart Failure Patients with Preserved Versus Reduced Left Ventricular Systolic Function

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ABSTRACT: **Background:** About half of all patients with heart failure are diagnosed with heart failure preserved ejection fraction (HFpEF). Until now, studies have failed to show that medical treatment improves the prognosis of patients with HFpEF.
Objectives: To evaluate changes in exercise capacity of patients with HFpEF compared to those with heart failure with reduced ejection fraction (HFrEF) following an exercise training program.
Methods: Patient data was retrieved from a multi-center registry of patients with heart failure who participated in a cardiac rehabilitation program. Patients underwent exercise testing and an echocardiogram prior to entering the program and were retested 6 months later.
Results: Of 216 heart failure patients enrolled in the program, 170 were diagnosed with HFrEF and 46 (21%) with HFpEF. Patients with HFpEF had lower baseline exercise capacity compared to those with HFrEF. Participating in a 6 month exercise program resulted in significant and similar improvement in exercise performance of both HFpEF and HFrEF patients: an absolute metabolic equivalent (MET) change (1.45 METs in HFrEF patients vs. 1.1 in the HFpEF group, $P = 0.3$).
Conclusions: An exercise training program resulted in similar improvement of exercise capacity in both HFpEF and HFrEF patients. An individualized, yet similarly structured, cardiac rehabilitation program may serve both heart failure groups, providing safety and efficacy.

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KEY WORDS: cardiac rehabilitation, exercise capacity exercise training, heart failure, preserved systolic function

Heart failure is a complex syndrome with varied ethology. Despite significant advances in diagnosis and management, morbidly and mortality remain high and impose a great burden on patients and the community [1,2]. One of the principal determinants of reduced quality of life, functional impairment, and disability is reduced functional capacity by complex interaction of induced symptoms and abnormal response to exercise [3-5]. About half of all patients with heart failure are diagnosed with heart failure with preserved ejection fraction (HFpEF) [6]. Unlike heart failure with reduced ejection fraction (HFrEF), studies have failed to show that pharmacotherapy improves the prognosis of patient with HFpEF or significantly improves functional capacity [7].

It is well documented that exercise training reduces heart failure-related hospitalizations and improves health-related quality of life for patients with HFrEF compared to usual care [8]. Similarly, exercise training has been shown to improve exercise capacity and quality of life in patients with HFpEF [9,10]; however, the degree of functional improvement in patients with heart failure classified as HFpEF vs. HFrEF have not been prospectively compared. Functional improvement remains a major goal of any intervention as even modest increases in exercise capacity are strongly correlated with clinical outcomes in varied populations, including patients with heart failure [11-13].

The purpose of the present study was to describe baseline characteristics and exercise parameters of patients with heart failure, evaluate changes in exercise capacity following a 6 month structured exercise training program using the same pre-specified exercise and management protocol in patients with HFpEF and HFrEF, compare functional changes as determined by exercise stress tests, and describe exercise-related adverse events and clinical outcomes in these heart failure patient populations.

PATIENTS AND METHODS

STUDY POPULATION

Patient data was derived from a prospective multi-center registry from five rehabilitation departments between April 2013 and June 2014. This registry was designed to assess characteristics and outcomes of patients with heart failure referred to institution-based cardiac rehabilitation programs. Patients with clinical diagnosis of heart failure were referred by treating cardiologists and included in the registry following verification of enrollment criteria. All participants provided informed consent.

For the present analysis we selected patients participating in an exercise training program who had undergone a symptom-limited exercise testing program before exercise training and another one after 6 months of training. Patients had a detailed echocardiogram prior to entering the program.

DEFINITIONS

Heart failure is a clinical diagnosis established by the referring cardiologist according to signs (elevated jugular venous pressure, peripheral edema, or pulmonary congestion) and symptoms of heart failure or prior hospitalization due to heart failure. In our study, optimization of treatment was performed in accordance with the European Society of Cardiology (ESC) heart failure guidelines prior to rehabilitation referral. All subjects underwent an echocardiographic examination and standard blood tests, including blood count and chemistry prior to study enrollment.

