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Major Article

Cardiac rehabilitation program in patients with Chagas heart failure: a single-arm pilot study

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Abstract

Introduction: The benefit of a cardiac rehabilitation (CR) program for patients with Chagas heart failure (CHF) remains unclear. Therefore, we aimed to investigate the effects of CR for CHF patients. **Methods:** A single-arm pilot study, including 12 patients with CHF, was performed. Patients participated in an 8-month physical exercise intervention, comprising aerobic, strength, and stretching exercises (3 times per week, 60 minutes per session). Nutritional and pharmaceutical counseling were also performed. Functional capacity (cardiopulmonary exercise test), muscle respiratory strength (manovacuometry), and body composition (anthropometry and skinfolds) were evaluated at baseline, and after 4 and 8 months of intervention. Cardiac function (echocardiography), biomarkers (lipid profile, glucose, and glycated hemoglobin) and quality of life (Minnesota Living with Heart Failure Questionnaire) were assessed at baseline and at the end of the intervention. **Results:** Seven of 12 patients included in the study completed the 8-month follow-up period. Only 2 moderate adverse events occurred during the exercise training. Functional capacity improved after 4 months of CR, while left ventricular ejection fraction (LVEF) and respiratory strength improved after 8 months. Patients with right ventricular (RV) dysfunction at baseline exhibited an improvement in functional capacity after 4 months, and improvements in left ventricular (LV) diastolic pressure, respiratory strength, and quality of life at the end of follow-up. Conversely, those with normal baseline RV function demonstrated LVEF increases that were not observed in patients with RV dysfunction. **Conclusions:** CR was feasible, safe, and has important clinical benefits for patients with CHF, specifically for cardiac function and muscle respiratory strength.

Keywords: Chagas disease. Physical activity. Cardiac rehabilitation.

INTRODUCTION

Chagas disease (*American trypanosomiasis*) is an important public health problem, affecting approximately 10 million people worldwide, most of which live in Latin America[1]. However, migratory movements have increased the number of cases reported in non-endemic areas, such as Europe, North America, and Oceania[2][3].

Cardiomyopathy is the most frequent and severe clinical manifestation of Chagas disease, affecting 20-30% of individuals during the chronic phase of the disease[4]. Clinical presentation is characterized by thromboembolic events, arrhythmias, and heart failure (HF); such symptoms account for the majority of morbidity, mortality, and decreased quality of life attributable to Chagas disease[5][6][7]. Chagas heart failure (CHF) is associated with higher mortality rates than HF from other etiologies, and accounts for 25-30% of death among patients with Chagas disease[8].

CHF treatment aims to manage symptoms, decrease mortality, and improve quality of life for the patient[9]. However, therapeutic approaches for CHF remain limited to the standard recommendations for HF treatment due to other conditions[10]; therefore, studies evaluating the effects of CHF-specific strategies are necessary.

Cardiac rehabilitation (CR) has been extensively advocated as an important coadjuvant in the treatment of HF[11][12]. HF-ACTION, a major randomized controlled trial evaluating the effects of CR implementation among patients with HF, showed that after adjustment for prognostic predictors, exercise training reduced all-cause and cardiovascular mortality and hospitalizations, while simultaneously increasing maximum

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oxygen consumption and health-related quality of life[13] [14]. A subsequent meta-analysis conducted by Sagar et al.[15] confirmed the efficacy and safety of exercise on HF.

However, the majority of studies that have evaluated CR in HF have failed to include patients with Chagas disease, and the few studies evaluating the effects of exercise training on patients with Chagas disease have been limited by short-term follow-up (≤ 6 months), the lack of echocardiographic evaluation, and the inclusion of patients in the early stages of Chagas cardiomyopathy or even those without evidence of cardiac disease[16] [17] [18] [19] [20]. Therefore, the safety and efficacy of CR among patients with CHF remains unknown. We conducted this pilot study to investigate the long-term effects of a CR program on functional capacity, cardiac function, respiratory muscle strength, body composition, biomarkers, and quality of life in CHF patients.

METHODS

Study design

The present study was a single-arm intervention study conducted at the Evandro Chagas National Institute of Infectious Disease (INI), located in Rio de Janeiro, Brazil, during a period from March 2013 to December 2014. The INI is a national reference center for treatment and research in infectious diseases and tropical medicine in Brazil, and is responsible for following a large cohort of patients with Chagas disease, all of who have been diagnosed with 2 simultaneously positive serological tests (enzyme-linked immunosorbent assay and indirect immunofluorescence)[21].

Patients with stages C or D Chagas cardiomyopathy[22] were included if they presented with typical electrocardiographic alterations, left ventricular ejection fraction (LVEF) < 45%, HF symptoms, and were on standard optimized medical therapy with good adherence to outpatient treatment within the last 3 months. Those who were unable to attend 3 weekly exercise training sessions, had neuromuscular limitations, cardiopathies of non-Chagasic etiology (e.g ischemic), systemic conditions limiting exercise practice (e.g chronic obstructive pulmonary disease), or who regularly practiced physical exercise, were excluded from the study.

