

# Impact of cardiac rehabilitation on patients with heart failure with preserved ejection fraction

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## Abstract

**Background:** Heart failure with preserved ejection fraction (HFpEF) represents more than one half of the heart failure cases worldwide with increased morbidity and mortality. No proven medical treatment till now has shown mortality benefit in HFpEF. This study aims to elucidate the benefit of cardiac rehabilitation (CR) in HFpEF.

**Methods:** 60 patients with HFpEF included in 2 groups with 1:1 randomization. Group 1 received usual medical care plus 2-3 rehabilitation sessions per week using moderate exercise with 40-75% of heart rate reserve on treadmill (up to 60 minutes according to the functional capacity). Group 2 received only usual medical care. Comparison between the 2 groups using the percentage of improvement in echocardiographic diastolic function parameters, Minnesota living with heart failure questionnaire (MLWHFQ) and 6 -minute walk test at baseline and after 12 weeks.

**Results:** Group 1 showed significant improvement in the following: a. MLWHFQ (total score mean percentage of reduction)  $305.60 \pm 158.44$  versus (*vs.*)  $69.44 \pm 17.71$  ( $p < 0.001$ ). b. E/e' mean percentage of reduction  $65.96 \pm 34.55$  *vs.*  $18.23 \pm 13.98$  ( $p < 0.001$ ). c. Left atrial (LA) volume index mean percentage of reduction  $27.86 \pm 13.27$  *vs.*  $8.03 \pm 4.40$  ( $p < 0.001$ ). d. Pulmonary artery systolic pressure mean percentage of reduction was  $33.85 \pm 14.68$  *vs.*  $22.97 \pm 16.54$  ( $p = 0.02$ ). e. 6-minute walk test  $111.79 \pm 40.97$  *vs.*  $46.33 \pm 11.58$  ( $p < 0.001$ ). f. Body mass index percentage of reduction  $10.17 \pm 3.64$  *vs.*  $2.80 \pm 1.60$  ( $p < 0.001$ ). g. Percentage of patients with down-grading of the degree of diastolic dysfunction 10 patients (33.3%) *vs.* 3 patients (10%) ( $P = 0.028$ ). h. No significant difference in left ventricular ejection fraction or other parameters as E/A ratio, LA dimension, isovolumetric relaxation time, degree of left ventricular hypertrophy.

**Conclusion:** CR not only added significant functional improvement in the quality of life and functional capacity but also a significant structural improvement by improving the core items of diastolic function. In the Light of this study, we recommend CR in HFpEF management.

**Abbreviations:** HFpEF: Heart Failure preserved Ejection Fraction; HF: Heart Failure; HFrEF: Heart Failure reduced Ejection Fraction; HTN: Hypertension; DM: Diabetes Mellitus; AF: Atrial Fibrillation; ET: Exercise Training; CR: Cardiac Rehabilitation; CRF: Cardio Respiratory Fitness; AHA: American Heart Association; ACC: American College of Cardiology; ESC: European Society of Cardiology; COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; EDT: mitral E velocity Deceleration Time; IVRT: Isovolumetric Relaxation Time; DD: Diastolic Dysfunction; PASP: Pulmonary Artery Systolic Pressure; EF: Ejection Fraction; CW: Continuous Wave; TR: Tricuspid Regurge; TDI: Tissue Doppler Imaging; LA: Left Atrium; QOL: Quality Of Life; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; 6MWT: six-Minute Walk Test; HR: Heart Rate; TTE: TransThoracic Echocardiography; LVH: Left Ventricular Hypertrophy.

## Background

The incidence of Heart Failure with preserved ejection fraction (HFpEF) is growing globally. Recent trials show that approximately 50 % of Heart failure (HF) hospitalized patients have HFpEF [1,2]. The prevalence of HFpEF in an Egyptian cohort of hospitalized patients with heart failure was 22% [3]. Women were more likely to present with HFpEF than were men (29.7% *vs.* 10.6%,  $P < 0.001$ ) [4].

The main clinical characteristics of HFpEF patients according to data of previous HF surveys are old age, female gender, Hypertension (HTN), diabetes mellitus (DM) and atrial fibrillation (AF) [5].

