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ABOUT COVER

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Prospective Study

Effects of exercise training on diastolic and systolic dysfunction in patients with chronic heart failure

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Abstract**BACKGROUND**

Chronic heart failure (CHF) is a complex syndrome characterized by a progressive reduction of the left ventricular (LV) contractility, low exercise tolerance, and increased mortality and morbidity. Diastolic dysfunction (DD) of the LV, is a keystone in the pathophysiology of CHF and plays a major role in the progression of most cardiac diseases. Also, it is well estimated that exercise training induces several beneficial effects on patients with CHF.

AIM

To evaluate the impact of a cardiac rehabilitation program on the DD and LV ejection fraction (EF) in patients with CHF.

METHODS

Thirty-two stable patients with CHF (age: 56 ± 10 years, EF: $32\% \pm 8\%$, 88% men) participated in an exercise rehabilitation program. They were randomly assigned to aerobic exercise (AER) or combined aerobic and strength training (COM), based on age and peak oxygen uptake, as stratified randomization criteria. Before and

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after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography evaluation to evaluate peak oxygen uptake (VO_{2peak}), peak workload (W_{peak}), DD grade, right ventricular systolic pressure (RVSP), and EF.

RESULTS

The whole cohort improved VO_{2peak} and W_{peak} as well as DD grade ($P < 0.05$). Overall, 9 patients (28.1%) improved DD grade, while 23 (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.05$). In addition, the whole cohort improved RVSP and EF ($P < 0.05$). Not any between-group differences were observed in the variables assessed ($P > 0.05$).

CONCLUSION

Exercise rehabilitation improves indices of diastolic and systolic dysfunction. Exercise protocol was not observed to affect outcomes. These results need to be further investigated in larger samples.

Key Words: Chronic heart failure; Cardiovascular effects; Cardiac rehabilitation; Aerobic exercise; Strength training; Diastolic dysfunction

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Core Tip: In this study, the exercise training rehabilitation (aerobic exercise with/without strength training) effects on indices of diastolic and systolic cardiac function, were evaluated in stable chronic heart failure patients. Exercise training overall induced benefits on the diastolic dysfunction grade, the ejection fraction of the left ventricle, the right ventricular systolic pressure, as well as aerobic exercise capacity.

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INTRODUCTION

Chronic heart failure (CHF) is a multisystem syndrome, characterized by an abnormality of the cardiac structure or function, condition, which leads to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures[1].

Left ventricular diastolic dysfunction plays an essential role in the pathophysiology of the CHF. The term "diastolic dysfunction" (DD) refers to abnormalities in right or/and left ventricular relaxation[2-5]. Although DD most frequently refers to the context of HF with preserved ejection fraction (EF), due to its central role in its pathophysiology, impaired diastolic function often coexists with systolic dysfunction. HF patients may not accomplish the necessary increase in diastolic relaxation to accommodate the preload increase[1]. Severity of exercise intolerance is associated with left ventricular filling pressure and so the strong relationship between diastolic abnormality and exercise limitation should be underlined[6-8]. It is in that context, that exercise training is currently being extensively evaluated for additional benefits, over the classical medication, in the treatment of DD in patients with CHF[9].

As mentioned before, in patients with CHF, the exercise capacity may be limited by the number of frequently coexisting factors such as decreased contractility, DD, chronotropic incompetence, oxygen metabolism, or skeletal muscle mass disorders. This importance of skeletal muscle dysfunction provides part of the rationale for the use of cardiac rehabilitation[10]. It is well established that exercise training improves functional capacity, quality of life, and clinical outcomes in patients with stable CHF [10,11]. Specifically, in patients with reduced EF, exercise is beneficial in total and HF-

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related hospitalizations and relieves the symptoms of depression. Also, it decreases myocardial oxygen demands for the same level of external work performed, as demonstrated by the product of heart rate \times systolic blood pressure, reducing in that way the likelihood of myocardial ischemia[12,13]. In major Cardiology Society Guidelines, exercise training is recommended in all patients with New York Heart Association functional class II to III, no matter of the EF[14-16].

Finally, aerobic regimes have been a major component of exercise rehabilitation to improve cardiorespiratory fitness and disease symptoms[16]. As skeletal muscle abnormalities are an important limitation to exercise intolerance and muscular strength impacts patients' capacities to perform daily tasks, combined regimes of aerobic exercise (AER) and strength training have been employed to induce additional benefit[17,18]. However, there have not been any data on the effects of different regimes on diastolic dysfunction.