Ethical considerations

All participants received information about the goals and procedures of the study and agreed to participate with signing of an informed consent. The study was performed in keeping with the revised Helsinki Declaration, and was approved by the Institutional Ethics Committee of the Evandro Chagas National Institute of Infectious Disease (CAAE: 0055.0.009.000-11). All ongoing and related trials for this intervention are registered at the Clinicaltrials.gov website (NCT02516293).

Intervention

Patients included in the study participated in a physical exercise intervention protocol performed 3 times per week, 60 minutes per session, over an 8-month period. Each exercise training session consisted of 30 minutes of aerobic exercise on a treadmill or cycle ergometer, 20 minutes of strength exercises for the major muscle groups (sit-ups, push-ups, and pull-ups), and 10 minutes of stretching exercises. Exercise intensity was set according to the heart rate obtained during each maximal progressive cardiopulmonary exercise test, corresponding to the anaerobic threshold minus 10% in the first month of the exercise protocol and the anaerobic threshold plus 10% in the following months. Blood pressure and heart rate were measured before, during aerobic exercise (after 20 minutes of exercise), and at the end of each training session using an aneroid sphygmomanometer and a heart rate monitor (Polar FT1). Individuals with severe arrhythmias were also monitored with an electrocardiogram during exercise sessions. All training sessions were performed in the morning with medical supervision.

Nutritional and pharmaceutical counseling were provided on a monthly basis during the follow-up, and consisted of general guidance regarding adequate eating habits for patients with HF, primarily with respect to sodium and water intake and medication usage, particularly drug dosage and compliance.

Measurements

Patients included in the study were followed throughout an 8-month period, during which evaluations of functional capacity (maximal progressive cardiopulmonary exercise test), muscle respiratory strength (manovacuometry), and body composition (anthropometry and skinfolds) were performed at baseline, after 4 months, and at the end of follow-up. Assessments of cardiac function (2-dimensional echocardiography), biomarkers (lipid profile, glucose, and glycated hemoglobin), and quality of life (Minnesota Living with Heart Failure Questionnaire) were taken at baseline and at the end of follow-up.

Maximal progressive cardiopulmonary test

A treadmill symptom-limited incremental cardiopulmonary exercise test was performed (Master, Inbramed, BR) in a temperature controlled room set at 18-22ºC. All tests were performed using a ramp protocol, consisting of gradual increments in work rate (velocity and inclination) at intervals of 10 to 60 seconds, individually tailored to achieve a fatigue-limited exercise duration of approximately 8 to 12 minutes. Individuals were encouraged to provide maximal effort until exhaustion (score 10 in adapted Borg scale), excepting cases in which the test was stopped prior for clinical reasons.

Analysis of respiratory gas exchange at rest, during exercise, and recovery, and yield measures of oxygen uptake (VO_2), carbon dioxide output (VCO_2), and ventilation (VE), were performed using a gas analyzer (VO2000, MedGraphics, St. Paul, MS, USA). The flow meter and gas analyzer were calibrated before each test, according to manufacturer specifications. Peak VO_2 was determined as the maximum VO_2 achieved 60 seconds before or after the peak workload. The ventilatory threshold was determined with visual inspection of the breakpoint in pulmonary ventilation, defined by the exercise level at which VE began to increase exponentially relative to the increase in VO_2.

These parameters were integrated with standard variables measured during the exercise test, including heart rate, blood pressure, work rate, 12-lead electrocardiography, and clinical

symptoms, in order to provide a comprehensive assessment of tolerance and physiological responses during exercise[24]. Oxygen pulse (O_2 pulse), VE/VCO_2 slope (V-slope), oxygen uptake efficiency slope (OUES), and functional aerobic impairment (FAI) were also evaluated.

Manovacuometry

Evaluation of respiratory muscle strength was performed with assessment of the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), using a digital pressure manometer connected to a mouthpiece (MVD 3000, Globalmed, BR). For measurement of MIP and MEP, patients remained in a seated position with a nose clip, and were directed to make a maximum inspiratory or expiratory effort at residual volume and total lung capacity, respectively, sustaining the effort for 1 to 2 seconds[25]. Assessments were repeated 2 to 5 times, and the mean value was used for analysis.

Body composition

Anthropometric evaluation consisted of measurements of height, weight, and circumferences, with minimal clothing and without shoes. Height and body weight were measured using the same calibrated digital scale with a stadiometer for all participants. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2). Circumference measures were taken at the largest girth of the hip and smallest girth of the waist.