Although current pharmacological and device therapies showed beneficial effects in heart failure with reduced ejection fraction (HFrEF) patients regarding reduction in mortality, morbidity, hospitalization, and improvement of quality of life, they failed to show the same beneficial effects in HFpEF patients especially mortality reduction [6-8].

Exercise training (ET) based cardiac rehabilitation (CR) is documented to have beneficial effects among HFrEF patients in the form of better quality of life and exercise capacity [9,10].

The main impact of CR in heart failure patients is the improvement in the cardiorespiratory fitness (CRF) which could be due to reversing cardiac remodeling and amelioration of diastolic function especially in elderly patients [11,12].

The American Heart Association (AHA) and the American College of Cardiology (ACC) consider CR class I indication for HFrEF patients while HFpEF patients are not supported by the current guidelines [5]. The rationale beyond this that all previous large, randomized trials excluded HFpEF patients.

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Recently few randomized controlled trials including small number of patients showed beneficial impact of CR on HFpEF patients [12].

In this study we aimed to evaluate the impact of CR added to the standard medical therapy versus standard medical therapy alone on the functional aspects (quality of life and functional capacity) and the structural aspects (diastolic and systolic function parameters) of HFpEF patients.

## Methods

### Study design

This was a prospective randomized controlled study (1:1 randomization) conducted on 60 HFpEF patients who presented to Alexandria Main University hospital, Alexandria, Egypt between 1<sup>st</sup> July and 31<sup>st</sup> December 2019. The inclusion criteria were established diagnosis HFpEF defined according to the last European society of cardiology (ESC) recommendations [13]. While the exclusion criteria were haemodynamically significant valvular disease, acute coronary syndrome as the primary diagnosis, end stage heart failure, severe renal dysfunction (eGFR < 30 ml/min/1.73m<sup>2</sup> or renal replacement therapy), severe chronic obstructive pulmonary disease (COPD) or asthma, cognitive decline or major psychiatric pathology, non-ambulatory conditions and orthopedic problems interfering with exercise and life expectancy < 12 months.

Patients were divided into two groups

**Group 1:** Included 30 HFpEF patients receiving CR plus pharmacological therapies.

**Group 2:** Included 30 HFpEF patients receiving pharmacological therapies only.

### Data collection

Regarding demographic data, we registered age, gender, associated comorbidities such as hypertension, diabetes, atrial fibrillation, prior hospitalization with heart failure and smoking.

### Functional class assessment

We used the New York Heart Association functional classification (NYHA class) [14,15] to assess the functional class.

### Transthoracic Echocardiography (TTE)

Done at baseline and at the end of ET program with special focus on diastolic function assessment as follows:

a. Mitral A velocity b. Mitral E velocity c. mitral E/A ratio d. Mitral E velocity deceleration time (EDT) e. isovolumetric relaxation time (IVRT) f. pulsed wave tissue Doppler imaging (TDI) derived mitral annular velocities (septal and lateral e') g. estimated LV filling pressures mitral E/e' ratio h. Left atrial (LA) volume index i. LA dimension j. estimated Pulmonary artery systolic pressure (PASP) by continuous wave (CW) Doppler TR jet velocity k. Diastolic dysfunction (DD) grade (impaired relaxation, pseudo-normal and restrictive filling patterns) [16].

### Quality of life (QOL) assessment

Done at baseline and at the end of CR program using the Minnesota living with Heart Failure Questionnaire (MLWHFQ) [17].

## Pharmacological therapies

Patients of both groups received optimum medical treatment in the form diuretics, beta blockers, mineralocorticoid antagonists, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) according to the clinical situation and the recommendations of the latest guidelines [18].

### Six-minute walk test (6MWT) [19,20]

Patients of both groups performed 6MWT at the beginning of the study.

### Symptom limited exercise test

Group 1 patients only had symptom limited exercise test which was done before CR program for assessment of functional capacity and for utilization of the maximum achieved heart rate during the exercise test in calculating the target heart rate for the CR sessions individually [19-21]. The test was performed on treadmill using Naughton's protocol [22] which is a submaximal exercise stress protocol used for high-risk patients.

Clinical assessment of all patients done before and after the symptom limited exercise test [23].

The following data were obtained: resting heart rate, maximum symptom limited heart rate, resting blood pressure, maximum METs achieved.