HFpEF was defined as pre-specified signs and symptoms of heart failure (not otherwise explained by alternative diagnosis) and left ventricular ejection fraction (LVEF) ≥ 50% per echocardiography within 1 month of enrollment. Exclusion criteria for this study included valvular abnormality > mild (per echocardiography), chronic obstructive pulmonary disease (COPD) > mild (prior pulmonary function test or medical record), uncontrolled hypertension, angina class > 2, severe morbid obesity (body mass index [BMI] > 40), and marked orthopedic or neurological limitations.

EXERCISE PROTOCOL AND CLINICAL MANAGEMENT

Patients participated in a 6 month cardiac rehabilitation program, which consisted of structured 60 minute bi-weekly exercise training sessions according to a predefined protocol that was individualized according to the ESC heart failure rehabilitation consensus paper [14]. Exercise prescription was based on a symptom limited exercise stress test (Bruce or modified Bruce) that was individually prescribed by senior exercise physiologists. In addition, all patients consulted with cardiologists, dietitians, and nursing staff. Psychological support was available to all patients.

After 5–10 minutes warm-up, aerobic exercise training was performed at moderate to high exercise intensity for up to 45 minutes. Starting target heart rate goal was 40–50% of heart rate reserve (HRR) with a gradual increment up to 70–80% of HRR while subjectively maintaining an exertion level of 12–14/20 on the Borg rate of perceived exertion (RPE) scale. The exercise training session ended with a 5 minute cool-down phase. Resistance training was 15 minutes, exercising large muscle groups, mainly the chest, shoulder girdle, and hip musculature, with an intensity permitting initially 10–12 repetitions and later 15–18, with an RPE of up to 15 according to the Borg scale. Special attention was given to prevent abdominal straining (valsalva maneuver). Institution-based exercise consisted of aerobic training using a treadmill, bicycle, and recumbent stepper in addition to low intensity endurance training with weights, elastic bands, and balls. The same protocol was used for all subjects regardless of systolic function, and they exercised together in groups designated for heart failure patients. Patients were encouraged to complement institution-based training with an additional 120 minutes of light to moderate activity weekly.

After 6 months of program participation, all subjects underwent a second symptom limited stress test and clinical evaluation by a rehabilitation physician. Most (69%) also underwent a second echocardiographic examination. After the active training period, most (78%) continued exercise in the community under the care of their family physician and cardiologist while 23% continued to exercise in a hospital-based setting.

ENDPOINTS

The primary endpoint selected was change in exercise capacity expressed in estimated metabolic equivalents (METS). Secondary endpoints included time to first heart failure hospitalization or death, change in New York Heart Association (NYHA) functional class, change in LVEF and left atrial area (LAA), and all-cause mortality.

Clinical events were recorded by research personal through contact with patients, primary care physicians, and hospital records. We collected follow-up information for 96% of subjects. Mortality data was obtained from the national population registry by matching national identification numbers.

STATISTICAL ANALYSIS

Normally distributed continuous data are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median with 25th–75th percentiles. Categorical variables are presented as percentage and compared using the chi-square test. Continues values were compared by Student's t-test, or Mann–Whitney U test for non-normally distributed variables. For the description of effects, we presented changes in absolute values and percent changes from the baseline value.

All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

BASELINE CHARACTERISTICS

We prospectively enrolled 216 consecutive stable heart failure patients who completed an echocardiographic evaluation and a symptom limited exercise stress test (EST). Of these 216 patients, 170 had HFrEF and 46 (21%) fulfilled definitions for HFpEF. Patient baseline characteristics are summarized in Table 1. As expected, HFpEF patients were mostly women with low prevalence of prior myocardial infarction and past CABG compared to patients with HFrEF, and were more likely to have a history of COPD, atrial fibrillation, or flutter, and they had a higher BMI. Patients with HFrEF were more likely to be treated with angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), beta blockers, and mineralocorticoid receptor antagonists (MRA) compare to HFpEF patients. Both groups were of similar age and presented comparable rates of diabetes, peripheral vascular disease (PVD), and smoking status.