Measurements of skinfold thickness were taken at the chest, midaxillary, triceps, subscapular, abdomen, suprailiac, and thigh sites on the right side of the body while standing in a relaxed position. Skinfold thickness was measured to the nearest 0.1cm using a Lange skinfold caliper (Beta Technology Inc, Cambridge, MD, USA). Measurements were taken twice at each site and averaged. The sum of these 7 skinfold thicknesses was used to estimate body composition using the Jackson & Pollock equation[26].

Two-dimensional echocardiography

Echocardiographic studies were performed by a single trained physician using a phased-array ultrasound system (Vivid 7, GE Medical Systems, Milwaukee, WI) equipped with an MS4 phased-array transducer. Cardiac dimensions and Doppler measurements were obtained in accordance with American Society of Echocardiography recommendations[27], and as described elsewhere[28]. M-mode echocardiography was used to measure the end-diastolic and end-systolic diameters. Two-dimensional LV end-diastolic and end-systolic volumes were determined using the modified Simpson's rule, with images obtained from apical 4-chamber and 2-chamber views. Pulsed-wave Doppler was performed in the apical 4-chamber view. From transmitral recordings, the peak early (E) and late (A) diastolic filling velocities were obtained.

Right ventricular (RV) systolic pressure was derived from continuous-wave Doppler interrogation of tricuspid regurgitation. RV systolic function was evaluated with measurement of the peak systolic myocardial velocity (RVS') of the lateral tricuspid annulus. Tissue Doppler of the mitral annulus was obtained at the septal and lateral positions. Values shown for peak systolic myocardial velocity (S') and peak early (E') and late (A') diastolic myocardial velocities are averages of the values obtained at the septal and lateral positions.

Biomarkers

Total cholesterol, triacylglycerol, high-density lipoprotein (HDL)-cholesterol, glucose, and glycated hemoglobin were measured using Siemens Dimension® reagent cartridges with an intra- and inter-assay coefficient of variation < 5%. Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)-cholesterol concentrations were calculated according to the Friedewald equation, based on triacylglycerol measures[29]. All biochemical measurements were performed in a laboratory accredited by the College of American Pathologists.

Minnesota Living with Heart Failure Questionnaire

The Portuguese version of the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a 21-item questionnaire that covers HF-related physical, psychological, and social impairments during the previous month, was used to evaluate quality of life. Items of the MLHFQ are assessed according to patient perceptions on a scale ranging from 0 (none) to 5 (very much), where 0 represents no limitation and 5 represents maximal limitation. The total MLHFQ score was obtained by adding the scores for all 21 items (0 to 105), where a higher score indicated a poorer quality of life[30].

Data analysis

A sample size calculation was based on a peak oxygen consumption increase of 2.9ml/kg/min, with a standard deviation of 2.0ml/kg/min[23]. Assuming a 90% power and a 5% significance level, and allowing for 30% of loss to follow-up, the total sample size required was 11 patients.

Descriptive statistics are expressed as mean (standard deviation) for continuous variables, and percentages for categorical variables. Testing of skewness and kurtosis was performed to evaluate the normality of data, which were subsequently log-transformed in cases of skewed distribution. Linear mixed models were performed to evaluate longitudinal changes over time. The likelihood-ratio test was used to compare random intercept and random slope models. Residual plots of all models were examined, with no major deviations from regression assumptions noted.

A subgroup analysis, with stratification according to the presence or absence of RV dysfunction (RVS' < 10cm/s) at baseline, was also performed. All calculations were accomplished using Stata 13.0 software (College Station, TX, 2013), and the significance level was set at 0.05.

RESULTS

Baseline characteristics

A total of 12 patients were selected for the present study. Of this cohort, 9 (75%) were female and 3 (25%) were male, with a mean age of 56.1 ± 13.8 years; the majority self-reported their race as mulatto (66.6%, n = 8). All participants were

TABLE 1 - Baseline characteristics of participants included in the study.

