

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/idre20

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

Aline Maria Nunes Viana, Marcelo Carvalho Vieira, Flavia Mazzoli-Rocha, Rudson Santos Silva, Aline Xavier Frota, Henrique Silveira Costa, Juliana Pereira Borges, Gilberto Marcelo Sperandio da Silva, Paula Simplício da Silva, Alejandro Marcel Hasslocher-Moreno, Roberto Magalhães Saraiva, Andrea Silvestre de Sousa, Fernanda de Souza Nogueira Sardinha Mendes & Mauro Felippe Felix Mediano

To cite this article: Aline Maria Nunes Viana, Marcelo Carvalho Vieira, Flavia Mazzoli-Rocha, Rudson Santos Silva, Aline Xavier Frota, Henrique Silveira Costa, Juliana Pereira Borges, Gilberto Marcelo Sperandio da Silva, Paula Simplício da Silva, Alejandro Marcel Hasslocher-Moreno, Roberto Magalhães Saraiva, Andrea Silvestre de Sousa, Fernanda de Souza Nogueira Sardinha Mendes & Mauro Felippe Felix Mediano (2022): Comparative effects of a cardiovascular rehabilitation program on functional capacity in patients with chronic chagasic cardiomyopathy with or without heart failure, Disability and Rehabilitation, DOI: 10.1080/09638288.2021.2024282

To link to this article: https://doi.org/10.1080/09638288.2021.2024282



Published online: 10 Jan 2022.

Submit your article to this journal



View related articles 🗹



View Crossmark data 🗹

ORIGINAL ARTICLE

Taylor & Francis

(Check for updates

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

Aline Maria Nunes Viana^{a,b} (b), Marcelo Carvalho Vieira^{a,c} (b), Flavia Mazzoli-Rocha^a (b), Rudson Santos Silva^a (b), Aline Xavier Frota^a (b), Henrique Silveira Costa^d (b), Juliana Pereira Borges^e (b), Gilberto Marcelo Sperandio da Silva^a (b), Paula Simplício da Silva^a (b), Alejandro Marcel Hasslocher-Moreno^a (b), Roberto Magalhães Saraiva^a (b), Andrea Silvestre de Sousa^a (b), Fernanda de Souza Nogueira Sardinha Mendes^a (b) and Mauro Felippe Felix Mediano^{a,f} (b)

^aEvandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; ^bHealth Center, Veiga de Almeida University, Rio de Janeiro, Brazil; ^cCenter for Cardiology and Exercise, Aloysio de Castro State Institute of Cardiology, Rio de Janeiro, Brazil; ^dPhysical Therapy Department, Federal University of Jequitinhonha and Mucuri Valleys, Diamantina, Brazil; ^eLaboratory of Physical Activity and Health Promotion, State University of Rio de Janeiro, Rio de Janeiro, Brazil; ^fDepartment of Research and Education, National Institute of Cardiology, Rio de Janeiro, Brazil

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.

► 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.

CONTACT Mauro Felippe Felix Mediano anauro.mediano@ini.fiocruz.br; mffmediano@gmail.com 🗈 Evandro Chagas National Institute of Infectious Disease, Avenida Brasil 4365, Rio de Janeiro, RJ 21040-900, Brazil

ARTICLE HISTORY

Received 25 June 2021 Revised 14 December 2021 Accepted 24 December 2021

KEYWORDS

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

^{© 2022} Informa UK Limited, trading as Taylor & Francis Group

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 period-ical 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). VO₂ peak, the primary outcome of the present study, was determined as the maximum value of VO2 reached 60s 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 (Δ SBP), HR decrease at the first minute of recovery (Δ HR_{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 (PuO₂), the equivalent ventilation slope for carbon dioxide output (VE/ VCO₂ 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