The main aim of this study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the EF of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

MATERIALS AND METHODS

Study population and design of the study

The study population consisted of 32 consecutive CHF patients. The demographic, anthropometric, and clinical characteristics of these patients at baseline are described in Table 1. The patients were referred to our hospital's laboratory by HF outpatient clinics, screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations including echocardiography assessment. They randomly assigned to AER ($n = 17$) or combined aerobic and strength training (COM, $n = 15$). Randomization process, based on age (50 years as cut-off value) and peak oxygen uptake (16 mL/kg/min as cut-off value) as stratified randomization criteria, was made by a researcher not involved in the rest of the tasks, such as exercise sessions and pre/post evaluations. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

CHF diagnosis was based on history forms, clinical evaluation, and laboratory testing. Patients were considered for inclusion in the study in case they were on stable systolic CHF, under optimal medication for at least 3 mo and had an EF value up to 49%. Exclusion criteria were severe valvulopathy, uncontrolled arterial hypertension, severe chronic obstructive pulmonary disease, severe peripheral angiopathy, neuromuscular diseases and contraindications for CPET. The patients were mainly treated with diuretics, b-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors or sacubitril/valsartan. There were not any changes in treatment regimen during the study.

The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Administration Board and the Ethics Committee of our Hospital. Informed consent was provided by the participants.

Exercise training program

Participants attended supervised exercise sessions at the laboratory three times per week for 12 wk in the early afternoon hours. If any sessions were missed, the duration of the program was extended so that the 36 sessions were accomplished. AER and COM protocols have been previously described in detail[19]. In short, the AER group performed 31 min of interval training (4×4 -min at 80% $\text{VO}_{2\text{peak}}$ – 5×3 -min at 50% $\text{VO}_{2\text{peak}}$) on a cycle ergometer (Ironman M3 Cycle) followed by balance and coordination exercises. The COM group performed 31 min of AER (in the same way as the AER group) followed by 14 min of strength training (2–3 sets, 10–12 repetitions, 60%–75% of 1 repetition maximum test-knee extension, knee flexion, chest press). Both regimes were of the same total duration.

Cardiopulmonary exercise testing

Participants underwent a ramp incremental CPET on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, United States), before and after completion of the program. Individualized workload increments were estimated according to the equation of Hansen *et al*[20]. Gas exchange was measured

Table 1 Demographic, anthropometric, and clinical characteristics of all chronic heart failure patients at the beginning of the study

Patients, <i>n</i>	32
Age ¹ , yr	56 ± 10
Gender (Males/Females)	30/2
Height ¹ , cm	178 ± 8
Body mass ¹ , kg	93 ± 25
BMI ¹ , kg/m ²	29 ± 6
NYHA class (I/II/III)	3/21/ 8
LVEF ¹ , %	32 ± 8
VO _{2peak} ¹ , mL/kg/min	19.4 ± 4.5
Etiology of CHF, <i>n</i>	
Ischemic/Dilated/Other cardiomyopathy	20 / 10 / 2

¹Values are mean ± SD.

BMI: Body mass index; CHF: Chronic heart failure; LVEF: Ejection fraction of the left ventricle; NYHA: New York Heart Association; VO_{2peak}: Peak oxygen uptake.

with the patient breathing through a low resistance valve, with the nose clamped, using an ergospirometry system (Vmax229D; Sensor Medics) calibrated with a known gas mixture before each test. Respiratory indicators (breath-by-breath oxygen uptake [VO₂], carbon dioxide output [VCO₂] and ventilation [V_E]) were measured. Peripheral O₂ saturation was monitored continuously by pulse oximetry. Heart rate and rhythm were monitored by a MAX 1, 12-lead electrocardiographic system (Marquette Electronics, Milwaukee, WI, United States) and blood pressure was measured every 2 min with a mercury sphygmomanometer. All patients were verbally encouraged to exercise to intolerable leg fatigue or dyspnea. CPET variables employed in the study were VO_{2peak} and peak workload (W_{peak}). VO_{2peak} was determined as the average value of VO₂ data measured at the final 20-s period of the exercise phase, and W_{peak} as the corresponding work rate[20].

