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ORIGINAL ARTICLE

Comparative effects of a cardiovascular rehabilitation program on functional capacity in patients with chronic chagasic cardiomyopathy with or without heart failure

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ABSTRACT

Purpose: The aim of the present study was to evaluate the effects of cardiovascular rehabilitation (CR) on functional capacity of patients with chronic chagasic cardiomyopathy (CCC) and to compare the responses between CCC patients without and with heart failure (HF).

Materials and methods: A longitudinal observational retrospective study was carried out including 36 patients with CCC without HF (stage B2 [$n = 7$]) and with HF (stage C [$n = 29$]), who participated in a CR program. Functional capacity was assessed by a maximal progressive cardiopulmonary exercise test performed on a treadmill. The longitudinal effects of the CR on functional capacity were determined by linear mixed models that included an interaction term to evaluate the differential responses between patients without and with HF.

Results: Significant improvements in peak oxygen consumption, resting heart rate and blood pressure, and maximum pulmonary ventilation were observed for the overall study sample, with no apparent differential effects according to the presence of HF.

Conclusions: CR significantly improved functional capacity of patients with CCC. The responses to CR appear to be similar among patients without and with HF, reinforcing the need for its inclusion as a standard treatment strategy of CCC.

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Cardiac rehabilitation; cardiopulmonary exercise test; Chagas disease; cardiomyopathy; exercise

➤ IMPLICATIONS FOR REHABILITATION

- Exercise-based cardiovascular rehabilitation (CR) is a safe strategy that improves functional capacity, cardiac function, and quality of life in patients with several cardiovascular diseases, and recent studies also suggested a potential beneficial effect of CR in chronic chagasic cardiomyopathy (CCC).
- In this observational study, CR seems to equally improve exercise capacity, resting heart rate, resting blood pressure, and maximum pulmonary ventilation in patients with CCC without (stage B2) and with heart failure (stage C).
- Cardiovascular rehabilitation should be included as a standard treatment strategy for patients with CCC, regardless the severity of cardiomyopathy.

Introduction

Chagas disease (CD) is a neglected tropical disease caused by the protozoan *Trypanosoma cruzi* that affects 6–8 million people worldwide, with most of patients living in Latin America, and some cases found in USA and Europe [1]. Chronic chagasic cardiomyopathy (CCC) affects around 30% of patients with CD and represents the most severe clinical manifestation associated with high morbidity and mortality rates with a great impact for health care systems [2,3]. The main clinical manifestations of CCC are cardiac arrhythmias, thromboembolism, and heart failure (HF) [4]. The 2015 Brazilian Consensus on CD [5] classifies CCC into five different stages according to electrocardiogram, echocardiogram, and HF findings reflecting prognosis, as follows: stage A – altered electrocardiogram and no left ventricular (LV) wall motion changes on echocardiogram; stage B1 – altered electrocardiogram and LV wall motion changes with a LV ejection fraction (LVEF) $\geq$45%; stage B2 – altered electrocardiogram and LVEF $<$45% and no HF symptoms; stage C – compensated HF; and stage D – end-stage HF.

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Exercise-based cardiac rehabilitation (CR) has been shown to be a safe strategy capable of improving functional capacity, cardiac function, and quality of life of overall patients with CCC [6–9]. However, the differential responses to exercise-based CR programs among patients across different CCC stages is uncertain, especially those related or not to the presence of HF. Evidence in this sense can be clinically relevant for optimizing care and exercise training prescription for this population. Therefore, the aim of the present study was to evaluate the effects of CR on functional capacity of patients with CCC and to compare their responses according to the presence of HF (stages B2 vs. C). We hypothesized that individuals without HF, that usually present less severe cardiac impairments and clinical decompensations, would better benefit from a CR program.

Methods

Study design and population

This is a retrospective longitudinal observational study including patients with CCC that participated in a CR program between September 2013 and December 2019 at the Evandro Chagas National Institute of Infectious Diseases – INI (Rio de Janeiro, Brazil). The study was approved by the INI institutional ethics committee (CAAE 0055.0.009.000-11). Included patients had LVEF lower than 45% without (stage B2) or with HF symptoms (stage C) and were clinically stable during the previous three months, adherent to clinical treatment, and older than 18 years. Patients with neuromuscular or systemic conditions limiting physical exercise or the cardiopulmonary exercise test (CPET), practitioners of regular exercise before enrollment in the CR program (>1x week, 60 min per session in the last three months), unable to attend three weekly exercise sessions, and pregnant women were excluded.