Variable	Overall (n = 12)	Stratified	
		no RV dysfunction (n = 6)	RV dysfunction (n = 6)
Age (years)	56.1 (13.8)	63.5 (10.0)	48.7 (13.6)
Body weight (kg)	60.5 (12.3)	56.1 (6.9)	64.9 (15.4)
Height (m)	1.54 (0.1)	1.51 (0.07)	1.56 (0.12)
BMI (kg/m^2)	25.5 (4.2)	24.4 (2.7)	26.6 (5.4)
Fat mass (%)	26.3 (8.5)	23.7 (3.3)	29.0 (11.5)
Waist circumference (cm)	81.6 (9.0)	80.2 (8.5)	83.0 (10.1)
Hip circumference (cm)	93.3 (9.8)	90.3 (5.9)	96.3(12.5)
Waist-to-hip ratio	0.88 (0.06)	0.89 (0.79)	0.86 (0.04)
VO_2 peak (ml/kg/min)	15.8 (5.2)	17.4 (5.9)	14.2 (4.3)
AT (ml/kg/min)	9.7 (3.3)	10.5 (3.7)	8.9 (2.9)
RCP (ml/kg/min)	13.4 (4.7)	14.5 (5.6)	12.3 (3.7)
V-slope	28.1 (9.6)	28.5 (11.4)	27.7 (8.5)
OUES	1296.7 (608.9)	1183.1 (344.2)	1410.3 (816.3)
O_2 pulse (ml/beat)	8.5 (2.3)	9.4 (2.1)	7.6 (2.3)
FAI (%)	44.4 (15.8)	35.5 (15.1)	53.3 (11.4)
MIP (cmH_2O)	62.3 (26.6)	64.3 (14.7)	60.5 (35.1)
MEP (cmH_2O)	97.9 (23.2)	100.5 (19.2)	95.8 (27.8)
LVDd (mm)	66.1 (4.4)	66.7 (5.0)	65.5 (4.2)
LVDs (mm)	54.6 (4.8)	54.3 (5.8)	54.8 (4.1)
LVEF (%)	31.9 (7.7)	31.2 (9.3)	32.7 (6.7)
RVS' (cm/s)	8.9 (2.4)	10.5 (1.2)	7.3 (2.1)
E/E' ratio	19.3 (5.5)	15.0 (2.2)	23.5 (4.2)
Glucose (mg/dl)	89.8 (7.2)	92.7 (8.8)	87.0 (4.3)
Glycated hemoglobin (%)	5.8 (0.2)	5.8 (0.2)	5.8 (0.2)
Total cholesterol (mg/dl)	150.5 (33.8)	168.3 (35.7)	132.7 (21.6)
HDL-cholesterol (mg/dl)	45.4 (12.5)	48.8 (9.2)	42.0 (15.1)
LDL-cholesterol (mg/dl)	87.0 (26.4)	97.8 (32.2)	76.2 (14.6)
VLDL-cholesterol (mg/dl)	18.1 (10.2)	21.7 (11.4)	14.5 (8.4)
Triacylglycerol (mg/dl)	90.1 (51.8)	107.5 (57.9)	72.7 (42.5)
MLHFQ	41.0 (25.4)	28.0 (24.2)	54.0 (20.8)

RV: Right ventricular; **BMI:** body mass index; **VO_2 peak:** peak of oxygen consumption; **AT:** anaerobic threshold; **RCP:** respiratory compensation point; **V-slope:** ventilation (VE)/carbon dioxide output (VCO_2) slope; **OUES:** oxygen uptake efficiency slope; **O_2 pulse:** pulse of oxygen; **FAI:** functional aerobic impairment; **MIP:** maximal inspiratory pressure; **MEP:** maximal expiratory pressure; **LVDd:** end-diastolic left ventricular diameter; **LVDs:** end-systolic left ventricular diameter; **LVEF:** left ventricular ejection fraction; **RVS':** peak systolic myocardial velocity of the lateral tricuspid annulus; **E/E' ratio:** ratio of mitral velocity to early diastolic velocity of the mitral annulus; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **VLDL:** very-low--density lipoprotein; **MLHFQ:** Minnesota Living with Heart Failure Questionnaire.

illiterate or had failed to complete elementary school. The majority were classified as having stage C Chagas cardiomyopathy (83.3%, n = 10); the remaining 2 participants had stage D Chagas cardiomyopathy. Nine participants had pacemaker or cardioverter defibrillator devices (75%, n = 9). The cohort exhibited New York Heart Association (NYHA) class I (25%, n = 3), class II (58.3%, n = 7), and class III (16.7%, n = 2) functional classifications. The mean LVEF and VO_2 peak were 31.9 ± 7.7% and 15.8 ± 5.2ml/kg/min, respectively. Half of the participants included in the study had baseline RV dysfunction. Overall characteristics and characteristics stratified according to RV dysfunction are shown in **Table 1**.

All participants were receiving beta-blockers (carvedilol), 75% used angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (44.4% losartan, 44.4% enalapril, 11.2% captopril), and 91.6% used an aldosterone antagonist (spironolactone).

Follow-up period

The flow chart of participant inclusion and follow-up throughout the present study is depicted in **Figure 1**. Losses to

follow-up during the 8-month period were 42% (1 death due to complication of an acute respiratory infection, 3 clinical HF decompensation events, and 1 participant who was unable to afford transportation to the exercise center). Only 2 moderate adverse events were observed during exercise training sessions (symptomatic exertional hypotension).

The effects of the CR program throughout the study are displayed in **Table 2** and **Table 3**. There were significant improvements in peak VO_2 (+1.8ml/kg/min; p = 0.05) and FAI (-8.5%; p = 0.02) during the first 4 months, and LVEF (+6.6%; p = 0.02), MIP (+8.1cmH_2O; p = 0.005), and MEP (+14.7cmH_2O; p < 0.001) at the end of 8 months.