Variable Overall (p = 36) B2 (p = 7) C (p = 2) p Value Age (pears) 581. (±1.17) 61.6 (±9.7) 572. (±12.2) 0.38 See (%) 43.0 (13.10) 14.3 (1) 41.4 (12) 0.38 Memen 6.3 (23) 28.7 (6) 56.6 (7) 0.35 See (%) 53.3 (21) 28.5 (7) 54.5 (7) 0.45 See (%) 53.3 (21) 28.5 (7) 54.5 (7) 0.42 What 47.7 (15) 57.1 (6) 37.6 (13) 0.42 Nort-White 53.3 (21) 74.4 (5) 58.7 (20) 0.24 Mort-White 79.1 (20) 28.6 (7) 0.31 0.31 Socking (%) 32.2 (1) 0.0 (0) 34.0 (1) 0.02 Socking (%) 28.1 (31) 77.4 (5) 88.7 (20) 0.24 Socking (%) 23.0 (7) 57.1 (4) 79.3 (23) 0.33 Socking (%) 23.0 (7) 57.1 (4) 79.3 (23) 0.33 Ves 32.0 (7) 57.1 (4) 79.3 (23)			Percentage (frequency) or mean (±standard deviation)						
Ape (spars) SR1 (±1.7) 0.16 (±37) 7.7 (±12.2) 0.38 Worment 3.61 (13) 1.4.3 (11) 1.4.4 (12) 0.38 Worment 0.3.9 (2.3) 8.7 (0) 9.50 (17) 9.50 (17) S.5 yers 3.5 (2.1) 7.4 (4.17) 9.60 (17) 0.42 (17) S.5 yers 5.3 (2.1) 7.4 (5.1) 0.42 (18) 0.42 (18) Marind 5.3 (2.1) 7.4 (5.1) 0.2 (16) 0.42 (18) Marind faste (%) 3.8 (2.1) 7.4 (5.1) 0.4 (18) 0.6 (19) Marind faste (%) 3.8 (2.1) 7.4 (19) 0.5 (2.1 (16) 0.6 (19) Marind faste (%) 7.5 (2.2) (18) 0.00 (7) 0.6 (2.8) 0.00 (19) Marind faste (%) 7.5 (0.7) 5.1 (4) 7.4 (17) 0.2 (17) Marind faste (%) 7.5 (0.7) 5.7 (4) 7.4 (7) 0.2 (17) Marind faste (%) 7.5 (0.7) 5.7 (4) 7.4 (7) 0.00 (10) 0.0 (10) 0.0 (10) 0.0 (10) 0.0 (10) 0.0 (10) 0.0 (10) 0.0 (10)	Variable	Overall ($n = 36$)	B2 (<i>n</i> = 7)	C (n = 29)	p Value				
Ser, Rey Manual 36.1 (13) 14.2 (1) 41.4 (12) 0.3.8 Schooling (%) 36.1 (13) 85.7 (6) 36.6 (17) 36.5 (19) 0.0 Schooling (%) 41.7 (15) 26.6 (2) 65.5 (19) 0.0 0.0 Schooling (%) 41.7 (15) 25.6 (2) 65.5 (19) 0.0 0.0 Schooling (%) 41.7 (15) 25.6 (2) 62.1 (18) 0.0	Age (years)	58.1 (±11.7)	61.6 (±9.7)	57.2 (±12.2)	0.38				
Mean 63.9 23.7 16 32.6 17 52.0 Solonling (%) 45.7 15.7 25.6 17.7 15.2 16.6 17.7 17.1	Sex (%) Women	36 1 (13)	14.3 (1)	<i>41 4</i> (17)	0.38				
Schooling (%) - 5 years 35 (21) - 71.4 (5) 24.6 (2) 65.5 (18) 0.0 Pace (%) Near Solution (%) - 72.1 (4) 77.4 (5) 73.0 (11) 0.0 Mariel status (%) - 72.1 (5) 24.6 (2) 44.8 (13) - 74.4 (5) 73.0 (11) 0.0 Single or videowed 41.7 (15) 24.6 (2) 44.8 (13) - 74.4 (5) 73.0 (11) 0.0 Single or videowed 41.7 (15) 24.6 (2) 44.8 (13) - 74.4 (5) 73.0 (11) 0.0 (0) 74.0 (10)	Men	63.9 (23)	85.7 (6)	58.6 (17)	0.50				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Schooling (%)								
jack jack jack jul jack jul jack jul jack jul white 447 (15) 57.1 (4) 37.9 (1) 0.42 Non-White 58.3 (21) 42.0 (3) 62.1 (18) 0.67 Maried 58.3 (21) 71.4 (5) 52.2 (16) 0.67 Single or valueded 47.7 (15) 57.1 (4) 52.5 (16) 0.67 Maried Jatts (b) 0.67 58.6 (2) 44.8 (13) 0.67 Single or valueded 47.7 (15) 57.1 (4) 59.7 (26) 0.24 Single or valueded 12.9 (5) 28.6 (2) 48.0 (10) 0.7 (20) 0.24 Non dispate heart disease (%) 72.2 (25) 1000 (7) 96.6 (28) 0.00 No 72.0 (27) 57.1 (4) 73.9 (21) 0.7 (20) 0.00 Ves 11.1 (4) 14.3 (1) 10.3 (3) 0.00 0.00 (7) 100.0 (28) 10.00 Ves 0.00 (3.00 (10) 0.7 (14) 73.9 (27) 57.1 (4) 73.9 (27) 0.17 Ves 0.00 (3.6)	≤5 years	41.7 (15)	28.6 (2)	65.5 (19) 24.5 (10)	0.10				
Think 41 /7 (15) 57 /1 (4) 37 9 (11) 0.42 Martied 58 2 (2) 42 0 (3) 62.1 (18) 0.67 Martied 58 3 (21) 71.4 (5) 58 2 (2) 0.42 Sonking (W) 86.1 (11) 71.4 (5) 89.7 (28) 0.42 Non-Namber 86.1 (11) 71.4 (5) 89.7 (28) 0.42 Non-Chargies heart disease (%) 97.2 (35) 1000 (7) 96.6 (28) 100 Non-Chargies heart disease (%) 97.2 (35) 1000 (7) 96.6 (28) 0.33 Yes 28.0 (27) 57.1 (6) 79.3 (23) 0.33 Yes 28.0 (27) 57.1 (6) 79.3 (23) 0.33 Yes 30.6 (11) 57.1 (6) 24.1 (7) 11.7 No 66.4 (25) 42.9 (3) 75.9 (22) 0.17 Ves 30.6 (11) 57.1 (6) 79.3 (23) 0.33 Ves 30.6 (11) 77.1 (6) 79.3 (23) 0.33 Ves 30.6 (11) 77.1 (6) 79.3 (23)	>5 years Race (%)	58.3 (21)	/1.4 (5)	34.5 (10)					