### Exercise training cardiac rehabilitation program

The core rehabilitation program was as follows:

- Mode of exercise: aerobic in nature on a treadmill, consisted of a 12-week program
- Duration of session: 15-60 minutes depending on patient's physical work capacity.
- Frequency of sessions: 2-3 sessions per week.
- Rate of progression was individually tailored according to each patient's physical capacity.

Intensity of exercise corresponding to 40-75% of heart rate reserve (HRR) based on maximum heart rate that was achieved during symptom limited exercise test.

$$\text{HRR} = (\text{maximum HR during exercise test} - \text{resting HR})$$

$$\text{Target HR} = (\text{HRR} \times (40-75\%)) + \text{resting HR} [24].$$

All sessions were medically supervised via:

- Borg scale for rate of perceived exertion [25].
- Telemetry: ECG telemetric monitoring and ambulatory ECG recording enabled the assessment of disturbances of cardiac rhythm or occurrence of myocardial ischemia during session. The telemetry system that was used in the study is manufactured by DMS, model 300-2W wireless system using software Cardiovision 4 that enabled monitoring of up to 4 patients at a time [24].

### Follow up after 12 weeks

At the end of the training program all patients' functional capacity and clinical status were reassessed using:

-6MWT

-MLWHFQ.

-TTE

## Endpoint measurements

The study outcomes were the symptomatic improvement (functional capacity and clinical status) and the improvement in diastolic function by TTE at the end of the CR program.

## Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS version 20.0. Armonk, NY: IBM Corp [26]. We described qualitative data using number and percent and we described quantitative data using range (minimum and maximum), mean, standard deviation and median. The used tests were Chi-square test for categorical variables to compare between different groups, Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5, Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. Values below 0.05 are considered significant for all tests.

## Results

### Demographic data

The two groups were well matched regarding the baseline characteristics and demographic data. Table 1 summarize the demographic data of the study population.

As shown in Table 1, CR has a statistically significant impact on the reduction of the body mass index (BMI). The mean percentage of reduction was  $10.17 \pm 3.64$  in group 1 versus  $2.80 \pm 1.60$  in group 2 ( $p < 0.001$ ).

### Improvement in the NYHA class

There was a statistically significant difference ( $p=0.006$ ) between the 2 groups in the number of patients who showed improvement in their NYHA class as shown in Table 2 where CR added more significant improvement in the functional class.

### Impact of ET on diastolic function parameters

**Diastolic dysfunction (DD) grade:** 10 patients (33.3%) in group 1 showed improvement in their baseline DD grade on follow up versus only 3 patients (10%) in group2 ( $P=0.028$ ) denoting more symptomatic improvement in group 1 (Table 3).

**E, A and E/A ratio:** The mean percentage of reduction in the E wave peak velocity was  $25.77 \pm 24.65$  % in group1 versus  $7.67 \pm 13.95$  in group 2 ( $p=0.001$ ).

On the other hand, we found no statistically significant difference between the 2 groups regarding the A wave peak velocity percentage of reduction ( $p=0.089$ ) and the E/A ratio percentage of change ( $p=0.068$ ). Table 3 summarizes the previously described findings in the E, A and E/A ratio at baseline and on follow up after 12 weeks in the 2 groups.

**EDT and IVRT:** The mean percentage of increase in the EDT was  $15.22 \pm 16.38$  % in group 1 versus  $1.76 \pm 15.36$  in group 2 ( $p= 0.003$ ). The comparison between the 2 groups regarding the IVRT percentage of change did not show any statistically significant difference ( $p=0.267$ ). Table 3 summarizes the obtained data of the EDT and IVRT in the 2 groups.