Before the beginning of the CR program, patients underwent a comprehensive evaluation including sociodemographic, clinical and anthropometric assessments (weight, height, and waist circumference), CPET and cardiac image examination to determine LVEF (two-dimensional echocardiography). Two-dimensional LV end-diastolic and end-systolic volumes were determined using the modified Simpson's rule, with images obtained from apical four-chamber and two-chamber views [10]. Patients underwent periodical CPET re-evaluations during the period that they participated in the CR program, usually every 3–4 months.

Intervention

Patients were consecutively enrolled in an exercise-based CR program that comprised exercise training, daily clinical evaluation, nutritional counseling, and pharmaceutical care interventions. The exercise training was performed three times a week, 60 min per session, divided into 30 min of aerobic exercises on a treadmill or cycle ergometer (according to the availability of equipment during the sessions), 20 min of strength exercises for the major muscle groups (major pectoralis, latissimus dorsi, deltoid, quadriceps femoris, gluteus maximus, and calf) and 10 min of flexibility and balance exercises, without break between the different exercise modalities [7,9]. The intensity of aerobic exercise was prescribed according to the anaerobic threshold obtained in the initial CPET, from 90% to 100% in the first month of training and from 100% to 110% in the following months. For those patients whose anaerobic threshold was not identified during the CPET, training intensity was prescribed according to Hellerstein's formula (heart rate (HR)=(102 + maximum metabolic equivalents achieved)/1.41)), with the target HR ranging from 70% of maximum HR obtained in the CPET to Hellerstein's formula percentage in the first month, and from Hellerstein's formula percentage to 85% of maximum HR in the following months. The exercise training workloads were adjusted after every CPET. Training sessions were supervised by trained professionals and occurred in the morning.

Nutritional counseling and pharmaceutical care were monthly provided and consisted of general orientation about healthy eating, reduced sodium and water intake, and medication usage, particularly drug dosage and compliance.

Measurement procedures

Functional capacity was assessed three times during the period in which patients participated in the CR program, usually at baseline, after 3–4 months and 6–8 months. A maximal progressive CPET was performed on a treadmill (Inbramed®, Porto Alegre, Brazil) in a temperature-controlled environment (between 22° and 24° C [71.6° and 75.2° F]), using the ramp protocol that consisted of gradual increases in speed and inclination at intervals of 10–60 s, individually tailored to achieve a fatigue-limited exercise duration of approximately 8–12 min. Patients were encouraged to perform maximum effort until exhaustion according to the modified Borg scale, except in cases in which the CPET was interrupted for clinical reasons [11].

Gas exchange analysis at rest, during the test and recovery were performed using a VO2000 gas analyzer (MedGraphics, St. Paul, MN). VO_2 peak, the primary outcome of the present study, was determined as the maximum value of VO_2 reached 60 s before or after the peak workload [11]. Other parameters assessed during CPET were resting and maximum HR, resting and maximum systolic blood pressure (SBP) and diastolic blood pressure (DBP) blood pressure, maximum double product (DP, multiplying the HR and SBP), SBP changes between maximal and resting values (ΔSBP), HR decrease at the first minute of recovery (ΔHR_{1min}), presence of dysautonomia (ΔHR_{1min} equal to or less than 12 bpm), maximum metabolic equivalent (MET max), and maximum pulmonary ventilation (VE max). The oxygen pulse (PuO_2), the equivalent ventilation slope for carbon dioxide output (VE/VCO_2 slope), the slope of the oxygen uptake (OUES), and functional aerobic impairment (FAI) were also evaluated [12].

Data analysis

Descriptive statistics consisted of mean and standard deviation for continuous variables and number of observations and percentage for categorical variables. Baseline characteristics were compared using independent *t*-test or Fisher's exact test. The longitudinal effects of the exercise training program on studied variables were determined using a linear mixed model adjusted by age and sex. An interaction term (time vs. CCC stage) was included in the model to compare the effects of exercise training on functional capacity in patients with and without HF. Significance level was set at 0.05 and all analyses were performed using Stata13.0 software (StataCorp 2013, College Station, TX).