Norwhite Martal stars (%) SS 2(1) 42 2(3) 62,1 (18) Marted Marted Single or violawed 58,3 (21) 71,4 (5) 52,2 (16) Marted Single or violawed 13,7 (1,7) 28,6 (2) 10,3 (3) Non-ronder more or noncer weit 13,9 (5) 28,6 (2) 10,3 (3) Non-chagasch hart disease (%) 96,6 (28) 10,00 Non chagasch hart disease (%) 94,4 (1) 0,00 34,4 (1) Non chagasch hart disease (%) 93,2 (2) 63,7 (2) 10,00 Non chagasch hart disease (%) 93,2 (2) 63,7 (2) 10,00 No marker of more moker 25,0 (9) 57,1 (4) 93,3 (2) 63,7 (2) No marker of more moker 25,0 (9) 42,3 (3) 75,9 (2) 10,00 No marker of more moker 70,0 (7) 10,00 (2) 10,00 No marker of more moker 70,0 (7) 73,1 (4) 73,1 (2) 73,1 (2) 73,1 (2) 10,00 No marker of more more (m) (n = 34) 66,0 (1) 57,1 (4) 73,1 (4) 74,1 (7) 10,00 10,00 10,00 10,00	White	41.7 (15)	57.1 (4)	37.9 (11)	0.42				
Married Marri Married Married Married Married Married Married M	Non-White	58.3 (21)	42.9 (3)	62.1 (18)					
Singler widword 41.7 (15) 28.6 (2) 44.8 (13) Non-smoker 66.1 (31) 71.4 (5) 89.7 (26) 0.24 Non-smoker 35.9 (5) 28.6 (2) 10.3 (3) 1000 (7) 96.6 (28) 1.00 Non-chagais heart disease (%) 72.0 (3) 0.00 (0) 3.4 (1) 0.00 3.4 (1) Non-chagais heart disease (%) 75.0 (27) 5.7 1 (4) 79.3 (23) 0.3 Ves 25.0 (0) 42.9 (3) 20.7 (6) 1000 Potementitus (%) 88.9 (32) 85.7 (6) 89.7 (26) 10.0 Ves 11.1 (4) 14.3 (1) 10.3 (3) 0.33 Stocker (%) 75.0 (27) 5.7.1 (4) 79.3 (23) 0.33 Ves 25.0 (9) 42.9 (3) 20.7 (6) 75.0 (27) 5.7.1 (4) 79.3 (23) 0.34 Ves 25.0 (9) 25.0 (9) 20.9 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (10) 0.00 (1	Marital status (%) Married	58 3 (21)	71.4 (5)	55.2 (16)	0.67				
Snoking (%) Since subset of former snoker (b)	Single or widowed	41.7 (15)	28.6 (2)	44.8 (13)					
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Smoking (%)	/							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Non-smoker Smoker er former smoker	86.1 (31)	71.4 (5)	89.7 (26)	0.24				
No972 (26)100.0 (7)96.6 (28)1.00Hypertension (%)75.0 (7)77.1 (4)79.3 (23)0.33Yes25.0 (9)42.9 (3)20.7 (6)0.00Diabetes mellus (%)88.9 (22)85.7 (6)89.7 (26)1.00Yes11.1 (4)14.3 (1)10.3 (3)0.010.01 (3.3 (3)0.01Dyslipctimia (%)75.0 (27)57.1 (4)79.3 (23)0.030.03No69.4 (25)42.9 (3)75.9 (22)0.170.01 (3.0 (3.0 (3.0 (3.0 (3.0 (3.0 (3.0 (3.0	Non-chagasic heart disease (%)	13.9 (5)	20.0 (2)	10.5 (5)					
Yes2.8 (1)0.0 (0)3.4 (1)No75.0 (27)7.7.1 (4)79.3 (23)0.33Ves25.0 (9)9.2.9 (3)2.0.7 (6)Dabetes mellitus (%)71.1.1 (4)1.4.3 (1)10.3 (3)Ves1.1.1 (4)1.4.3 (1)10.3 (3)0.7.1 (4)Dyslpidemia (%)6.9.4 (2.5)4.2.9 (3)2.0.7 (6)0.3.1 (7)Strate (%)3.0.6 (11)7.7.1 (4)7.9.3 (2.3)0.3.3 (7)Strate (%)7.50 (27)7.7.1 (4)7.9.3 (2.3)0.3.3 (7)Ves20.0 (0)0.00 (0)0.0 (0)0.00 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.0 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.0 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.0 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.00 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.00 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.00 (0)Ves0.0 (0)0.0 (0)0.0 (0)0.0 (0)Ves0	No	97.2 (35)	100.0 (7)	96.6 (28)	1.00				
$\begin{tabular}{ c c c } & respectively (respectively (r$	Yes	2.8 (1)	0.0 (0)	3.4 (1)					
Yes 25.0 (9) 42.9 (3) 20.7 (a) Constrained and a set of the se	No	75 0 (27)	57 1 (4)	79 3 (23)	0 33				
$\begin{split} \begin{tabular}{ c c c c } begin{tabular}{ c c c c } begin{tabular}{ c c c c c } begin{tabular}{ c c c c c c } begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Yes	25.0 (9)	42.9 (3)	20.7 (6)	0.55				
No 88.9 (32) 85.7 (6) 89.7 (26) 1.00 Yes 11.1 (4) 13.3 (1) 13.3 (3) Dyslipctinia (%)	Diabetes mellitus (%)								
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	No	88.9 (32)	85.7 (6) 14.3 (1)	89.7 (26) 10.3 (3)	1.00				
$\begin{array}{cccc} & 694 (25) & 42.9 (3) & 75.9 (22) & 0.17 \\ Yes & 30.6 (11) & 57.1 (4) & 24.1 (7) \\ \hline \\ No & 75.0 (27) & 57.1 (4) & 79.3 (23) & 0.33 \\ Yes & 25.0 (9) & 42.9 (3) & 20.7 (6) \\ \hline \\ Chronic obstructive pulmonary disease (%) & & & & & & & & & & & & & & & & & & &$	Dyslipidemia (%)	11.1 (4)	14.5 (1)	(5)					