Participants with RV dysfunction at baseline exhibited improvements in peak VO_2 (+1.6ml/kg/min; p = 0.04), O_2 pulse (+2.0ml/beat; p = 0.009), and FAI (-7.8%; p = 0.002) after the first 4 months, and O_2 pulse (+2.7ml/beat; p = 0.007), E/E' ratio (-4.5; p < 0.0001), MIP (+9.8cmH_2O; p = 0.02), MEP (+15.3cmH_2O; p < 0.001), and quality of life (-32.0;

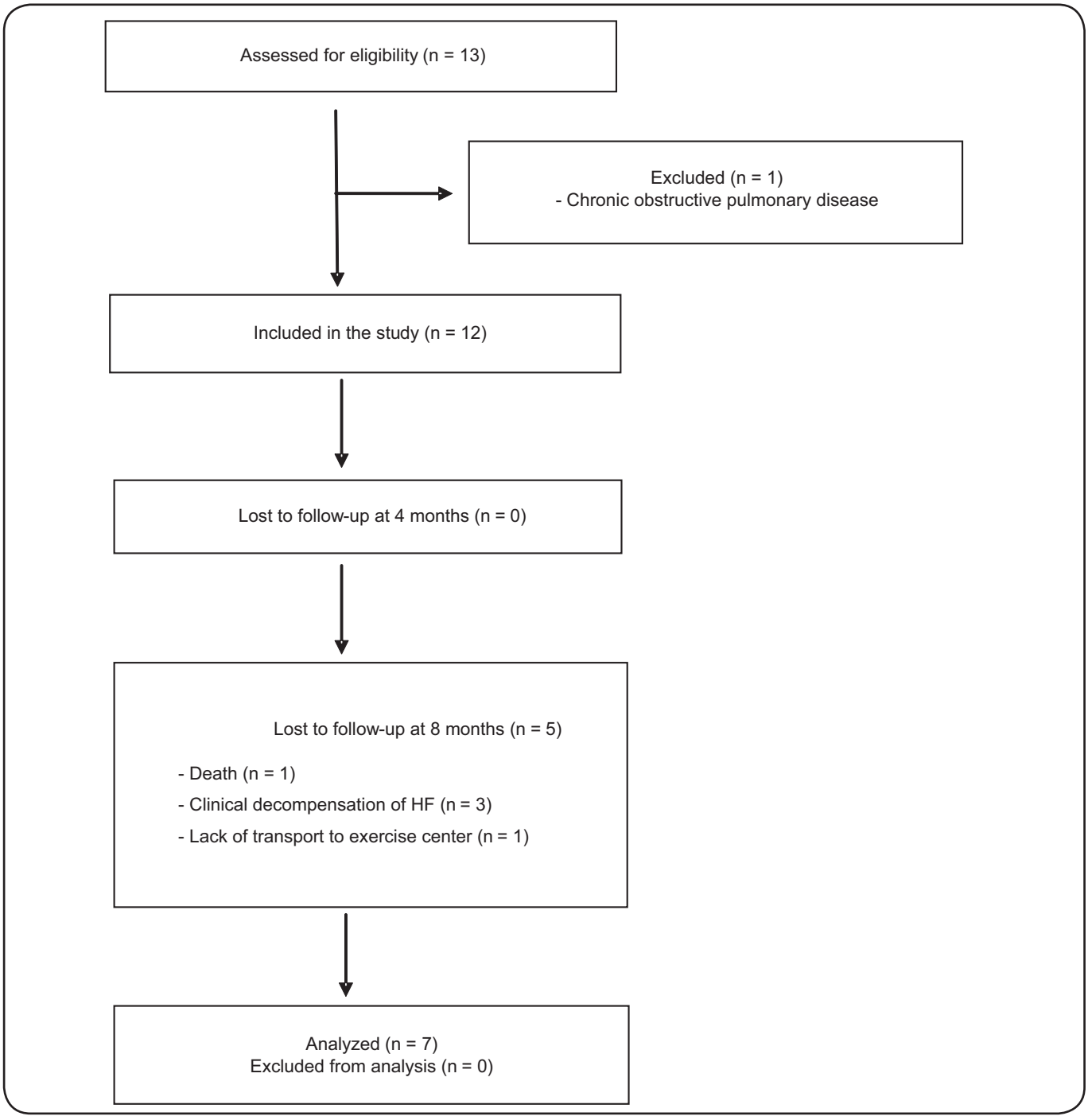

FIGURE 1 - Flow diagram of participants included in the study. HF: heart failure.

TABLE 2 - Crude means (standard deviation), slope (β), and changes from baseline (Δ) for functional capacity, muscle respiratory strength, and body composition.