Results

The baseline characteristics of the 36 patients included in the study are shown in Table 1. Briefly, mean age was 58.1 years, with a predominance of men (63.9%), more than five years of education (58.3%) and 47.2% presenting cardiac device. The mean VO_2

Table 1. Characteristics of participants included in the study ($n = 36$).

	Percentage (frequency) or mean (±standard deviation)			
Variable	Overall ($n = 36$)	B2 ($n = 7$)	C ($n = 29$)	p Value
Age (years)	58.1 (±11.7)	61.6 (±9.7)	57.2 (±12.2)	0.38
Sex (%)				
Women	36.1 (13)	14.3 (1)	41.4 (12)	0.38
Men	63.9 (23)	85.7 (6)	58.6 (17)	
Schooling (%)				
$\leq$5 years	41.7 (15)	28.6 (2)	65.5 (19)	0.10
>5 years	58.3 (21)	71.4 (5)	34.5 (10)	
Race (%)				
White	41.7 (15)	57.1 (4)	37.9 (11)	0.42
Non-White	58.3 (21)	42.9 (3)	62.1 (18)	
Marital status (%)				0.67
Married	58.3 (21)	71.4 (5)	55.2 (16)	
Single or widowed	41.7 (15)	28.6 (2)	44.8 (13)	
Smoking (%)				
Non-smoker	86.1 (31)	71.4 (5)	89.7 (26)	0.24
Smoker or former smoker	13.9 (5)	28.6 (2)	10.3 (3)	
Non-chagasic heart disease (%)				
No	97.2 (35)	100.0 (7)	96.6 (28)	1.00
Yes	2.8 (1)	0.0 (0)	3.4 (1)	
Hypertension (%)				
No	75.0 (27)	57.1 (4)	79.3 (23)	0.33
Yes	25.0 (9)	42.9 (3)	20.7 (6)	
Diabetes mellitus (%)				
No	88.9 (32)	85.7 (6)	89.7 (26)	1.00
Yes	11.1 (4)	14.3 (1)	10.3 (3)	
Dyslipidemia (%)				
No	69.4 (25)	42.9 (3)	75.9 (22)	0.17
Yes	30.6 (11)	57.1 (4)	24.1 (7)	
Stroke (%)				
No	75.0 (27)	57.1 (4)	79.3 (23)	0.33
Yes	25.0 (9)	42.9 (3)	20.7 (6)	
Chronic obstructive pulmonary disease (%)				
No	100.0 (36)	100.0 (7)	100.0 (29)	1.00
Yes	0.0 (0)	0.0 (0)	0.0 (0)	
Weight (kg)	68.0 (±15.5)	78.0 (±11.6)	65.6 (±15.5)	0.06
Height (cm)	160.9 (±9.7)	168.4 (±8.4)	159.0 (±9.2)	0.02
Waist circumference (cm) ($n = 34$)	84.2 (±18.0)	84.7 (±36.6)	84.1 (±12.3)	0.94