Yes30.6 (1)57.1 (4)24.1 (7)No75.0 (27)57.1 (4)79.3 (23)0.33Yes25.0 (9)42.9 (3)20.7 (6)No100.0 (36)100.0 (7)100.0 (29)1.00Yes0.0 (0)0.0 (0)0.0 (0)0.0 (0)Yes0.0 (0)0.0 (0)0.0 (0)0.0 (0)Weight (kg)68.0 (±15.5)78.0 (±11.6)65.6 (±15.5)0.06Height (cm)160.9 (±9.7)16.8 (±8.4)159.0 (±9.2)0.02Waist circumference (cm) (n = 34)84.2 (±18.0)84.7 (±3.6.6)84.1 (±12.3)0.94BM (kg/m ²)25.2 (±1.2)27.7 (±5.2)25.8 (±5.2)0.39Overweight (BM > 25 kg/m ²)77.8 (28)71.4 (5)79.3 (23)0.64Yes22.2 (8)28.6 (2)51.7 (15)0.07Cardiac device (%)1.1 (±0.2)1.3 (±0.3)0.27Vers47.2 (17)28.6 (2)51.7 (15)0.031.4 (±3.4)0.01Yes47.2 (17)28.6 (2)51.7 (15)0.031.4 (±0.3)0.27UVEF (%) (n = 33)1.3 (±0.3)0.021.4 (±0.3)0.120.03He at anaerobic threshold (mkg ⁻¹ min ⁻¹) (n = 21)1.2 (±4.4)15.4 (±1.9)1.14 (±4.4)0.10Resting HR (hopm)66.7 (±10.2)66.3 (±7.3)66.8 (±10.9)0.090.91Resting DP (mmHg)109.7 (±16.8)1.29 (±4.11.0)1.8 (±6.6)0.000.01Vo at an aerobic threshold (mkg ⁻¹ min ⁻¹)1	No	69.4 (25)	42.9 (3)	75.9 (22)	0.17				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Yes	30.6 (11)	57.1 (4)	24.1 (7)					
Yes25.0 (r)42.9 (s)20.7 (c)Chonic obstructive pulmonary disease (%)70.000 (36)100.0 (7)100.0 (29)1.00No0.00 (0)0.0 (0)0.0 (0)0.0 (0)0.0 (0)0.0 (0)Yes0.00 (9)0.0 (0)0.0 (0)0.0 (0)0.0 (0)Weight (kg)66.0 (±15.5)78.0 (±1.6)65.6 (±15.5)0.066Height (cm)160.9 (±9.7)168.4 (±8.4)159.0 (±9.2)0.02Waist circumference (cm) (n = 34)84.2 (±18.0)84.7 (±36.6)84.1 (±1.2)0.94BMI (kg/m ²)0.22 (k5.1)27.7 (±5.2)2.5.8 (±5.2)0.39Overweight (kM) > 25.8 (m ²)77.8 (28)7.1.4 (5)7.9.3 (23)0.64Yes22.2 (8)2.8.6 (2)51.7 (15)0.07Cardiac device (%)7.8 (28)7.1.4 (5)3.1.3 (±0.3)0.27Urea (mg/dl)43.6 (±18.6)3.23 (±5.2)46.3 (±19.6)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27UVEF (%) (n = 33)49.7 (±5.5)3.1.7 (±8.6)0.03Resting BK (mmHg)109.7 (±16.8)129.4 (±1.9)1.1.4 (±4.4)0.10Resting JSP (mmHg)109.7 (±16.8)129.4 (±1.9)1.1.4 (±4.4)0.00Resting DSP (mmHg)109.7 (±16.8)129.4 (±1.2)1.5.6 (±1.3)0.01Resting DSP (mmHg)109.7 (±16.8)129.4 (±1.2)1.5.6 (±1.3)0.01Vox an acrosic threshold (mLg ⁻¹ ,min ⁻¹)16.4 (±4.7)199.6 (±1.27)	No	75.0 (27)	57.1 (4)	79.3 (23)	0.33				
Chronic obstructive pulmonary disease (%) No Yes 0.00 (0) 0.00 (0) 0.00 (0) Weight (kg) 6.00 (4155) 7.80 (411.6) Height (cm) (n = 34) 6.40 (4155) 7.80 (411.6) BMI (kg/m ²) 2.58 (45.2) 0.02 Waist dircumference (cm) (n = 34) 8.42 (±18.0) 8.47 (±36.6) 8.4.1 (±12.3) 0.94 BMI (kg/m ²) 2.52 kg/m ²) No Yes 2.22 (8) 2.86 (2) 2.07 (6) Cardiac device (%) No Yes 47.2 (17) 2.86 (2) 51.7 (15) 7.7 (±5.2) View (Mg/d) 4.56 (±18.6) 2.23 (±5.2) 4.83 (14) 0.41 Yes 47.2 (17) 2.86 (2) 51.7 (15) 7.7 (±5.6) 0.007 Creatinie (mg/d) 1.2 (±0.3) 1.1 (±0.2) 1.3 (±0.3) 0.277 (Vrea (mg/d) 1.2 (±0.3) 1.1 (±0.2) 1.3 (±0.3) 0.277 Creatine (mg/d) 1.2 (±1.8) 9.96 (±5.72) 9.82 (±21.1) 0.88 VO ₂ at anerobic threshold (mkg ⁻¹ ,min ⁻¹) (n = 21) 1.2 (±4.4) 1.54 (±1.9) 1.14 (±4.4) 0.100 Resting DBP (mmHg) 7.06 (±10.7) 81.4 (±11.4) 66.0 (±8.9) 0.002 VO ₂ paek (mkkg ⁻¹ ,min ⁻¹) (n = 21) 1.2 (±6.8) 1.294 (±14.2) 1.56 (±1.3) 0.111 WE max 4.7 (±1.3) 5.4 (±1.2) 4.5 (±1.3) 0.111 Ne max (Mrmin) (n = 31) 3.59 (±11.8) 3.79 (±12.8) 4.40 (13.2) (±5.0) (±1.3) 0.002 VO ₂ paek (mkkg ⁻¹ ,min ⁻¹) (n = 21) 1.2 (±1.68) 1.294 (±14.2) 1.56 (±6.9.9) 0.002 Creating DBP (mmHg) 1.0 1.2 (±1.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.3) 1.35 (±12.8) 1.35 (±12.8) 1.35 (±12.8) 1.35 (±12.8) 1.35 (±12.8) 1.35 (±12.8) 1.35	Yes	25.0 (9)	42.9 (3)	20.7 (6)					