Echocardiographic measurements

Detailed echocardiography assessment was performed in all patients. A Philips E 33 Doppler analyzer equipped with tissue Doppler imaging (TDI) was used. The period between echocardiography assessment and cardiopulmonary exercise testing was less than 2 wk. Each patient was examined, according to the guidelines of the European Society of Echocardiography (2016 update[21]), in the left lateral and supine position. The EF was calculated using the modified Simpson method from apical two- and four-chambers view (2D and 4D). Analysis of pulsed Doppler mitral flow velocity was attained, and three consecutive cardiac cycles were analyzed and averaged for each patient. Transmitral inflow velocities (E, A, deceleration time of E [DTe] and E/A ratio) were assessed by pulsed-wave Doppler, with the sample volume placed between the mitral leaflet tips in the apical four-chamber view during diastole. When from the Echo-TDI the septal e' was less than 8 and the lateral e' less than 10, the Echo-Doppler transmitral flow was examined. Based on this, three grades of diastolic dysfunction (DD) are described: Grade I (impaired relaxation) is characterized by E/A ratio less than 0.8 and DTe more than 200 ms. Grade II (pseudonormal) is characterized by elevated left atrial pressures. The E/A ratio is 0.8–2 and the DTe is more than 200 ms. Grade III (restrictive pattern), is characterized by a marked decrease in left ventricular compliance (E/A ratio more than 2, DTe less than 160 ms[15]). Another grade, grade 0, refers to normal diastolic function. The E/A ratio was considered as normal if it was 0.78–1.78 and the DTe 150–200 ms. Valsalva maneuver was used to discriminate pseudo normal from true normal pattern. From the apical four-chamber view, a 10 mm³ sample volume was placed at the septal and lateral mitral annulus, and spectral TDI was recorded, calculating septal e', lateral e' and the mean value (E'). Left atrial volume was measured at end-systole and it was normalized to body surface area (LAVI, mL/m²). Finally, the right ventricular systolic pressure (RVSP) was calculated using the Bernoulli equation $RVSP = 4(V)^2$ of peak tricuspid regurgitation velocity (V).

Statistical analyses

Continuous variables were tested for normality of distribution with Shapiro-Wilk test. Within-group differences were assessed with paired sample Student *t*-test or Wilcoxon signed-rank test, based on normality of distribution. Chi-square test was employed to check for between-group differences on categorical variables. Between-group differences of ordinal variables were assessed with Mann-Whitney *U* test. McNemar-Bowker test was also used to check for differences on diastolic dysfunction grade before and after exercise intervention. Time by group interactions were assessed with factorial 2×2 analysis of variance. Correlations between variables were tested with Pearson or Spearman coefficient. Continuous variables were presented as mean \pm SD. Level of statistical significance *P* was set at 0.05. Statistical computations were made with IBM SPSS 26 statistics.

RESULTS

The whole cohort improved indices of AER capacity, namely $\text{VO}_{2\text{peak}}$ (from 19.4 ± 4.5 to 21.3 ± 6.0 mL/kg/min, $P = 0.03$) and W_{peak} (from 109 ± 39 to 130 ± 43 watts, $P < 0.01$).

The whole group improved DD, as assessed with grades. Before the exercise program, the number of patients categorized as grade -0, -I, -II, or -III were 1 (3.1%), 18 (56.3%), 10 (31.2%), 3 (9.4%) respectively. After the program, the respective patients were 4 (12.5%), 21 (65.6%), 6 (18.8%), 1 (3.1%). A significant difference was found between total pre- and post-values ($P = 0.01$) (Figure 1A). That was also the case when analysis was performed based on change of DD grade ($P = 0.06$) (Figure 1B). Overall, 9 patients (28.1%) improved DD grade, while 23 ones (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.01$) (Figure 1C). In addition, $\text{VO}_{2\text{peak}}$ tended to improve more in patients that also improved grade ($P = 0.09$), while W_{peak} was improved more in these patients ($P = 0.04$) (Figure 2).