BMI (kg/m^2)	26.2 (±5.1)	27.7 (±5.2)	25.8 (±5.2)	0.39
Overweight (BMI > 25 kg/m^2)				
No	77.8 (28)	71.4 (5)	79.3 (23)	0.64
Yes	22.2 (8)	28.6 (2)	20.7 (6)	
Cardiac device (%)				
No	52.8 (19)	71.4 (5)	48.3 (14)	0.41
Yes	47.2 (17)	28.6 (2)	51.7 (15)	
Urea (mg/dl)	43.6 (±18.6)	32.3 (±5.2)	46.3 (±19.6)	0.07
Creatinine (mg/dl)	1.2 (±0.3)	1.1 (±0.2)	1.3 (±0.3)	0.27
LVEF (%) ($n = 33$)	33.3 (±9.3)	40.7 (±9.5)	31.7 (±8.6)	0.03
HR at anaerobic threshold (bpm) ($n = 25$)	98.4 (±18.9)	99.6 (±5.72)	98.2 (±21.1)	0.88
VO_2 at anaerobic threshold ($ml.kg^{-1}.min^{-1}$) ($n = 21$)	12.1 (±4.4)	15.4 (±1.9)	11.4 (±4.4)	0.10
Resting HR (bpm)	66.7 (±10.2)	66.3 (±7.3)	66.8 (±10.9)	0.91
Resting SBP (mmHg)	109.7 (±16.8)	129.4 (±14.2)	105.0 (±13.8)	<0.001
Resting DBP (mmHg)	70.6 (±10.7)	81.4 (±11.4)	68.0 (±8.9)	0.002
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	16.4 (±4.7)	19.0 (±4.1)	15.8 (±4.6)	0.10
MET max	4.7 (±1.3)	5.4 (±1.2)	4.5 (±1.3)	0.11
VE max (l/min) ($n = 31$)	35.9 (±11.8)	37.9 (±12.7)	35.4 (±11.8)	0.65
VE/VCO_2 slope	27.4 (±6.8)	24.8 (±3.5)	28.0 (±7.3)	0.27
OUES	1436.6 (±554.3)	1889.8 (±544.0)	1327.2 (±506.9)	0.01
FAI (%)	42.2 (±14.7)	30.9 (±9.8)	44.9 (±14.5)	0.02
Oxygen-pulse (ml/bpm)	10.1 (±3.1)	12.1 (±3.0)	9.6 (±2.9)	0.05
Respiratory coefficient ($n = 32$)	1.1 (±0.14)	1.0 (±0.1)	1.1 (±0.2)	0.20
HR max (bpm)	109.1 (±24.0)	111.0 (±14.1)	108.7 (±26.0)	0.83
SBP max (mmHg) ($n = 35$)	115.6 (±27.3)	142.9 (±19.4)	108.9 (±24.8)	0.002
DBP max (mmHg) ($n = 35$)	67.3 (±12.8)	72.0 (±9.4)	66.1 (±13.4)	0.28
DP max (mmHg.bpm) ($n = 32$)	12904.3 (±4578.1)	16266.0 (±4563.7)	12128.5 (±4299.5)	0.04
ΔSBP (mmHg) ($n = 35$)	5.7 (±19.3)	13.4 (±14.7)	3.7 (±20.0)	0.24
ΔHR_{1min} (bpm)	−15.7 (±12.7)	−9.7 (±5.5)	−17.2 (±13.6)	0.17
Dysautonomia				
No	58.3 (21)	28.6 (2)	65.5 (19)	0.10
Yes	41.7 (15)	71.4 (5)	34.5 (10)	