Table 1. Patient characteristics

	HFpEF n=46	HFrEF n=170	*P* value
Age (mean ± SD)	65 ± 14	64 ± 12	0.7
BMI (kg/m2)	29.3 ± 5.5	27.5 ± 4.9	0.005
Female gender (%)	55	16	0.0001
DM (%)	41	47	0.65
Dyslipidemia (%)	63	74	0.11
Hypertension (%)	68	66	0.95
Current smoker (%)	6.4	8.3	0.53
Past smoker (%)	28	37	0.18
Past CVA (%)	13	13	0.95
CRF (%)	15.4	21.5	0.47
COPD (%)	19.2	9.5	0.038
Past MI (%)	13	57	0.0001
Past CABG (%)	11.5	28	0.009
PVD (%)	7.7	9.7	0.80
LVEF (%)	60 ± 6	30 ± 8	0.0001
LVESD (mm)	27 ± 5	45 ± 11	0.0001
LA area (cm2)	25 ± 5	24 ± 6	0.81
SPAP (mm Hg)	37 ± 11	37 ± 12	0.95
ACEI or ARB (%)	49	83	0.0001
Beta blockers (%)	65	89	0.0001
MRA (%)	23	44	0.0001
Warfarin (%)	37	26	0.07

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, CVA = cerebrovascular accident, DM = diabetes mellitus, HFpEF = heart failure preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LA = left atrium, LVEF = left ventricular ejection fraction, LVESD = left ventricular end systolic diameter, MI = myocardial infarction, MRA = mineralocorticoid receptor antagonist, PVD = peripheral vascular disease, SD = standard deviation, SPAP = systolic pulmonary artery pressure

Table 2. Baseline and post training parameters

	HFpEF			HFrEF		
	Baseline	Follow-up visit	*P* value	Baseline	Follow-up visit	*P* value
Exercise duration*	5:51 ± 3	6:32 ± 2.7	‹ 0.001	6:46 ± 3	8:22 ± 2.6	‹ 0.001
METS	4.91 ± 2.4	6.39 ± 2.5	0.001	6.14 ± 3.1	7.75 ± 2.9	0.001
HRR, mean	45.7 ± 17.6	59.2 ± 16.9	0.01	44.1 ± 21.7	47.4 ± 22.1	0.04
LVEF (%)	60 ± 6	58.7 ± 6.3	0.4	30 ± 8	35.6 ± 10	0.001
LA area (cm2)	25 ± 5	24.5 ± 4	0.1	24 ± 6	24 ± 6	0.4

HFpEF = heart failure preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HRR = heart rate reserve, LA = left atrium, LVEF = left ventricular ejection fraction, METS = metabolic equivalents

*expressed in minutes:seconds

EXERCISE STRESS TEST RESULTS

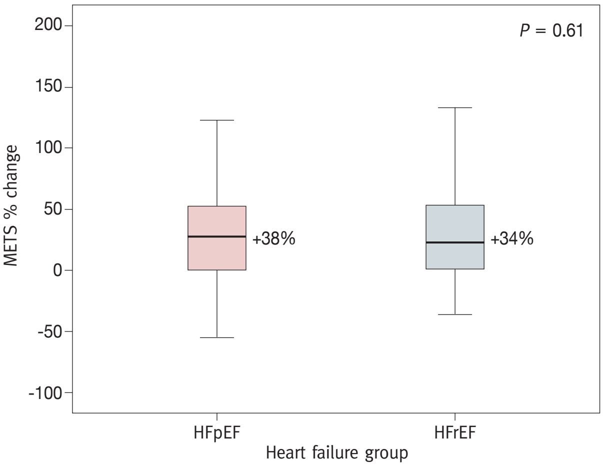
Patients with HFpEF had lower baseline exercise capacity as expressed by METS and shorter EST duration, yet heart rate reserve was similar to subjects with HFrEF [Table 2].