The whole sample did not improve any of the other DD variables examined individually. These were E/A ratio (from 1.00 ± 0.64 to 0.88 ± 0.35 , $P = 0.27$), LAVI (from 38.70 ± 13.74 to 38.44 ± 17.03 mL/m², $P = 0.14$), E' (from 7.74 ± 2.31 to 7.55 ± 1.85 cm/s, $P = 0.62$), E/E' ratio (from 9.15 ± 3.41 to 8.48 ± 3.45 , $P = 0.15$), and DTe (from 213.34 ± 41.60 to 212.38 ± 32.99 m/s, $P = 0.59$). In addition, the whole cohort improved RVSP (from 28.92 ± 7.75 to 27.75 ± 6.46 mmHg, $P = 0.05$) and EF (from $32\% \pm 8\%$ to $36\% \pm 8\%$, $P < 0.01$), after completion of the exercise rehabilitation program.

Pre- and post-values of the variables examined in relation to AER and COM groups comparison are presented in Table 2. The AER group improved DD grades ($P = 0.02$) and tended to improve LAVI ($P = 0.10$). The COM group improved RVSP ($P = 0.01$) and tended to improve grades ($P = 0.10$). Both groups improved EF ($P < 0.01$). Not any between-group differences were observed in the variables observed ($P > 0.05$).

DISCUSSION

The exercise rehabilitation effects on parameters of diastolic and systolic dysfunction were explored among CHF patients in this study. Exercise training overall beneficially affected DD stage, RVSP, EF of the left ventricle and AER capacity. Not any differences between the aerobic and combined group were observed.

HF is currently considered a pathophysiological syndrome of multifactorial origin and not just a disease. DD is a common characteristic of the HF patients[22]. Hamlin *et al*[4] showed that CHF patients present with reduced ability to augment the diastolic relaxation, accountable for the inability to accommodate the increase in estimated preload during exercise, resulting in turn in higher filling pressure. Also, HF patients have generally shorter diastolic periods, situation that lead to inability of the myocardium to relax and accept the large volume of blood[23]. The inability to perform exercise without discomfort may be one of the first symptoms experienced by patients with HF and is often the principal reason for seeking medical care[14,24]. Therefore, exercise intolerance is inextricably linked to the diagnosis of HF. Exercise training has been an important means of rehabilitation, with a class IA recommendation on the improvement of functional capacity and symptoms[16]. In line with previous studies[17,25], indices of aerobic capacity as assessed with peak oxygen uptake ($\text{VO}_{2\text{peak}}$) and workload (W_{peak}) were also improved in this study. A significant improvement in the DD grades was found in this study. Other diastolic indices, such as E/E', were not found to improve, which may be related to the small sample size.

Table 2 Values of the variables evaluated before and after the exercise training intervention

	Aerobic group		Combined group	
	Pre	Post	Pre	Post
VO _{2peak} (ml/kg/min)	19.0 ± 5.5	22.2 ± 7.8 ^a	19.8 ± 3.1	20.3 ± 2.9
W _{peak} (watt)	111 ± 46	129 ± 48 ^a	108 ± 31	131 ± 39 ^a
E/A	1.15 ± 0.80	1.00 ± 0.41	0.83 ± 0.37	0.74 ± 0.20
LAVI (ml/m ²)	38.83 ± 12.75	37.23 ± 11.78	38.55 ± 15.23	39.81 ± 21.91
E' (cm/s)	8.00 ± 2.81	7.74 ± 1.97	7.45 ± 1.61	7.33 ± 1.74
E/E'	9.09 ± 4.06	8.76 ± 4.57	9.22 ± 2.63	8.15 ± 1.51
DTe (m/s)	220.65 ± 51.59	213.00 ± 38.08	205.07 ± 25.54	211.67 ± 27.41
RVSP (mmHg)	28.56 ± 7.65	28.23 ± 6.36	29.33 ± 8.10	27.20 ± 6.74 ^a
EF (%)	34 ± 8	38 ± 9 ^a	29 ± 6	33 ± 6 ^a
DD grade 0/I/II/III (n)	1/9/4/3	3/10/3/1 ^a	0/9/6/0	1/11/3/0

Values are mean ± SD.

^aP < 0.05, significant within-group difference.

DD: Diastolic dysfunction; DTe: Deceleration time of E wave; E': Mean value of the septal and lateral e' of TDI of the mitral annulus; E/A: Ratio of the E and A waves of the transmitral inflow; E/E': Ratio of the E wave to E' wave; EF: Ejection fraction; LAVi: Left atrial volume index; RVSP: Right ventricular systolic pressure; VO_{2peak}: Peak oxygen uptake; W_{peak}: Peak workload.