BMI: body mass index; cardiac device: pacemaker, implantable cardio-defibrillator or resynchronizer; LVEF: left ventricular ejection fraction; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2 peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO_2 slope: ventilatory equivalent inclination for carbon dioxide output; OUES: slope of oxygen consumption efficiency; FAI: functional aerobic impairment; DP: double product; Δ SBP: maximum SBP-resting SBP; B2: chronic heart disease classification at stage B2; C: chronic heart disease classification at stage C.

Table 2. Longitudinal effects of the cardiovascular rehabilitation program on cardiopulmonary exercise testing variables of overall participants included in the study.

	CPET 2 ($n = 26$; B2 = 4 and C = 22) (median follow-up: 3.7 months; IQR 25–75%: 3.3–4.1)			CPET 3 ($n = 17$; B2 = 4 and C = 13) (median follow-up: 6.6 months; IQR 25–75%: 6.2–7.5)		
Variable	Overall	β^a	p Value	Overall	β^a	p Value
Resting HR (bpm)	65.6 (±12.4)	−1.0	0.66	61.5 (±15.5)	−4.9	0.07
Resting SBP (mmHg)	97.1 (±16.7)	−12.6	<0.001	103.4 (±18.3)	−9.2	0.004
Resting DBP (mmHg)	62.5 (±11.4)	−8.0	<0.001	68.5 (±12.7)	−3.8	0.14
VO_2 peak (ml.kg^{-1}.min^{-1})	18.8 (±6.1)	+2.4	<0.001	19.8 (±6.1)	+1.6	0.03
MET max	5.4 (±1.7)	+0.7	<0.001	5.7 (±1.8)	+0.5	0.03
VE max (l/min)	40.4 (±12.9)	+6.0	<0.001	45.7 (±10.3)	+7.5	<0.001
VE/VCO_2 slope	27.8 (±4.0)	+0.2	0.83	30.3 (±5.1)	+2.6	0.06
OUES	1369.6 (±498.7)	−43.5	0.60	1374.4 (±431.6)	−180.7	0.06
FAI (%)	20.2 (±15.9)	−7.8	0.001	20.3 (±20.4)	−5.6	0.04
Oxygen-pulse (ml/bpm)	10.9 (±3.9)	+1.2	0.05	11.3 (±3.6)	+0.9	0.20
HR max (bpm)	115.8 (±21.4)	+6.3	0.11	117.8 (±20.9)	+3.6	0.44
SBP max (mmHg)	109.2 (±31.1)	−5.4	0.27	112.6 (±22.6)	−7.8	0.17
DPB max (mmHg)	61.2 (±17.3)	−5.7	0.06	63.4 (±13.3)	−5.3	0.14
DP max (mmHg.bpm)	12623.3 (±4684.3)	−98.2	0.90	13580.8 (±3909.4)	−467.8	0.60
ΔSBP (mmHg)	12.1 (±24.7)	+6.9	0.12	9.2 (±14.3)	+2.0	0.70
ΔHR_{1min} (bpm)	−17.2 (±14.5)	−1.3	0.67	−18.6 (±14.5)	−1.6	0.64
Dysautonomia						
No	79.6 (20)	−1.4	0.09	64.7 (11)	−0.2	0.85
Yes	23.1 (6)			35.3 (6)		

CPET: cardiopulmonary exercise test; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2 peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO_2 slope: ventilatory equivalent inclination for carbon dioxide outlet; OUES: slope of oxygen consumption efficiency; FAI: functional aerobic impairment; DP: double product; Δ SBP: maximum SBP-resting SBP; B2: chronic heart disease classification at stage B2; C: chronic heart disease classification at stage C.
[a]Unstandardized beta values from linear mixed model adjusted by age and sex (stage C vs. B2).

peak was 16.4 ± 4.7 ml.kg^{-1}.min^{-1}. Most patients were receiving beta-blockers (97.2%, $n = 35$), 91.7% were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ($n = 33$), 83.3% used diuretics ($n = 30$), and 58.3% ($n = 21$) used an aldosterone antagonist (spironolactone). The compliance rate to exercise training sessions was high (>70%). Regarding CCC stages, 19.4% ($n = 7$) were classified as stage B2 and 80.6% ($n = 29$) as stage C. Patients in stage B2 vs. C had higher LVEF (40.7% vs. 31.7%; $p = 0.03$), resting SBP (129.4 ± 14.2 vs. 105.0 ± 13.8 mmHg; $p < 0.001$), resting DBP (81.4 ± 11.4 vs. 68.0 ± 8.9 mmHg; $p = 0.002$), maximum SBP (142.9 ± 19.4 vs. 108.9 ± 24.8 mmHg; $p = 0.002$), DP (16266.0 ± 4563.7 vs. 12128.5 ± 4299.5 mmHg.bpm; $p = 0.04$), and OUES (1889.8 ± 544.0 vs. 1327.2 ± 506.9; $p = 0.01$). On the other hand, FAI was lower in stage B2 when compared to C (30.9 ± 9.8 vs. 44.9 ± 14.5%; $p = 0.02$).