**Tissue Doppler parameters:** Statistically significant difference was found between the two groups regarding the percentage of increase in both septal e' and lateral e'. The mean percentage of increase in the

**Table 1.** Comparison between the two studied groups according to demographic data

Demographic data	Rehabilitation (n = 30)	Control (n = 30)	Test of sig.	p
<b>Sex</b>				
Male	11 (36.7%)	13 (43.3%)	$\chi^2=0.278$	0.598
Female	19 (63.3%)	17 (56.7%)		
<b>Age (years)</b>	$57.47 \pm 6.10$	$58.50 \pm 6.31$	$t=0.645$	0.521
<b>BMI (kg/m<sup>2</sup>) (mean <math>\pm</math> SD)</b>				
Baseline	$33.89 \pm 5.17$	$34.48 \pm 5.35$	$t=0.435$	0.665
Follow up	$30.77 \pm 4.71$	$33.51 \pm 5.0$	$t=2.186^*$	0.033*
<b>% of reduction</b>	$10.17 \pm 3.64$	$2.80 \pm 1.60$	$U=39.0^*$	<0.001*
<b>Past history</b>				
DM	23 (76.7%)	20 (66.7%)	$\chi^2=0.739$	0.390
HTN	30 (100%)	28 (93.3%)	$\chi^2= 2.069$	<sup>FE</sup> $p=0.492$
Smoking	13 (43.3%)	14 (46.7%)	$\chi^2= 0.067$	0.795
<b>Drugs</b>				
ACEIs	13 (43.3%)	10 (33.3%)	$\chi^2= 0.635$	0.426
ARBs	4 (13.3%)	5 (16.7%)	$\chi^2= 0.131$	<sup>FE</sup> $p=1.000$
Diuretics	7 (23.3%)	7 (23.3%)	$\chi^2= 0.000$	1.000
B-blockers / Ca-blockers	15 (50%)	8 (26.7%)	$\chi^2=3.455$	0.063
<b>Symptoms</b>				
Dyspnea	30 (100%)	30 (100%)	–	–
Chest pain	8 (26.7%)	6 (20%)	$\chi^2= 0.373$	0.542
Palpitations	20 (66.7 %)	16 (53.3%)	$\chi^2= 1.111$	0.292
Syncope	0 (0%)	0 (0%)	–	–

$\chi^2$ : Chi square test, FE: Fisher Exact test, t: Student t-test, U: Mann Whitney test

p: p value for comparing between the studied groups

\*: Statistically significant at  $p \leq 0.05$

DM: Diabetes mellitus. HTN: Hypertension. ACEIs: Angiotensin converting enzyme inhibitors. ARBs: Angiotensin receptor blockers. Ca blockers: calcium channel blockers. B blockers: Beta receptors blockers. BMI: Body mass index

**Table 2.** Comparison between the two studied groups according to NYHA class

NYHA class	Rehabilitation (n = 30)	Control (n = 30)	$\chi^2$	p
<b>Baseline</b>				
II	14 (46.7%)	16 (53.3%)	0.267	0.606
III	16 (53.3%)	14 (46.7%)		
<b>Follow up</b>				
I	27 (90%)	16 (53.3%)	9.914*	<sup>MC</sup> p = 0.006*
I – II	0 (0%)	3 (10%)		
II	3 (10%)	11 (36.7%)		