Belardinelli *et al*[26,27] showed an improvement in DD, after a 2-mo exercise training intervention in HF patients with moderate/severe systolic dysfunction. Similarly, improved LV stiffness[28] and decreased filling pressure[29] have been also reported in other HF trials as a result of exercise training. A meta-analysis of 6 studies, with 144 patients with reduced EF[30], indicated a significant reduction in the ratio E/E' with exercise training. Among them, 3 studies in patients with reduced EF, reported post intervention improvement in all DD grades[31].

The RVSP improvement observed in this study is also in line with previous findings. Mehani *et al*[32] after a 5-mo training program, showed a significant decrease of RVSP by 12.05 mmHg in a group of patients suffering from pulmonary hypertension. Maximal exercise capacity and exercise-triggered symptoms are linked to increased pulmonary capillary pressure and therefore a subsequent increase of left ventricular filling pressure. In this way, filling pressures are directly associated to the LV diastolic function. This point can explain the beneficial reflection of DD improvement on the pulmonary hypertension and the ventilatory limitation of patients with CHF.

In our study, there was not any decrease in the LAVI, an important index in determination of DD. Previous studies showed that left atrial enlargement is an independent marker of adverse outcome in both primary and secondary cardiovascular prevention [33]. Limited data, however, have been reported on the exercise training effects on LAVI in CHF, suggesting conflicting results. Edelmann *et al*[34] reported a significant decrease in LAVI in the training group, while Palau *et al*[35] reported no change in LAVI after interval training. Sandri *et al*[36] also, failed to find a significant change in LA size after 4 wk of training.

A significant improvement in the left ventricular EF (LVEF) was also found in this study. This finding is in line with a recent metanalysis[37], which included trials reporting on LVEF, LV end-diastolic and end-systolic volumes. Overall, AER training improved these parameters. Both continuous and interval regimes were able to induce similar benefits, which may be also affected by the program duration.

Finally, considering the regimes of the exercise applied in this study, overall aerobic and combined regimes improved EF, RVSP, and DD grades. Not any between-group differences were observed. Aerobic training can induce beneficial effects also on skeletal muscles, and continuous aerobic training has been found to reverse partially skeletal myopathy of the HF[38]. Interval exercise training, which was also employed in the present study, can be an effective regime, as it can apply higher exercise stimuli on skeletal muscles *via* a higher exercise intensity[39,40]. Furthermore, strength training has been shown to induce muscle hypertrophy, while the combination of resistance training with aerobic training has the potential to induces greater benefits in