No 100.0 (36) 100.0 (7) 100.0 (29) 1.0 Yes 0.0 (0) 0.0 (0) 0.0 (0) 0.0 (0) Weight (kg) 66.0 (±15.5) 78.0 (±11.6) 65.6 (±15.5) 0.00 (0) Waist circumference (cm) (n = 34) 26.2 (±5.1) 27.7 (±5.2) 25.8 (±5.2) 0.02 Waist (kg/m ²) 0.22 (±5.1) 27.7 (±5.2) 25.8 (±5.2) 0.39 Overweight (BMI > 25 kg/m ²) 77.8 (28) 71.4 (5) 79.3 (23) 0.64 Yes 22.2 (8) 28.6 (2) 20.7 (6) 0.77 Cardiac device (%) - - - - No 52.8 (19) 71.4 (5) 48.3 (±19.6) 0.07 Creatinie (mg/dl) 1.2 (±0.3) 1.1 (±0.2) 1.3 (±0.3) 0.27 VEF (%) (n = 33) 40.7 (±9.5) 31.7 (±8.6) 0.03 Rat anaerobic threshold (ml.kg ⁻¹ min ⁻¹) (n = 21) 12.1 (±4.4) 15.4 (±1.9) 11.4 (±4.4) 0.10 Resting BP (mmHg) 66.7 (±10.2) 66.3 (±7.3) 66.8 (±10.9) 0.091	Chronic obstructive pulmonary disease (%)	100.0 (24)	100.0 (7)	100.0 (20)	1.00				
Weight (kg)Box (b) (kg)Box (b) <b< td=""><td>NO Yes</td><td>100.0 (36)</td><td>100.0 (7)</td><td>100.0 (29)</td><td>1.00</td></b<>	NO Yes	100.0 (36)	100.0 (7)	100.0 (29)	1.00				
Height (cm)160.9 (±9.7)168.4 (±8.4)159.0 (±9.2)0.02Waist circumference (cm) (n = 34)84.2 (±18.0)84.7 (±36.6)84.1 (±12.3)0.94BMI (kg/m)26.2 (±5.1)27.7 (±5.2)23.8 (±5.2)0.39Overweight (BM > 25 kg/m²)71.4 (5)79.3 (23)0.64No72.8 (28)71.4 (5)79.3 (23)0.64Yes22.2 (8)28.6 (2)51.7 (15)0.07Cardiac device (%)71.4 (5)48.3 (14)0.41Yes47.2 (17)28.6 (2)51.7 (15)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.07Kesting KB (mm/dg)109.7 (±16.8)99.6 (±5.72)98.2 (±21.1)0.88V0_2 at anaerobic threshold (mk/g ⁻¹ , min ⁻¹) (n = 21)1.2 (±4.4)1.54 (±1.9)11.4 (±4.4)0.10Resting SBP (mmHg)06 (±10.7)1.64 (±4.7)1.90 (±1.1)1.58 (±4.6)0.10VC paek (mk/g ⁻¹ , min ⁻¹)1.64 (±4.7)1.90 (±4.1)1.58 (±4.6)0.10VE max (Minin (n = 31)3.59 (±11.8)3.79 (±12.7)3.54 (±1.2)4.5 (±1.3)0.11VE max (Minin (n = 31)3.59 (±11.8)3.79 (±12.7)3.54 (±1.2)4.5 (±1.3)0.11VE max (Minin (n = 35)1.1 (±0.1)1.1 (±0.2)0.200.20VE max (Minin (n = 35)1.1 (±0.11)1.1 (±0.2)	Weight (kg)	68.0 (±15.5)	78.0 (±11.6)	65.6 (±15.5)	0.06				
Waist circumference (cm) $(n = 34)$ 84.2 (±18.0)84.7 (±36.6)84.1 (±1.2.3)0.94BMI (kg/m²)26.2 (±5.1)27.7 (±5.2)25.8 (±5.2)0.39Overweight (BMI > 25 kg/m²)71.8 (5)79.3 (23)0.64Yes22.2 (8)28.6 (2)20.7 (6)Cardiac device (%)71.4 (5)48.3 (14)0.41Yes47.2 (17)28.6 (2)51.7 (15)0.77Urea (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27Creatinie (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27LVEF (%) (n = 33)33.3 (±9.3)40.7 (±5.5)31.7 (±8.6)0.03HR at anaerobic threshold (bpm) (n = 25)98.4 (±18.9)99.6 (±5.72)98.2 (±21.1)0.88Vo 2, at anaerobic threshold (mkg ⁻¹ ,min ⁻¹) (n = 21)1.2.1 (±4.4)1.5.4 (±1.9)1.1 (±4.4)0.10Resting BP (mmHg)70.6 (±10.7)81.4 (±11.4)66.0 (±13.8)<0.001	Height (cm)	160.9 (±9.7)	168.4 (±8.4)	159.0 (±9.2)	0.02				
bin (kg/if) (Waist circumference (cm) $(n = 34)$	84.2 (±18.0)	84.7 (±36.6)	84.1 (±12.3)	0.94				
No77.8 (28)71.4 (5)79.3 (23)0.64Yes22.2 (8)28.6 (2)20.7 (6)Cardiac device (%)No52.8 (19)71.4 (5)48.3 (14)0.41Yes47.2 (17)28.6 (2)51.7 (15)Urea (mg/dl)43.6 (±18.6)32.3 (±5.2)46.3 (±19.6)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27LVEF (%) (n=33)33.3 (±9.3)40.7 (±9.5)31.7 (±8.6)0.03HR at anacrobic threshold (mlkg ⁻¹ .min ⁻¹) (n=21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.10Resting HR (bpm)66.7 (±10.2)66.3 (±7.3)66.8 (±10.9)0.91Resting BK (hpm)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001	Overweight (BMI > 25 kg/m^2)	20.2 (±3.1)	27.7 (±3.2)	23.0 (±3.2)	0.59				
Yes22.2 (8)28.6 (2)20.7 (6)Cardiac device (%) N_0 $52.8 (19)$ $71.4 (5)$ $48.3 (14)$ 0.41 Yes $47.2 (17)$ $28.6 (2)$ $51.7 (15)$ 0.77 Urea (mg/dl) $43.6 (\pm 18.6)$ $32.3 (\pm 5.2)$ $46.3 (\pm 9.6)$ 0.07 Creatinine (mg/dl) $1.2 (\pm 0.3)$ $1.1 (\pm 0.2)$ $1.3 (\pm 0.3)$ 0.27 LVEF (%) (n = 33) $1.2 (\pm 0.3)$ $1.1 (\pm 0.2)$ $1.3 (\pm 0.3)$ 0.27 LVEF (%) (n = 33) $0.27 (\pm 16.8)$ $996 (\pm 5.72)$ $98.2 (\pm 2.11)$ 0.88 Vo_a tanaerobic threshold (ml.kg ⁻¹ ,min ⁻¹) (n = 21) $12.1 (\pm 4.4)$ $154 (\pm 1.9)$ $11.4 (\pm 4.4)$ 0.10 Resting BP (mmHg) $66.7 (\pm 10.2)$ $66.3 (\pm 7.3)$ $66.8 (\pm 10.9)$ 0.91 Resting DBP (mmHg) $70.6 (\pm 10.7)$ $81.4 (\pm 11.4)$ $68.0 (\pm 8.9)$ 0.002 Vo_2 peak (ml.kg ⁻¹ ,min ⁻¹) $16.6 (\pm 4.7)$ $19.0 (\pm 4.1)$ $15.8 (\pm 4.6)$ 0.10 MET max $4.7 (\pm 1.3)$ $5.4 (\pm 1.2)$ $4.5 (\pm 1.3)$ 0.11 VE/VCO_5 lope $27.4 (\pm 6.8)$ $24.8 (\pm 3.5)$ $22.0 (\pm 7.3)$ 0.27 OUES $14366 (\pm 55.43)$ $1889.8 (\pm 54.40)$ $1327.2 (\pm 506.9)$ 0.01 FAI (%) $42.2 (\pm 14.7)$ $30.9 (\pm 2.9)$ 0.5 0.5 Respiratory coefficient (n = 32) $1.1 (\pm 0.14)$ $10.(\pm 0.1)$ $1.1 (\pm 0.2)$ 0.20 Outes $14366 (\pm 557.81)$ $122.66 (\pm 546.37)$ $1327.2 (\pm 506.9)$ 0.01 FAI (%) $0.10 (\pm 3.1)$ $12.1 (\pm 3.$	No	77.8 (28)	71.4 (5)	79.3 (23)	0.64				