The longitudinal effects of the CR program for the overall sample are depicted in Table 2. There were 10 losses to follow-up (3 stage B2 and 7 stage C) for the second CPET and 19 losses to follow-up (3 stage B2 and 16 stage C) for the third CPET, all of them due to reasons unrelated to the CR program. The median interval from the initial to the second CPET was 3.7 months, with significant improvements in VO_2 peak ($\beta = +2.4$ ml.kg^{-1}.min^{-1}; $p < 0.001$), FAI ($\beta = -7.8\%$; $p = 0.001$), MET max ($\beta = +0.7$; $p < 0.001$), VE max ($\beta = +6.0$ ml/min; $p < 0.001$), resting SBP ($\beta = -12.6$ mmHg; $p < 0.001$), and resting DBP ($\beta = -8.0$ mmHg; $p < 0.001$). The median interval from the initial to the third CPET was 6.6 months, with significant improvements in VO_2 peak ($\beta = +1.6$ ml.kg^{-1}.min^{-1}; $p = 0.03$), FAI ($\beta = -5.6\%$; $p = 0.04$), MET max ($\beta = +0.5$; $p = 0.03$), VE max ($\beta = +7.5$ ml/min; $p < 0.001$), and resting SBP ($\beta = -9.2$ mmHg; $p = 0.004$).

The comparison of responses to CR between patients according to the CCC stage is presented in Table 3. No statistically significant differences were observed for most of the studied variables, except for the HR reduction in the first minute of recovery in the second CPET, with a lower reduction in group C compared to B2 ($\beta = +19.9$; $p = 0.008$).

Discussion

The major finding of the present study was that CR improved the functional capacity among patients with CCC. The responses to CR appear to be similar among patients without and with HF (stages B2 and C), with no statistically significant differences for changes in functional capacity between groups. Although CR is a well-recognized lifestyle strategy advocated for secondary prevention of cardiovascular diseases in general [13,14], its effects on patients with CCC have only been recently investigated [6,7,9,15]. However, trials have included patients within overall stages of CCC, and severe patients are often underrepresented in these studies. Additionally, patients with CCC concomitant to HF diagnosis have worse prognosis [16,17], representing a higher-risk subgroup. Thus, improving their functional capacity is paramount to enhance their prognosis.

The improvements in variables that represent functional capacity such as VO_2 peak, MET max, and FAI are in accordance with previous research that included CCC patients with different levels of cardiac impairment [6,7,9,15,18]. CR program also promoted an improvement in VE, indicating that enhancements in pulmonary capacity, not only in cardiac function, may be one of the mechanisms that mediates the improvements in the maximal exercise capacity in patients with CCC [7,9].

The present study found a consistent long-term reduction in resting SBP and an initial reduction in resting DBP that was not sustained throughout the entire follow-up. Two previous studies examined the effects of exercise training on BP in patients with CCC [18,19], and presented discrepant results. While Mendes et al. found a significant decrease in SBP after six weeks of aerobic exercise [18], Oliveira et al. did not observe any significant changes on SBP or DBP in hypertensive patients with CCC after

Table 3. Comparison of longitudinal effects of the cardiovascular rehabilitation program on cardiopulmonary exercise testing (CPET) variables according to clinical stages of chronic chagasic cardiomyopathy (stage B2 vs. C).