Six months of participation in an exercise training program resulted in significant improvement in exercise performance of both HFpEF and HFrEF patients [Table 2]. Overall exercise performance of HFrEF patients was higher than HFpEF patients ($P < 0.001$); however, the magnitude of improvement was similar in both groups, with an absolute change of 1.45 METS in the HFrEF patients compare to 1.1 METS in the HFpEF group ($P = 0.3$). Consistently, HRR was similar between the two groups, as was the maximal heart rate achieved on the second stress test. Both groups improved their HRR, whereas the improvement in the HFpEF was relatively greater.

When we compared METS percent change (baseline METS subtracted from follow-up EST estimated METS divided by the baseline METS), the two groups (HFpEF vs. HFrEF) improved by a similar extent (34% vs. 38%; $P = 0.61$) [Figure 1]. In addition, HFrEF patients had a significant improvement of LVEF (+5.6%; $P < 0.01$), which was not observed in the HFpEF group.

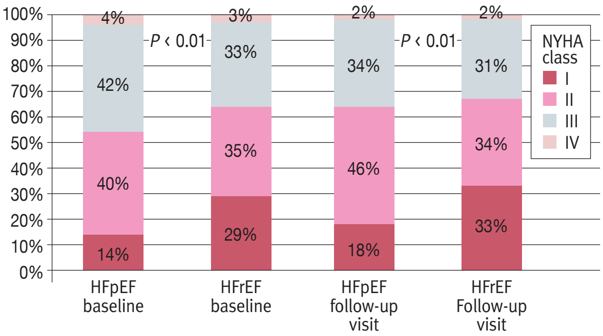
Changes in functional status as evaluated by NYHA functional classifications are presented in Figure 2.

Figure 1. Percent change in functional capacity of both HFpEF and HFrEF patients after participation in an exercise training program



HF = heart failure, HFpEF = heart failure preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, METS = metabolic equivalents

Figure 2. Changes in NYHA class from baseline to follow up evaluation



HFpEF = heart failure preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association

CLINICAL EVENTS

During the 29 month median follow-up period, 169 hospital admissions occurred (event rate of 45% in HFrEF groups vs. 43% in HFpEF, log rank $P = 0.42$), mostly due to heart failure-related hospitalizations (73%). All-cause mortality rates were similar between the HFrEF and HFpEF groups (18 and 3 events, respectively; $P = 0.18$). Exercise-related events were rare, with five minor trauma events that did not necessitate referral to the emergency department or management beyond examination and observation (3 in the HFpEF group and 2 in the HFrEF group).

During the 6 month active training period, medication changes were equally performed in subjects with and without functional improvement (16% vs. 14% overall dose or drug change, $P = 0.44$).

DISCUSSION

Our study recorded a number of important findings: exercise training programs improve exercise capacity in both HFpEF and HFrEF patients, the magnitude of improvement is similar in both groups despite the fact that HFpEF patients have lower baseline fitness, and an individualized yet similarly structured cardiac rehabilitation program can serve both heart failure groups, providing both safety and efficacy.

It is well documented that patients with HFpEF are different from patients with HFrEF. HFpEF patients are older, mostly female (60%) with hypertension (60–80%) and relatively low prevalence (less than 25%) of prior myocardial infarction [6,15-17]. Patients with HFpEF included in the present study had similar characteristics to those described in the medical literature [18,19].

A number of inherent differences exist between HFpEF and HFrEF stemming from differences in pathophysiological mechanisms responsible for the different cardiac abnormalities [19]; nevertheless, a number of similar abnormalities have been demonstrated in both. Importantly LV filling pressures increase proportionally with greater effort. Chronotropic reserve is blunted in both HFpEF and HFrEF, as is stroke volume reserve related to reduced ability to reduce LV end-systolic volume. Indeed, in our study patients with HFrEF had lower increase in HRR compared to HFpEF group. The more prevalent beta-blocker treatment could also have contributed to this finding. Peripheral abnormalities such as sympathetic vasoconstriction, endothelial dysfunction, reduced muscle oxygen diffusion, sarcopenia, and systemic inflammatory reaction are present in both conditions. A number of these abnormalities have been shown to be partially reversible [20]. While most of this evidence is derived from studies with HFrEF subjects [21,22], evidence from subject with HFpEF is rapidly increasing [19].