$\chi^2$ : Chi square test, MC: Monte Carlo test

p: p value for comparing between the studied groups

\*: Statistically significant at  $p \leq 0.05$

NYHA class: New York heart association class

**Table 3.** Comparison between the two studied groups according to echocardiography parameters (mean value  $\pm$  SD)

	Echocardiography	Rehabilitation (n = 30)	Control (n = 30)	Test of sig.	p
DD grade	<b>Baseline</b>				
	I	11 (36.7%)	11 (36.7%)	$\chi^2=0.220$	<sup>MC</sup> p = 1.00
	II	15 (50%)	14 (46.7%)		
	III	4 (13.3%)	5 (16.7%)		
	<b>Follow up</b>				
	I	19 (63.3%)	12 (40%)	$\chi^2=3.290$	<sup>MC</sup> p = 0.213
	II	9 (30%)	15 (50%)		
	III	2 (6.7%)	3 (10%)		
	<b>No change</b>	20 (66.7%)	27 (90%)	$\chi^2=4.812^*$	0.028*
	<b>Improvement</b>	10 (33.3%)	3 (10%)		
A	<b>Baseline</b>	85.63 $\pm$ 25.19	86.03 $\pm$ 24.54	U=438.0	0.859
	<b>Follow up</b>	83.60 $\pm$ 24.06	90.88 $\pm$ 27.86	U=398.5	0.446
	<b>% of reduction</b>	-0.77 $\pm$ 17.29	6.07 $\pm$ 12.42	U=335.0	0.089
E	<b>Baseline</b>	93.79 $\pm$ 23.96	96.03 $\pm$ 24.37	U= 406.5	0.520
	<b>Follow up</b>	76.28 $\pm$ 21.06	90.50 $\pm$ 26.59		
	<b>% of reduction</b>	25.77 $\pm$ 24.65	7.67 $\pm$ 13.95		
E/A	<b>Baseline</b>	1.20 $\pm$ 0.54	1.20 $\pm$ 0.51	U=435.0	0.824
	<b>Follow up</b>	1.01 $\pm$ 0.59	1.05 $\pm$ 0.46	U=373.0	0.254
	<b>% of reduction</b>	25.10 $\pm$ 29.64	15.35 $\pm$ 17.26	U=326.5	0.068
EDT	<b>Baseline</b>	177.57 $\pm$ 35.14	194.57 $\pm$ 52.62	U=357.50	0.171
	<b>Follow up</b>	201.80 $\pm$ 33.85	195.63 $\pm$ 52.37	U=424.50	0.706
	<b>% of increase</b>	15.22 $\pm$ 16.38	1.76 $\pm$ 15.36	U= 251.5*	0.003*
IVRT	<b>Baseline</b>	77.27 $\pm$ 13.66	76.80 $\pm$ 15.51	U=447.50	0.970
	<b>Follow up</b>	82.90 $\pm$ 12.14	79.90 $\pm$ 12.46	U=345.50	0.122
	<b>% of increase</b>	8.43 $\pm$ 11.64	5.85 $\pm$ 14.09	U=375.0	0.267
Septal e'	<b>Baseline</b>	5.16 $\pm$ 1.06	5.58 $\pm$ 0.98	U=32.50	0.100
	<b>Follow up</b>	6.71 $\pm$ 1.25	6.31 $\pm$ 1.07	U=363.50	0.189
	<b>% of increase</b>	32.08 $\pm$ 19.88	14.83 $\pm$ 19.44	U = 254.0*	0.004*
lateral e'	<b>Baseline</b>	6.74 $\pm$ 1.22	7.35 $\pm$ 1.16	U= 327.5	0.065
	<b>Follow up</b>	8.70 $\pm$ 1.21	7.90 $\pm$ 1.18	U= 284.0*	0.012*
	<b>% of increase</b>	31.45 $\pm$ 20.36	8.66 $\pm$ 14.87	U=169.0*	<0.001*
E/e'	<b>Baseline</b>	16.27 $\pm$ 5.12	14.97 $\pm$ 3.81	U=416.0	0.615
	<b>Follow up</b>	10.27 $\pm$ 4.27	12.85 $\pm$ 3.65	U=243.0*	0.002*
	<b>% of reduction</b>	65.96 $\pm$ 34.55	18.23 $\pm$ 13.98	U= 96.0*	<0.001*

$\chi^2$ : Chi square test, MC: Monte Carlo test U: Mann Whitney test

p: p value for comparing between the studied groups

\*: Statistically significant at  $p \leq 0.05$

DD: Diastolic dysfunction. DT: deceleration time.

IVRT: Isovolumetric relaxation time

septal e' was 32.08 ± 19.88 in group 1 versus 14.83 ± 19.44 in group 2 (P=0.004). The mean percentage of increase in the lateral e' was 31.45 ± 20.36 in group 1 versus 8.66 ± 14.87 in group 2 (P<0.001). A statistically significant difference in the percentage of reduction in the LV filling pressures (estimated by the ratio E/e') at baseline and on follow up between the two groups. The mean percentage of reduction was 65.96 ± 34.55 in group 1 versus 18.23 ± 13.98 in group 2 (p<0.001). This important finding denotes more improvement in the diastolic function and LV filling pressures in the rehabilitation group. Table 3 summarizes these findings.

**LA dimension, LA volume index, PASP:** We didn't find a statistically significant difference in the LA dimension percentage of reduction between the two groups where the mean percentage of reduction was 1.60 ± 15.04 in group 1 versus 2.47 ± 3.20 in group 2 (p=0.064) but we found statistically significant difference between the two groups in the LA volume index where the mean percentage of reduction was 27.86 ± 13.27 in group 1 versus 8.03 ± 4.40 in group 2 (p<0.001) as shown in Table 4.