Cardiac device (%)No52.8 (19)71.4 (5)48.3 (14)0.41Yes47.2 (17)28.6 (2)51.7 (15)Urea (mg/dl)43.6 (±18.6)32.3 (±5.2)46.3 (±19.6)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27LVEF (%) (n = 33)33.3 (±9.3)40.7 (±9.5)31.7 (±8.6)0.03HR at anaerobic threshold (ml.kg ⁻¹ .min ⁻¹) (n = 21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.10Resting SBP (mmHg)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.002VO2 peak (ml.kg ⁻¹ .min ⁻¹)166 (±4.7)19.0 (±4.1)15.8 (±4.6)0.10MET max4.7 (±1.3)5.4 (±1.2)4.5 (±1.3)0.11VCm ax (//min) (n = 31)35.9 (±11.8)37.9 (±12.7)35.4 (±1.8)0.65VE/VCO2 slope27.4 (±6.8)24.8 (±3.5)28.0 (±7.3)0.27OUES143.66 (±554.3)1889.8 (±54.40)1327.2 (±50.69)0.01Resign DRP10.1 (±3.1)12.1 (±3.0)9.6 (±2.9)0.05Respiratory coefficient (n = 32)1.1 (±0.14)1.0 (±0.1)1.1 (±0.2)0.20ODE11.5 (±27.3)142.9 (±19.4)108.9 (±24.8)0.002DBP max (mmHg) (n = 35)15.6 (±7.3)12.2 (±3.6)0.01DP max (mmHg) (n = 35)5.7 (±19.3)13.4 (±14.7)3.7 (±20.0)0.33DP max (mmHg) (n = 35)5.7 (±19.3)13.4 (±14.7)3.7 (±20.0)0.24DP max (mmHg) (n = 35)5.7 (±19.3)13.4 (Yes	22.2 (8)	28.6 (2)	20.7 (6)					
No22.63 (17)18.16 (2)10.5 (17)10.5 (17)0.17Yes47.2 (17)28.6 (2)51.7 (15)Urea (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27UVEF (%) (n = 33)33.3 (±9.3)40.7 (±5.5)31.7 (±8.6)0.03HR at anaerobic threshold (ml.kg ⁻¹ .min ⁻¹) (n = 21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.00Resting HR (bpm)66.7 (±10.2)66.3 (±7.3)66.8 (±10.9)0.91Resting BR (mmHg)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001	No	52.8 (19)	71.4 (5)	48 3 (14)	0.41				
Urea (mg/dl)43.6 (±18.6)32.3 (±5.2)46.3 (±19.6)0.07Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27UVEF (%) (n = 33)33.3 (±9.3)40.7 (±9.5)31.7 (±8.6)0.03HR at anaerobic threshold (bpm) (n = 25)98.4 (±18.9)99.6 (±5.72)98.2 (±21.1)0.88VO2 at anaerobic threshold (ml.kg ⁻¹ ,min ⁻¹) (n = 21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.10Resting HR (bpm)66.7 (±10.2)66.3 (±10.9)0.910.91Resting BP (mmHg)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001	Yes	47.2 (17)	28.6 (2)	51.7 (15)	0.11				
Creatinine (mg/dl)1.2 (±0.3)1.1 (±0.2)1.3 (±0.3)0.27LVEF (%) (n = 33)33.3 (±9.3)40.7 (±9.5)31.7 (±8.6)0.03HR at anaerobic threshold (bpm) (n = 25)98.4 (±18.9)99.6 (±5.72)98.2 (±21.1)0.88VO2 at anaerobic threshold (ml.kg ⁻¹ .min ⁻¹) (n = 21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.10Resting BR (bpm)66.7 (±10.2)66.3 (±7.3)66.8 (±10.9)0.91Resting SBP (mmHg)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001	Urea (mg/dl)	43.6 (±18.6)	32.3 (±5.2)	46.3 (±19.6)	0.07				
Left (v) $(n - 25)$ 35.5 (± 2) 44.7 (± 5.7) 31.7 (± 30) 0.83W2 at anaerobic threshold (bpm) $(n = 25)$ 98.4 (± 18.9) 99.6 (± 5.72) 98.2 (± 21.1) 0.88V0_2 at anaerobic threshold (ml.kg ⁻¹ .min ⁻¹) $(n = 21)$ 12.1 (± 4.4) 15.4 (± 1.9) 11.4 (± 4.4) 0.10Resting BR (bpm)66.7 (± 10.2) 66.3 (± 7.3) 66.8 (± 10.9) 0.91Resting BP (mmHg)109.7 (± 16.8) 129.4 (± 14.2) 105.0 (± 3.8) <0.001	Creatinine (mg/dl) LVEE $(%)$ (n - 33)	1.2 (±0.3)	1.1 (±0.2)	1.3 (±0.3) 31 7 (±8.6)	0.27				
VO2 at anaerobic threshold (ml.kg ⁻¹ .min ⁻¹) (n = 21)12.1 (±4.4)15.4 (±1.9)11.4 (±4.4)0.10Resting HR (bpm)66.7 (±10.2)66.3 (±7.3)66.8 (±10.9)0.91Resting SBP (mmHg)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001	HR at anaerobic threshold (bpm) $(n = 25)$	98.4 (±18.9)	99.6 (±5.72)	98.2 (±21.1)	0.88				