	Four months				Eight months			
Variable	**Mean (sd)**	**β***	**Δ***	**p-value***	**Mean (sd)**	**β***	**Δ***	**p-value***
VO_2 peak (ml/kg/min)	17.6 (6.3)	+0.46	+1.8	0.05	19.2 (7.8)	+0.21	+1.7	0.19
O_2 pulse (ml/beat)	9.5 (2.7)	+0.25	+1.0	0.21	10.3 (2.1)	+0.18	+1.4	0.08
V-slope	28.4 (4.9)	+0.80	+0.3	0.91	30.9 (5.7)	+0.32	+2.6	0.36
VO_2 AT (%)	61.5 (16.5)	-0.05	-0.3	0.96	64.9 (8.3)	+0.32	+2.2	0.61
OUES	1134.2 (316.5)	-40.6	-162.5	0.29	1190.1 (367.8)	-27.8	-222.2	0.17
FAI (%)	35.9 (21.5)	-2.10	-8.5	0.02	35.1 (26.2)	-0.92	-7.3	0.13
MIP (cmH_2O)	65.6 (27.8)	+1.10	+4.5	0.10	75.8 (30.8)	+1.1	+8.1	0.005
MEP (cmH_2O)	103.8 (24.8)	+1.20	+4.8	0.09	117.7 (20.6)	+1.8	+14.7	< 0.001
Body weight (kg)	60.5 (12.0)	+0.02	+0.1	0.93	61.8 (13.9)	-0.07	-0.5	0.57
BMI (kg/m^2)	25.5 (3.6)	-0.008	-0.1	0.92	25.2 (2.9)	-0.05	-0.3	0.32
Lean body mass (kg)	43.3 (6.3)	-0.13	-0.5	0.20	46.0 (6.8)	-0.04	-0.3	0.56
Fat mass (kg)	17.6 (7.3)	+0.21	+0.9	0.20	15.8 (7.7)	-0.03	-0.2	0.74
Fat mass (%)	26.6 (8.5)	+0.07	+0.2	0.77	24.4 (6.9)	-0.09	-0.7	0.54
Waist circumference (cm)	80.8 (8.9)	-0.19	-0.8	0.49	82.2 (10.0)	-0.15	-1.1	0.29
Hip circumference (cm)	94.1 (8.4)	+0.19	+0.8	0.28	93.3 (7.5)	+0.03	+0.3	0.75
Waist-to-hip ratio	0.86 (0.07)	-0.004	-0.02	0.18	0.88 (0.08)	-0.002	-0.01	0.21

sd: standard deviation; **VO_2 peak:** Peak of oxygen consumption; **O_2 pulse:** pulse of oxygen; **V-slope:** ventilation (VE)/carbon dioxide output (VCO_2) slope; **VO_2 AT:** oxygen consumption at anaerobic threshold; **OUES:** oxygen uptake efficiency slope; **FAI:** functional aerobic impairment; **MIP:** maximal inspiratory pressure; **MEP:** maximal expiratory pressure; **BMI:** body mass index. *Linear mixed models.

TABLE 3 - Crude means (standard deviation), slope (β), and changes from baseline (Δ) for cardiac function, biomarkers, and quality of life.

	Eight months			
Variable	**Mean (sd)**	**β***	**Δ***	**p-value***
LVEF (Simpson %)	37.3 (9.7)	+0.82	+6.6	0.02
E/E' ratio	15.6 (4.7)	-0.24	-2.0	0.08
Glucose (mg/dl)	89.7 (6.9)	-0.02	-0.1	0.95
Glycated hemoglobin (%)	5.8 (0.4)	+0.007	+0.1	0.67
Total cholesterol (mg/dl)	158.1 (25.3)	-0.20	-1.5	0.84
HDL-cholesterol (mg/dl)	44.7 (12.5)	+0.27	+2.2	0.43
LDL-cholesterol (mg/dl)	97.1 (20.4)	-0.08	-0.6	0.90
VLDL-cholesterol (mg/dl)	16.3 (7.6)	-0.45	-3.6	0.25
Triacylglycerol (mg/dl)	81.3 (38.8)	-2.25	-18.0	0.45
MLHFQ	25.0 (21.1)	-1.89	-15.1	0.11

sd: standard deviation; **LVEF:** left ventricular ejection fraction; **E/E' ratio:** ratio of mitral velocity to early diastolic velocity of the mitral annulus; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **VLDL:** very-low--density lipoprotein; **MLHFQ:** Minnesota Living with Heart Failure Questionnaire. *Linear mixed models.

p = 0.009) at the end of the follow-up; the same improvements were not observed among those without RV dysfunction at baseline. Conversely, participants without RV dysfunction at baseline demonstrated a significant increase in LVEF (+11%; p = 0.006), which was not observed in the subgroup with RV dysfunction (**Figure 2**).