Regarding the PASP, group 1 patients showed statistically significant reduction than patients in group 2, the mean percentage of reduction was 33.85 ± 14.68 in group 1 versus 22.97 ± 16.54 in group 2 (p=0.02) (Table 4)

**LVH and EF:** We didn't find a statistically significant difference between the two groups regarding the change in EF and degree of LVH. The mean percentage of increase in the EF was 1.05 ± 5.84 in group 1 versus 0.84 ± 9.27 in group 2 (p=0.970). The percentage of reduction of the LV septal thickness (as a LVH measure) was 6.22 ± 7.30 in group 1 versus 2.37 ± 6.17 in group 2 (p=0.065) as shown in Table 4.

**6MWT:** There was a statistically significant improvement in the rehabilitation group in comparison with the medical group. The mean

percentage of increase in the distance in the 6-minute walk test was 111.79 ± 40.97 in group 1 versus 46.33 ± 11.58 in group 2 (p<0.001) as shown in Table 5.

**Quality of Life (MLWHFQ):** The mean percentage of reduction in the total score was 305.60 ± 158.44 in group 1 versus 69.44 ± 17.71 in group 2 (p<0.001). Most items of the MLWHFQ showed statistically significant improvement on comparing the 2 groups as shown in Table 5. Only 3 items of the questionnaire didn't show a statistically significant difference in the percentage of improvement. Firstly, the degree of improvement of lower limb oedema didn't show statistically significant difference between the two groups where the mean percentage of change in the score of lower limb oedema was 183.3 ± 100.0 in group 1 versus 129.8 ± 72.35 in group 2 (p=0.159). Secondly, the rate of hospitalization where the mean percentage of change in the score of hospitalization was 100.0 in group 1 versus -62.50 ± 69.44 in group 2 (p=0.064). Thirdly, the medical care cost where the mean percentage of change was 98.81 ± 94.05 in the group 1 versus 75.56 ± 60.61 in group 2 (p= 0.605) as shown in table 5.

**Discussion**

This study was designed to evaluate the impact of exercise-based CR in HFpEF regarding the quality of life and a more detailed assessment of this impact on the LV diastolic and systolic function. Few trials in the literature have studied the impact of exercise-based CR on HFpEF patients using different protocols of exercise and different inclusion and exclusion criteria finally coming with variable results regarding the impact of CR on the improvement of LV diastolic function and QOL in HFpEF patients [27]. The duration of the ET protocol varied from 12 to 16 weeks in most studies [27], some studies used shorter protocols as the 4-week ET program in the study done by Angadi et al. [28] and other longer protocols such as the 20-week protocol which

**Table 4.** Comparison between the two studied groups according to echocardiography parameters (mean value ± SD)

	Echocardiography	Rehabilitation (n = 30)	Medical (n = 30)	Test of sig.	P
LAD	Baseline	42.40 ± 6.54	44.03 ± 3.07	U = 378.5	0.287
	Follow up	41.77 ± 2.39	43.0 ± 3.11	U= 336.50	0.091
	% of reduction	1.60 ± 15.04	2.47 ± 3.20	U = 325.0	0.064
LAVI	Baseline	41.07 ± 4.18	40.53 ± 3.87	U= 420.50	0.661
	Follow up	32.37 ± 3.99	37.53 ± 3.45	U = 126.5*	<0.001*
	% of reduction	27.86 ± 13.27	8.03 ± 4.40	U= 55.0*	<0.001*
PASP	Baseline	43.27 ± 8.99	41.70 ± 8.92	U= 393.0	0.395
	Follow up	32.50 ± 6.76	34.10 ± 7.13	U= 406.0	0.505
	% of increase	33.85 ± 14.68	22.97 ± 16.54	U= 242.5*	0.02*
EF	Baseline	66.93 ± 6.59	66.90 ± 7.40	U= 432.0	0.789
	Follow up	67.43 ± 5.61	67.20 ± 7.67	U= 433.50	0.807
	% of increase	1.05 ± 5.84	0.84 ± 9.27	U= 447.5	0.970
LVH (septal thickness)	Baseline	11.43 ± 1.76	11.43 ± 1.70	U= 443.5	0.922
	Follow up	10.80 ± 1.75	11.17 ± 1.53	U= 395.0	0.402
	% of decrease	6.22 ± 7.30	2.37 ± 6.17	U= 337.5	0.065

U: Mann Whitney test

p: p value for comparing between the studied groups

\*: Statistically significant at p ≤ 0.05

LAD: Left atrial dimension. LAVI: left atrial volume

index. PASP: Pulmonary artery systolic pressures. EF:

Ejection fraction. LVH: Left ventricular hypertrophy.