We have shown that significant functional and clinical improvements in HFpEF and HFrEF support the importance of these changes in the pathophysiological process. In the vast majority of exercise training studies, functional capacity in control groups did not improve, and actually a small decline has been frequently noted [20]. Even in the interventional arm, when program adherence was low, only minor improvements in exercise capacity were noted, as was the case in the largest heart failure exercise training study of patients with HFrEF: the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study (0.7 ml/kg/min peak VO2 increase in the intervention arm vs. 0.1 ml/kg/min in the control group) [20]. Indeed subjects who adhered to the exercise goals in the HF-ACTION trial enjoyed a marked reduction in heart failure hospitalizations and mortality [23]. Furthermore, clinical benefit was tightly correlated to the amount and intensity of exercise performed during the study [24]. In our study, the increase in functional capacity in both HFpEF and HFrEF patients (1.1 METs, ~3.85 ml/kg/min) is somewhat larger than reported values from two meta-regression analysis studies: one of subjects with HFpEF (2.72 ml/kg/min) [24] and the other performed in subjects with HFrEF (2.79 ml/kg/min) [25]. Average adherence in our cohort was good, approximately 72% and 80% of appointment in the HFpEF and HFrEF groups, respectively (P = NS).

Lack of function improvement following exercise programs has also been shown to be a strong indicator for poor prognosis [14]. Our cohort experienced a significant improvement in percent change from baseline METS, yet it is possible that prognosis is more tightly correlated to final result (second METS value) than the relative improvement. Aslanger and colleagues [13] demonstrated that the prognostic value of peak exercise oxygen consumption following an exercise training programs carries a greater prognostic value than baseline results and that functional improvement resulted in fewer cardiac events. Greater relative gain (percent change in METS) in exercise capacity has been reported in HFrEF cohorts, yet in our study gain was similar despite lower baseline functional capacity in the HFpEF group, perhaps due to multiple co-morbidities in the HFpEF group. We have shown that heart failure patients with preserved or reduced systolic function can exercise to obtain meaningful functional gain and that these improvements, based on previous results, are likely to result in clinically important benefits.

LIMITATIONS

Our study has a number of limitations. First, functional capacity was estimated according to well-recognized and validated formulas but not directly measured by a cardiopulmonary exercise test. Second, diagnosis of HFpEF was based on clinical findings and preserved systolic function and did not include biomarker assessment or stringent echocardiographic criteria based on mitral inflow patterns by Doppler or tissue Doppler; nevertheless, most of our subjects presented with diastolic abnormality or abnormal left atrial dimensions (72%). Our scope was to include subjects based on simple, easily reproducible criteria without the need for more complex or costly evaluations. Indeed numerous large prospective studies utilized similar criteria without evidence of diastolic abnormalities per echocardiography. Third, our present analysis excluded 28 subjects who did not complete the cardiac rehabilitation program due to non-medical reasons (mostly adherence, costs, or administrative difficulties). Forth, the number of subjects with HFpEF is relatively small in comparison with the HFrEF group. Our study also lacks the statistical power to evaluate hard clinical endpoints such as death or hospitalizations.

CONCLUSIONS

Despite lower initial functional capacity, absolute functional improvement and percent improvement are similar between HFpEF and HFrEF following a structured CR intervention. Functional class improvements following cardiac rehabilitation were similar in the groups. Our results support inclusion of HFpEF patients in exercise-based cardiac rehabilitation programs. Further research is needed to assess whether this functional gain will result in a similar improvement in clinical outcomes as well.

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