No significant changes were detected during the follow-up with respect to food consumption (energy intake and macronutrient distribution) and medication usage (drug classes and dosages). Compliance with exercise sessions was 76% during the first 4 months, and 65% from 4 to 8 months, with an overall 8-month compliance of 71%.

DISCUSSION

CHF management mirrors recommendations made for HF from other etiologies, despite that the majority of these interventions have not been specifically tested in patients with Chagas disease[9] [10]. In this context, CR programs have been extensively encouraged as an important coadjuvant in the treatment of HF, but studies evaluating the effects of CR on CHF remain scarce.

Lima et al.[16] conducted a study with the aim of evaluating the effects of exercise training in Chagas cardiomyopathy. A total of 40 patients were randomized to inactive control or exercise training groups, and followed up over 3 months. Patients included in the exercise training group exhibited improvements in estimated VO_2 max, 6-minute walk test distance, symptom severities, and the vitality, emotional functioning, and mental health domains of health-related quality of life. Similarly, in a single-arm study, Fialho et al.[18] observed improvements in peak VO_2, oxygen pulse (an indirect measure of cardiac function), and O_2 consumption at anaerobic threshold after 6-months of exercise training. However, a lack of direct measurements of cardiac function, the short-term follow-up period and the characteristics of patients included in these studies, most of them in the early stages of Chagas cardiomyopathy and without HF, limits the applicability of the results and reinforces the necessity for more research in this area.

Major findings of the present study were an improvement in cardiac function (17% in LVEF) and muscle respiratory strength (14% in MIP and 15% in MEP) following an 8-month CR program. Functional capacity was also improved after 4 months (11% in VO2 peak and 19% in FAI); however, these changes failed to persist throughout the entire follow-up.

Studies examining the effects of exercise on LVEF among patients with HF have shown controversial results. A study conducted by Hambrecht et al.[31] evaluated a total of 73 men, who were randomly assigned to home-based ergometer exercise (20 minutes per day at 70% of peak oxygen uptake) or no exercise intervention. Although resting LVEF increased from 30% at baseline to 35% at the 6-month follow-up (p = 0.003) in the exercise training group, no differences were observed with respect to the change from baseline between the exercise intervention group and controls (p = 0.47).

Conversely, Passino et al.[32] showed that a 9-month aerobic exercise training program improved LVEF, when compared to a group without exercise (+3.0 vs -1.0; p = 0.001). Similarly, a meta-analysis conducted by Chen et al.[33], including data from 16 trials (813 patients), demonstrated a standardized mean increase of 0.33 (95% CI 0.13-0.52) in LVEF following exercise interventions. Given that LV dysfunction is a primary predictor of mortality in Chagas heart disease[28] [34] [35], exercise training may constitute an important strategy to improve prognosis in CHF.