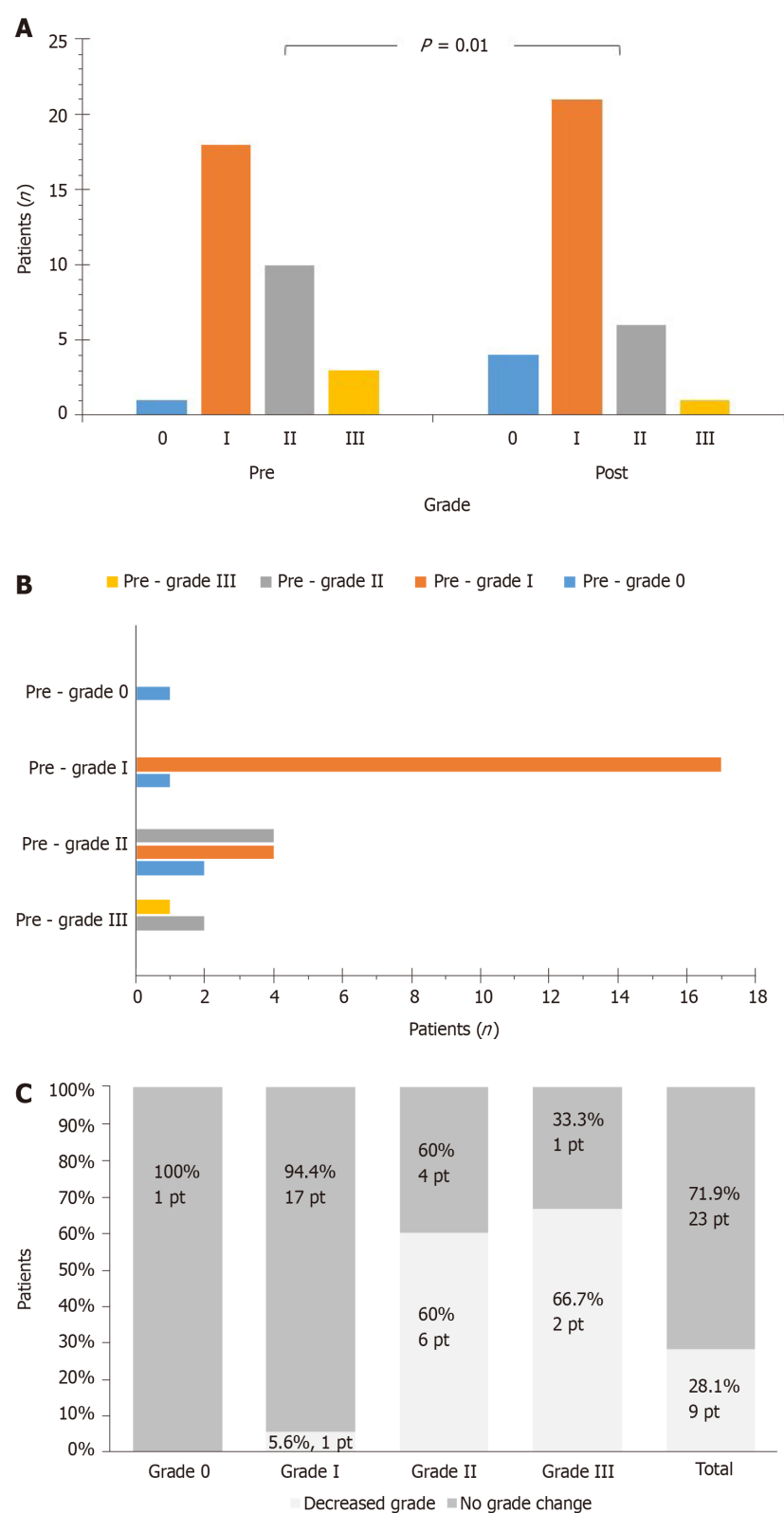


Figure 1 Changes in diastolic dysfunction grades. A: Pre- and post-number of grade-0, -I, -II, -III patients ($P = 0.01$, as assessed with Wilcoxon signed-rank test); B: Patients' distribution according to pre- and post-level of grade ($P = -0.06$, as analyzed with McNemar-Bowker test); C: Number of patients that decreased grade or remained at the same grade in relation to baseline grade ($P < 0.01$, as assessed with χ^2 test).

vascular endothelium[19], muscle strength and aerobic improvement of CHF patients than AER alone[17,18,41]. Interestingly, in a CHF study that employed a combined exercise protocol *vs* control, ventricular stroke volume and left ventricular diastolic indices were improved[28]. The effects of different exercise regimes on the diastolic dysfunction need to be further investigated.