**Table 5.** Comparison between the two studied groups according to Total score of MLWHFQ and 6MWT (mean value  $\pm$  SD)

		Rehabilitation (n = 30)	Control (n = 30)	Test of sig.	P
Total score MLWHFQ	Baseline	66.23 $\pm$ 11.13	62.23 $\pm$ 14.06	U =335.5	0.090
	Follow up	19.60 $\pm$ 11.95	37.23 $\pm$ 10.19	U = 80.0*	<0.001*
	% of reduction	305.60 $\pm$ 158.44	69.44 $\pm$ 17.71	U = 64.0*	<0.001*
6MWT	Baseline	225.33 $\pm$ 52.11	246.33 $\pm$ 45.45	U=338.50	0.098
	Follow up	466.67 $\pm$ 95.96	358.0 $\pm$ 58.92	U =154.5*	<0.001*
	% of increase	111.79 $\pm$ 40.97	46.33 $\pm$ 11.58	U =53.0*	<0.001*

U: Mann Whitney test

p: p value for comparing between the studied groups

\*: Statistically significant at  $p \leq 0.05$ 

MLWHFQ: Minnesota living with heart failure questionnaire. 6MWT: 6-minute walk test

was reported by Kitzman et al. [29]. Also, the ET was done in variable settings whether home based outpatient setting, or a supervised program done in rehabilitation centers. The mode of ET also varied where some studies used a combination of endurance and resistance training, others adopted walking on a treadmill and other studies used the bicycle ergometer [27].

In our study, we followed a 12-week ET program using walking on a treadmill as the core of our CR program. We do believe that this design was appropriate for keeping the compliance of the patients with no patients lost in the follow up in our study. This design with moderate intensity ET also was comfortable for the patients and helped them to complete all their rehabilitation sessions successfully. The patients in the control group were followed clinically on regular basis and they had open easy access to the cardiology clinic for any inquiries.

Nearly all the previously described studies focused on assessing two main parameters in general: the quality of life using different questionnaires and the echocardiographic parameters of systolic and diastolic function. In addition, some trials included the 6MWT, the peak oxygen uptake, ventilatory threshold (VT), arterial stiffness with endothelial dysfunction and heart rate variability in the assessment of the study population at base line and after follow up [27].

In our study we assessed the improvement in the QOL using the MLWHFQ with detailed comparison of all of its items to assess the change in physical and psychosocial aspects putting in consideration that it is a subjective method of assessment. we also used the 6MWT as a well-known test for assessment of the cardiorespiratory fitness of our patients at base line and on follow up to clarify the degree of improvement in both groups as an objective measurable parameter. In addition, we followed a detailed LV diastolic function assessment according to the latest guidelines [14] which also gave us the opportunity to assess a measurable objective parameter solidifying the obtained results. We included the LV filling pressures using  $E/e'$  and the LA volume index which were also included by Edelmann et al. [30] and Angadi et al. [28] beside all other diastolic parameters.

We also did a submaximal exercise stress test in the rehabilitation group at base line to help us estimating the average functional capacity and the target heart rate which was used during the CR sessions. We repeated it at the end of the follow up period with measuring the maximum heart rate and the maximum METS achieved after completing the CR program. On comparing the results of the submaximal stress test at baseline and on follow up, we obtained another measurable objective

parameter to show the improvement in the rehabilitation group per se although the submaximal stress test was not done in the medical group.