Resting HR (bpm) $667 (\pm 10.2)$ $66.3 (\pm 7.3)$ $66.8 (\pm 10.9)$ 0.91 Resting SBP (mmHg) $1097, (\pm 16.8)$ $129.4 (\pm 14.2)$ $105.0 (\pm 13.8)$ <0.001 Resting DBP (mmHg) $70.6 (\pm 10.7)$ $81.4 (\pm 11.4)$ $68.0 (\pm 8.9)$ 0.002 VO2 peak (ml.kg ⁻¹ .min ⁻¹) $16.4 (\pm 4.7)$ $19.0 (\pm 4.1)$ $15.8 (\pm 4.6)$ 0.10 MET max $4.7 (\pm 1.3)$ $5.4 (\pm 1.2)$ $4.5 (\pm 1.3)$ 0.11 VE max (l/min (n = 31) $35.9 (\pm 11.8)$ $37.9 (\pm 12.7)$ $35.4 (\pm 11.8)$ 0.65 VE/VCO2 slope $27.4 (\pm 6.8)$ $24.8 (\pm 3.5)$ $28.0 (\pm 7.3)$ 0.27 OUES $143.66 (\pm 554.3)$ $1889.8 (\pm 544.0)$ $1327.2 (\pm 506.9)$ 0.01 FAI (%) $42.2 (\pm 14.7)$ $30.9 (\pm 9.8)$ $44.9 (\pm 14.5)$ 0.02 Oxygen-pulse (ml/bpm) $10.1 (\pm 3.1)$ $12.1 (\pm 3.0)$ $9.6 (\pm 2.9)$ 0.05 Restiratory coefficient (n = 32) $1.1 (\pm 0.14)$ $1.0 (\pm 0.1)$ $1.1 (\pm 0.2)$ 0.20 NBP max (mmHg) (n = 35) $15.6 (\pm 27.3)$ $142.9 (\pm 19.4)$ $108.9 (\pm 24.8)$ 0.002 DBP max (mmHg) (n = 35) $5.7 (\pm 19.3)$ $13.4 (\pm 14.7)$ $3.7 (\pm 20.0)$ 0.24 AHR min (bpm) $-15.7 (\pm 12.7)$ $-9.7 (\pm 5.5)$ $-17.2 (\pm 13.6)$ 0.17 Dysautonomia N_0 $58.3 (21)$ $28.6 (2)$ $65.5 (19)$ 0.10	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 SbP (miHing)109.7 (±16.8)129.4 (±14.2)105.0 (±13.8)<0.001Resting DBP (mmHg)70.6 (±10.7) $81.4 (\pm11.4)$ $68.0 (\pm 8.9)$ 0.002 VO2 peak (ml.kg ⁻¹ .min ⁻¹)16.4 (±4.7)19.0 (±4.1)15.8 (±4.6) 0.10 MET max4.7 (±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 (±1.1.8) 0.65 VE/VCO2 slope27.4 (±6.8)24.8 (±3.5)28.0 (±7.3) 0.27 OUES1436.6 (±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 OVES10.1 (±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)67.3 (±12.8)72.0 (±9.4)66.1 (±13.4) 0.28 DP max (mmHg) (n = 35)67.3 (±12.8)72.0 (±9.4)66.1 (±13.4) 0.28 DP max (mmHg) (n = 35)57. (±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	Resting HR (bpm)	66.7 (±10.2)	66.3 (±7.3)	66.8 (±10.9)	0.91				
Next of B b (14.19)Note (14.1)Note (14.1)Note (14.1)Note (14.1)Note (14.1)MET max4.7 (±1.3)5.4 (±1.2)4.5 (±1.3)0.11VE max (l/min) (n = 31)35.9 (±11.8)37.9 (±12.7)35.4 (±1.18)0.65VE/VCO2 slope27.4 (±6.8)24.8 (±3.5)28.0 (±7.3)0.27OUES1436.6 (±554.3)1889.8 (±544.0)1327.2 (±506.9)0.01OVES1436.6 (±554.3)1889.8 (±544.0)1327.2 (±506.9)0.02Oxygen-pulse (ml/bpm)10.1 (±3.1)12.1 (±3.0)9.6 (±2.9)0.05Respiratory coefficient (n = 32)1.1 (±0.14)1.0 (±0.1)1.1 (±0.2)0.20HR max (bpm)109.1 (±24.0)111.0 (±14.1)108.7 (±26.0)0.83SBP max (mmHg) (n = 35)67.3 (±12.8)72.0 (±9.4)66.1 (±13.4)0.28DP max (mmHg) (n = 35)5.7 (±12.7)-9.7 (±5.5)-17.2 (±13.6)0.17Dysautonomia-15.7 (±12.7)-9.7 (±5.5)-17.2 (±13.6)0.17No58.3 (21)28.6 (2)65.5 (19)0.10	Resting SBP (mmHg) Resting DBP (mmHg)	109.7 (±16.8) 70.6 (+10.7)	129.4 (±14.2) 81.4 (+11.4)	105.0 (±13.8) 68.0 (+8.9)	< 0.001				
MET max $4.7 (\pm 1.3)$ $5.4 (\pm 1.2)$ $4.5 (\pm 1.3)$ 0.11 VE max (l/min) (n = 31) $35.9 (\pm 11.8)$ $37.9 (\pm 12.7)$ $35.4 (\pm 11.8)$ 0.65 VE/VCO2 slope $27.4 (\pm 6.8)$ $24.8 (\pm 3.5)$ $28.0 (\pm 7.3)$ 0.27 OUES $1436.6 (\pm 554.3)$ $1889.8 (\pm 544.0)$ $1327.2 (\pm 506.9)$ 0.01 FAI (%) $42.2 (\pm 14.7)$ $30.9 (\pm 9.8)$ $44.9 (\pm 14.5)$ 0.02 Oxygen-pulse (ml/bpm) $10.1 (\pm 3.1)$ $12.1 (\pm 3.0)$ $9.6 (\pm 2.9)$ 0.5 Respiratory coefficient (n = 32) $1.1 (\pm 0.14)$ $1.0 (\pm 0.1)$ $1.1 (\pm 0.2)$ 0.20 HR max (bpm) $109.1 (\pm 24.0)$ $111.0 (\pm 14.1)$ $108.7 (\pm 26.0)$ 0.83 SBP max (mmHg) (n = 35) $115.6 (\pm 27.3)$ $142.9 (\pm 19.4)$ $108.9 (\pm 24.8)$ 0.002 DP max (mmHg.hpm) (n = 32) $12904.3 (\pm 4578.1)$ $16266.0 (\pm 4563.7)$ $12128.5 (\pm 4299.5)$ 0.04 $\Delta SBP (mmHg) (n = 35)$ $5.7 (\pm 19.3)$ $13.4 (\pm 14.7)$ $3.7 (\pm 20.0)$ 0.24 ΔHR_{1min} (bpm) $-15.7 (\pm 12.7)$ $-9.7 (\pm 5.5)$ $-17.2 (\pm 13.6)$ 0.17 Dysautonomia v_{20} $58.3 (21)$ $28.6 (2)$ $65.5 (19)$ 0.10 No $58.3 (21)$ $28.6 (2)$ $65.5 (19)$ 0.10	VO_2 peak (ml.kg ⁻¹ .min ⁻¹)	16.4 (±4.7)	19.0 (±4.1)	15.8 (±4.6)	0.10				