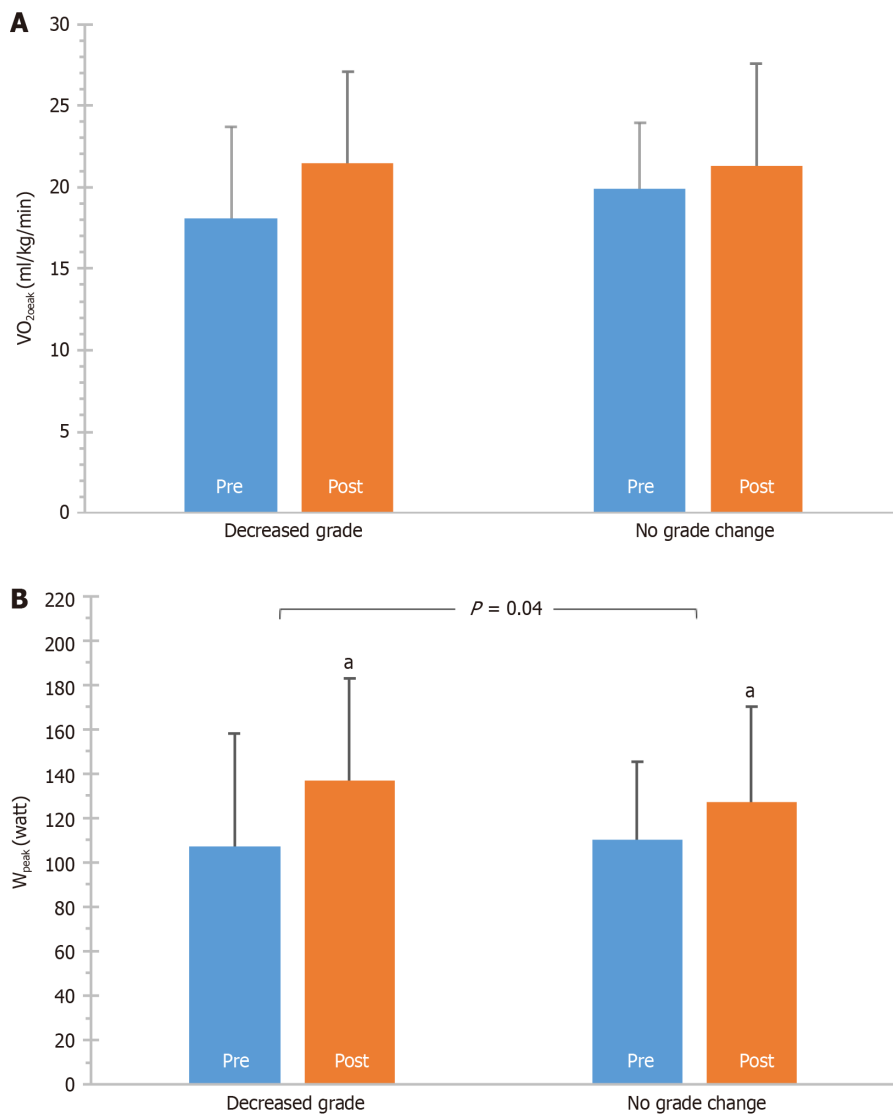


Figure 2 Values of VO_{2peak} (A) and W_{peak} (B) before and after the program for the groups of patients according to DD grade alteration *i.e.* "decreased grade" vs "no grade change". ^a $P < 0.05$, significant within-group difference.

This study had some limitations. First, there is no single non-invasive measure that quantifies the LV diastolic function. Instead, a number of indices are utilized, and current recommendations use a combination of conversational and TDI parameters to determine the diastolic function of the LV[21]. In our study, there was a statistically significant improvement on the DD grades, but other parameters, such as E/A and E/E', were not found to improve. This may be related to the method used to determine the diastolic stage and the sample size. In fact, some results were underpowered to reach definite conclusion. Also, LV diastolic filling patterns as evaluated with transmitral Echo-Doppler are influenced by a variety of factors including valvular insufficiency, myocardium viscoelastic properties, ventricular compliance and loading conditions[21]. However, all patients were under constant medication during the study and all of them had mild degree of mitral regurgitation. Finally, considering that the exercise benefits on CHF have already been well documented, a control group was not employed, and patients randomized in two groups, AER and COM, to explore any potential differences on the diastolic dysfunction.

CONCLUSION

In conclusion, DD plays an essential role in the pathophysiology of the HF syndrome and interventions that improve it can be beneficial in terms of symptoms and outcome. In this study, the effects of an exercise training rehabilitation program (AER with/

without strength training), were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

ARTICLE HIGHLIGHTS

Research background

Diastolic dysfunction (DD) of the left ventricular (LV) is a keystone in the pathophysiology of chronic heart failure (CHF). Exercise training in general induces several beneficial effects in CHF patients, including functional capacity, quality of life and clinical outcomes. In this study, the impact of a rehabilitation program on the DD and the ejection fraction (EF) of the LV is evaluated in patients with CHF and EF < 50%.

Research motivation

Exercise training induces several beneficial effects on CHF patients. However, the effects of exercise training on diastolic DD have not been adequately studied. This is also the case for the effects of different exercise regimes on DD.

Research objectives

The main aim of the study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the ejection fraction (EF) of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

Research methods

In this randomized clinical trial study, 32 patients with CHF were screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations. They randomly assigned to aerobic exercise (AER) or combined aerobic and strength training, by a researcher not involved in the rest of the tasks. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

Research results

Exercise training overall beneficially affected DD grade, right ventricular systolic pressure (RVSP), EF of the LV and AER capacity. No differences between the aerobic and combined group were observed.

Research conclusions

In this study, the effects of an exercise training rehabilitation program (AER with/without strength training) were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

Research perspectives

Future research is warranted to further explore the effects of different exercise training regimes on diastolic dysfunction.

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