### Improvement in echocardiographic parameters

We found a statistically significant difference between the two groups regarding the number of patients who showed improvement of their diastolic dysfunction grade. This finding was not reported in any of the previous trial discussing the impact of CR on HFpEF [27] except Angadi et al. [28] who reported significant change in the DD grade (2.1  $\pm$  0.3 pre-ET vs. 1.3  $\pm$  0.7 post ET,  $p < 0.01$ ) with high intensity interval training. Our finding is consistent with Angadi et al. [26] despite we used different ET protocol with larger study population and longer duration of the ET program in our study.

In our study, we found a statistically significant difference between the 2 groups in the E wave peak velocity percentage of reduction which implies more reduction in the LV pressures with CR. On the other hand, we found no statistically significant difference between the 2 groups regarding the A wave peak velocity percentage of reduction and the E/A ratio percentage of change. Similar findings were reported by Angadi et al. [28], Kitzman et al. [31], Kitzman et al. [32] and Smart et al. [33]. Alves et al. [34] reported that ET increased the mean E/A ratio and decreased DT of early filling in patients with mild and preserved EF.

Also, we found a statistically significant difference between the 2 groups in the DT percentage of increase denoting a positive impact of CR which is consistent with Angadi et al who reported significant change in the DT with high intensity interval training [28].

Regarding IVRT, we did not find any statistically significant difference between the 2 groups. This is consistent with the results of the available trials discussing the issue of CR in HFpEF [27].

Many of the previous trials didn't include the estimation of the LV filling pressures using the  $E/e'$  in its results for assessing the diastolic function improvement [27]. Edelmann et al. [30] reported statistically significant improvement in the  $E/e'$  with CR in HFpEF. In contrary to our study, Edelmann et al. [30] did not include patients with grade III diastolic dysfunction and used a combination of resistance and endurance ET in the CR program. We also found a consistent finding in our study where CR resulted in a significant reduction in the  $E/e'$  ratio denoting an important structural basis for the benefit of CR in HFpEF. Other trials as Smart et al. [33], Angadi et al. [28] and Kitzman [29] didn't report statistically significant difference in the LV filling pressures with ET.

An additional point in our study is the statistically significant increase in the septal and lateral e' with CR. This represents another point in the structural basis of the CR benefit in HFpEF.

LA volume index was significantly reduced with CR in our study, similar findings were reported by Edelmann et al. [30] who reported a statistically significant reduction in the LA volume index with ET (-4.0, 95% CI: -5.9 to -2.2, p<0.001. Angadi et al. [28] did not find a statistically significant difference in the LA volume index with ET. We do believe that the significant improvement in the LA volume index, septal e', lateral e' and E/e' represents a core of structural basis for the significant additive benefit of CR.

None of the previous trials reported significant change in the PASP with CR [27]. In our study we found a significant reduction in the PASP with CR adding a more benefit in the structural basis of the CR benefit in HFpEF.

As previous trials we did not find any significant change in LVH or EF with CR.

### QOL improvement

In our study we found a significant improvement in the quality of life using the MLWHFQ, similar findings were reported by Gary et al. [35] and Alves et al. [34] although they used different modalities or questionnaires. Fu et al. [36] used the MLWHFQ and found a reduction in it with CR. other trials assessed the peak oxygen uptake and found a significant improvement as Kitzman et al. [32] and smart et al. [33].

6 MWT significantly improved with CR in our study. This result is consistent with Gary et al. [35] and Kitzman et al. [31] reports. On the other hand, Maldonado et al. [37] reported no significant difference in the 6MWT with CR.

### Conclusion

In the light of the results of this study, CR has a beneficial impact on patients with HFpEF. This positive impact has 2 aspects: structural benefit with improvement in the LV diastolic function and functional aspect with improvement in the functional capacity and quality of life. Till further evidence comes to light, we recommend CR as an essential strategy in the management of patients with HFpEF.

### Declarations

**Ethics approval and consent to participate:** The study was approved by the local ethical committee.

**Consent for publication:** Not applicable (no individual personal data are included in the study).

**Availability of data and materials:** All data analyzed during this research are included in this published article.

**Competing interests:** All authors declare that they have no competing interests.

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**Authors' contributions:** SWA, MAH, and AME searched the literature, collected the data, performed the statistical analyses, and wrote the manuscript; SWA, AME, and FWE contributed to conception, design, data interpretation, and supervision of the study. All authors read and approved the final manuscript.

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