	CPET 2 ($n = 26$; B2 = 4 and C = 22) (median follow-up: 3.7 months; IQR 25–75%: 3.3–4.1)				CPET 3 ($n = 17$; B2 = 4 and C = 13) (median follow-up: 6.6 months; IQR 25–75%: 6.2–7.5)			
Variable	B2 ($n = 4$)	C ($n = 22$)	β^a	p Value	B2 ($n = 4$)	C ($n = 13$)	β^a	p Value
Resting HR (bpm)	67.5 (±4.9)	65.2 (±13.4)	−3.0	0.63	61.0 (±2.7)	61.7 (±14.3)	+0.3	0.96
Resting SBP (mmHg)	111.0 (±21.9)	94.5 (±14.9)	+12.3	0.08	120.5 (±10.9)	98.2 (±17)	+4.8	0.51
Resting DBP (mmHg)	73.0 (±13.6)	60.5 (±10.2)	+4.2	0.47	76.5 (±5.5)	66.0 (±13.4)	+5.1	0.40
HR max (bpm)	116.2 (±23.9)	115.8 (±21.5)	+0.7	0.95	105.2 (±30.8)	121.6 (±16.7)	+11.5	0.30
VO_2 peak (ml.kg^{-1}.min^{-1})	24.4 (±3.7)	17.8 (±5.9)	−2.1	0.22	23.4 (±5.2)	18.7 (±6.1)	−2.1	0.25
MET max	6.9 (±0.9)	5.1 (±1.7)	−0.5	0.28	6.7 (±1.5)	5.3 (±1.8)	−0.6	0.24
VE max (l/min)	47.0 (±8.4)	39.2 (±13.3)	−2.2	0.61	49.0 (±10)	44.7 (±10.6)	−3.1	0.49
VE/VCO_2 slope	25.0 (±2.2)	28.3 (±4.1)	+0.2	0.95	26.2 (±1.7)	31.6 (±5.2)	+1.9	0.55
OUES	2127.2 (±317.1)	1231.8 (±390.6)	−217.9	0.32	1842.2 (±263.3)	1230.4 (±368.2)	−31.4	0.89
FAI (%)	20.2 (±15.9)	38.0 (±19.9)	+4.1	0.53	20.3 (±20.4)	36.2 (±23.6)	+7.1	0.29
Oxygen-pulse (ml/bpm)	15.7 (±3.2)	10.1 (±3.4)	−2.4	0.14	15.9 (±2.9)	9.9 (±2.4)	−3.2	0.06
ΔSBP (mmHg)	16.5 (±11.4)	11.3 (±26.5)	+3.5	0.77	4.5 (±18.4)	10.6 (±13.3)	+12.6	0.31
DP max (mmHg.bpm)	14175.5 (±2589.3)	12431.1 (±4962.1)	+2965.0	0.15	14072 (±6155)	13429.7 (±3286.6)	+2706.5	0.20
SBP max (mmHg)	127.5 (±12.5)	105.8 (±32.5)	+14.7	0.25	125.0 (±10.5)	108.8(±24.2)	+15.4	0.25
DBP max (mmHg)	70.5 (±9.1)	59.5 (±18.1)	−4.9	0.55	70.0 (±7.1)	61.4 (±14.3)	−4.1	0.62
ΔHR_{1min} (bpm)	−27.8 (±11.3)	−15.3 (±14.4)	+19.9	0.008	−10.0 (±15.1)	−21.2 (±13.8)	−2.5	0.75
Dysautonomia								
No	75.0 (3)	68.2 (15)	+1.7	0.38	25.0 (1)	76.9 (10)	−0.7	0.73
Yes	25.0 (1)	31.8 (7)			75.0 (3)	23.1 (3)		

CPET: cardiopulmonary exercise test; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2 peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO_2 slope: ventilatory equivalent inclination for carbon dioxide outlet; OUES: slope of oxygen consumption efficiency; FAI: functional aerobic impairment; DP: double product; Δ SBP: maximum SBP-resting SBP; B2: chronic heart disease classification at stage B2; C: chronic heart disease classification at stage C.

[a]Unstandardized beta values from linear mixed model adjusted by age and sex (stage C vs. B2).

24 weeks of regular physical exercise [19]. These conflicting results may be attributed to methodological differences across studies that included participants with a variety of clinical conditions and diseases submitted to different exercise protocols, making difficult the comparison between studies [19].

Contrary to our hypothesis, the responses to CR program appeared to be similar between patients without (stage B2) and with HF (stage C). This finding strengthens the importance of CR program as a feasible and clinically relevant intervention strategy that should be considered and implemented in the first-line treatment of patients with CCC, even for those with more severe cardiac damage. Accordingly, a pilot study previously published by our group confirmed the beneficial effects of a CR program in severe CCC patients, with marked improvements in cardiac function and muscle respiratory strength [7]. In addition, considering that reductions in functional capacity are already observed in early stages of CCC [20], CR can be considered as an important low-cost strategy to reverse the decreased functional capacity observed in these patients.

The present study has some limitations that should be acknowledged. Due to the retrospective design, the small sample size and the relatively large percentage of losses to follow-up, our results should be interpreted with caution. Despite these limitations, to our knowledge, this is the first study that compared the responses to a CR program between patients within different levels of cardiac impairment, especially considering the presence of HF. Our findings provide an important insight about the wide beneficial effect of CR for patients with CCC. Future studies are necessary to investigate the influence of CR on clinical stages progression.

Conclusions

CR significantly improved functional capacity of patients with CCC. Most responses to CR appear to be similar among patients without and with HF, reinforcing the need for its inclusion as a standard treatment strategy of CCC.

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