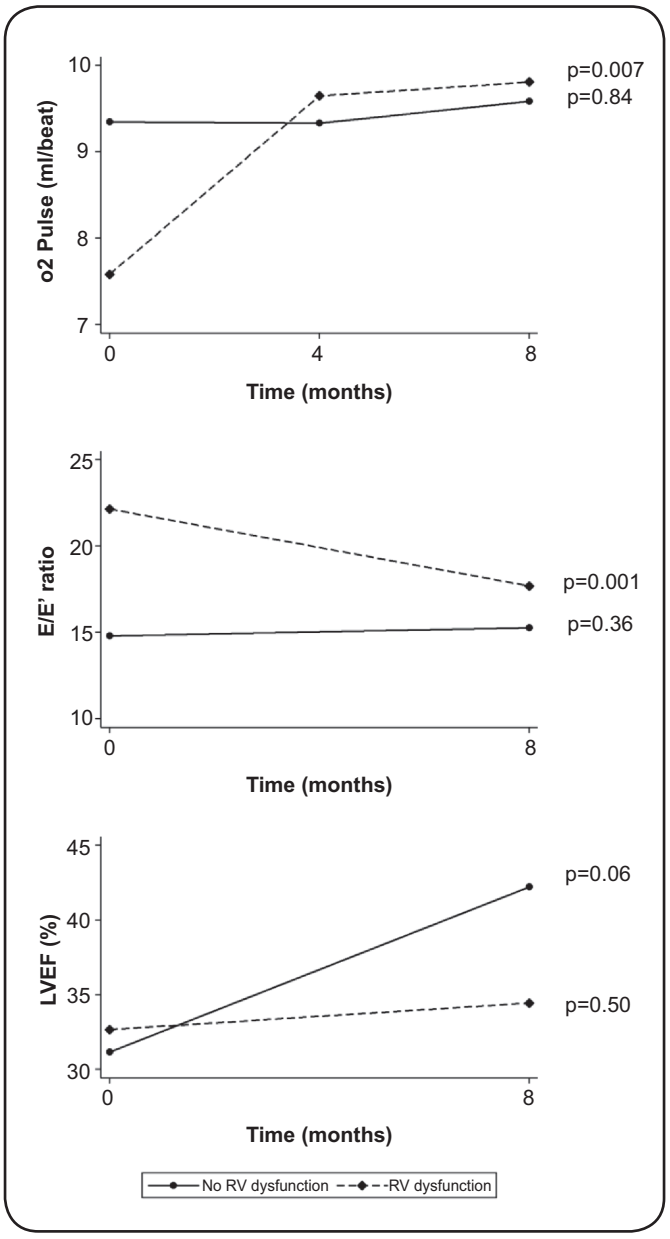

FIGURE 2 - Estimated changes for O_2 pulse, E/E' ratio, and LVEF, as stratified by RV dysfunction at baseline. E/E' ratio: ratio of mitral velocity to early diastolic velocity of the mitral annulus; **LVEF:** Left ventricular ejection fraction; **RV:** Right ventricular.

Another important finding of the present work was an increase in both inspiratory and expiratory muscle strength, even without specific exercise prescription for these muscles. All participants included in the study exhibited reduced respiratory muscle strength at baseline, as previously shown in patients

with Chagas cardiomyopathy[36] [37]. Indeed, it is possible that any training stimulus, regardless of specificity to respiratory muscles, may improve respiratory muscle strength and decrease related symptoms, such as dyspnea and exercise intolerance[38]. In a recent clinical trial, Adamapoulos et al.[39] demonstrated important benefits with aerobic training exercise for respiratory muscle strength, supporting the results observed in this study.

The majority of studies in the literature have demonstrated that CR programs improve functional capacity in HF over both short[40] and long-term follow-ups[14]. Moreover, a meta-analysis conducted by Lewinter et al.[41] showed an increase in standardized exercise capacity of 0.98 (95%CI 0.59-1.37; $p < 0.001$) when comparing exercise intervention groups against controls over a minimum of 6 months, thus confirming the favorable long-term effects of CR programs in HF.

In our study, although a significant benefit associated with the CR program was noted over the short-term, changes in peak VO_2 were not sustained throughout the entire follow-up. CHF presents with greater myocardial damage, abnormal autonomic regulation, low-grade chronic inflammation, and microvascular disturbance than other cardiomyopathies[42] [43], which may have contributed to the poorer long-term effects of exercise on functional capacity observed in the present study.

Despite numerous studies having previously documented the favorable effects of exercise[44], the lack of change observed in body composition and biomarkers in the present study might be attributable to the relative normality of these variables at baseline.

RV dysfunction is a marker of severity and an independent prognostic factor in patients with Chagas disease[45]. In this study, only participants with RV dysfunction at baseline achieved improvements in O2 pulse, E/E' ratio, MIP, MEP, and quality of life. Conversely, LVEF only increased in the group with normal RV function at baseline. Therefore, participants with the greatest severity of cardiac impairment were those who obtained the most substantial benefits from the CR program, especially with respect to cardiac hemodynamics, respiratory strength, and quality of life, but were unable to improve cardiac mechanics, as assessed by LVEF. This is likely due to substantial structural myocardial damage in the group with RV dysfunction.

Overall, exercise training for CHF patients was well tolerated and safe. No serious events, such as cardiorespiratory arrest, malignant ventricular arrhythmias, or cardiogenic shock, were observed during training sessions. In addition, the only death occurring during follow-up was due to complication of an acute respiratory infection, and was unrelated to the exercise intervention. The 3 clinical decompensations noted during the study were likely due to the relatively poor clinical condition of these participants at baseline.

Low compliance remains a significant barrier for CR programs to overcome before beneficial results can be obtained[46]. However, relatively high compliance with the exercise protocol used in the present study suggests that CR is feasible and should be encouraged as a coadjuvant in the treatment of CHF.

Limitations of the present study included the lack of a control group and the small sample size. Conversely, the main purpose of this single-arm pilot study was to obtain preliminary evidence regarding the efficacy and safety of CR for CHF. The results observed in this study will require confirmation in randomized clinical trials. However, the major strengths of our study were the long-term follow-up, the inclusion of participants with severe cardiac dysfunction, and the use of linear mixed models for data analysis, a statistical method which takes into consideration the covariance structure to obtain valid estimates of regression parameters.

In conclusion, the CR program implemented was feasible, safe, and had important clinical benefits for participants with CHF, primarily with respect to cardiac function and muscle respiratory strength. Participants with RV dysfunction at baseline, an important indicator of disease severity, were those who obtained the greatest benefits from the CR program. Given the simple, single-arm nature of the present study, larger randomized clinical trials are necessary to confirm the results observed.

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Conflict of interest

The authors declare that there is no conflict of interest.

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