VE max (l/min) $(n = 31)$ $35.9 (\pm 11.8)$ $37.9 (\pm 12.7)$ $35.4 (\pm 11.8)$ 0.65 VE/VCO2 slope $27.4 (\pm 6.8)$ $24.8 (\pm 3.5)$ $28.0 (\pm 7.3)$ 0.27 OUES $1436.6 (\pm 554.3)$ $1889.8 (\pm 544.0)$ $1327.2 (\pm 506.9)$ 0.01 FAI (%) $42.2 (\pm 14.7)$ $30.9 (\pm 9.8)$ $44.9 (\pm 14.5)$ 0.02 Oxygen-pulse (ml/bpm) $10.1 (\pm 3.1)$ $12.1 (\pm 3.0)$ $9.6 (\pm 2.9)$ 0.05 Respiratory coefficient $(n = 32)$ $1.1 (\pm 0.14)$ $1.0 (\pm 0.1)$ $1.1 (\pm 0.2)$ 0.20 HR max (bpm) $109.1 (\pm 24.0)$ $111.0 (\pm 14.1)$ $108.7 (\pm 26.0)$ 0.83 SBP max (mmHg) $(n = 35)$ $115.6 (\pm 27.3)$ $142.9 (\pm 19.4)$ $108.9 (\pm 24.8)$ 0.002 DP max (mmHg.bpm) $(n = 32)$ $12904.3 (\pm 4578.1)$ $16266.0 (\pm 4563.7)$ $12128.5 (\pm 4299.5)$ 0.04 $\Delta SBP (mmHg) (n = 35)$ $5.7 (\pm 19.3)$ $13.4 (\pm 14.7)$ $3.7 (\pm 20.0)$ 0.24 $\Delta HR_{1min} (bpm)$ $-15.7 (\pm 12.7)$ $-9.7 (\pm 5.5)$ $-17.2 (\pm 13.6)$ 0.17 Dysautonomia $Vort58.3 (21)28.6 (2)65.5 (19)0.10$	MET max	4.7 (±1.3)	5.4 (±1.2)	4.5 (±1.3)	0.11				
VEX Cos stope27.4 (150)24.6 (17.5)20.6 (17.5)0.27OUES1436.6 (± 554.3)1889.8 (± 544.0)1327.2 (± 506.9)0.01FAI (%)42.2 (± 14.7)30.9 (± 9.8)44.9 (± 14.5)0.02Oxygen-pulse (ml/bpm)10.1 (± 3.1)12.1 (± 3.0)9.6 (± 2.9)0.05Respiratory coefficient ($n = 32$)1.1 (± 0.14)1.0 (± 0.1)1.1 (± 0.2)0.20HR max (bpm)109.1 (± 24.0)111.0 (± 14.1)108.7 (± 26.0)0.83SBP max (mmHg) ($n = 35$)115.6 (± 27.3)142.9 (± 19.4)108.9 (± 24.8)0.002DP max (mmHg.bpm) ($n = 32$)12904.3 (± 4578.1)16266.0 (± 4563.7)12128.5 (± 4299.5)0.04 $\Delta SBP (mmHg) (n = 35)5.7 (\pm 19.3)13.4 (\pm 14.7)3.7 (\pm 20.0)0.24\Delta HR_{1min} (bpm)-15.7 (\pm 12.7)-9.7 (\pm 5.5)-17.2 (\pm 13.6)0.17Dysautonomiav_{20}41.7 (15)71.4 (5)34.5 (10)$	VE max (I/min) $(n=31)$ VE/VCO, slope	35.9 (±11.8) 27.4 (+6.8)	37.9 (±12.7) 24.8 (+3.5)	35.4 (±11.8) 28.0 (+7.3)	0.65				
FAI (%) $42.2 (\pm 14.7)$ $30.9 (\pm 9.8)$ $44.9 (\pm 14.5)$ 0.02 Oxygen-pulse (ml/bpm) $10.1 (\pm 3.1)$ $12.1 (\pm 3.0)$ $9.6 (\pm 2.9)$ 0.05 Respiratory coefficient ($n = 32$) $1.1 (\pm 0.14)$ $1.0 (\pm 0.1)$ $1.1 (\pm 0.2)$ 0.20 HR max (bpm) $109.1 (\pm 24.0)$ $111.0 (\pm 14.1)$ $108.7 (\pm 26.0)$ 0.83 SBP max (mmHg) ($n = 35$) $115.6 (\pm 27.3)$ $142.9 (\pm 19.4)$ $108.9 (\pm 24.8)$ 0.002 DBP max (mmHg.hpm) ($n = 32$) $67.3 (\pm 12.8)$ $72.0 (\pm 9.4)$ $66.1 (\pm 13.4)$ 0.28 DP max (mmHg.hpm) ($n = 35$) $5.7 (\pm 19.3)$ $13.4 (\pm 14.7)$ $3.7 (\pm 20.0)$ 0.24 $\Delta SBP (mmHg) (n = 35)-15.7 (\pm 12.7)-9.7 (\pm 5.5)-17.2 (\pm 13.6)0.17Dysautonomiav_{20}41.7 (15)71.4 (5)34.5 (10)$	OUES	1436.6 (±554.3)	1889.8 (±544.0)	1327.2 (±506.9)	0.27				
Oxygen-pulse (ml/bpm)10.1 (±3.1)12.1 (±3.0)9.6 (±2.9)0.05Respiratory coefficient $(n = 32)$ 1.1 (±0.14)1.0 (±0.1)1.1 (±0.2)0.20HR max (bpm)109.1 (±24.0)111.0 (±14.1)108.7 (±26.0)0.83SBP max (mmHg) $(n = 35)$ 115.6 (±27.3)142.9 (±19.4)108.9 (±24.8)0.002DBP max (mmHg) $(n = 35)$ 67.3 (±12.8)72.0 (±9.4)66.1 (±13.4)0.28DP max (mmHg) $(n = 35)$ 5.7 (±19.3)13.4 (±14.7)3.7 (±20.0)0.24 $\Delta SBP (mmHg) (n = 35)$ 5.7 (±12.7) $-9.7 (\pm5.5)$ $-17.2 (\pm13.6)$ 0.17Dysautonomia No 58.3 (21)28.6 (2)65.5 (19)0.10	FAI (%)	42.2 (±14.7)	30.9 (±9.8)	44.9 (±14.5)	0.02				
Respiratory conductive $(n-52)$ 1.1 (±0.1)1.1 (±0.2)0.20HR max (bpm)109.1 (±24.0)111.0 (±14.1)108.7 (±26.0)0.83SBP max (mmHg) $(n = 35)$ 115.6 (±27.3)142.9 (±19.4)108.9 (±24.8)0.002DBP max (mmHg, bpm) $(n = 32)$ 67.3 (±12.8)72.0 (±9.4)66.1 (±13.4)0.28DP max (mmHg, lopm) $(n = 35)$ 5.7 (±19.3)13.4 (±14.7)3.7 (±20.0)0.24 $\Delta SBP (mmHg) (n = 35)$ 5.7 (±12.7)-9.7 (±5.5)-17.2 (±13.6)0.17Dysautonomia58.3 (21)28.6 (2)65.5 (19)0.10Vor41.7 (15)71.4 (5)34.5 (10)0.10	Oxygen-pulse (ml/bpm) Perpiratory coefficient $(n - 22)$	$10.1 (\pm 3.1)$	12.1 (±3.0)	9.6 (±2.9)	0.05				
SBP max (mmHg) $(n = 35)$ 115.6 (±27.3)142.9 (±19.4)108.9 (±24.8)0.002DBP max (mmHg) $(n = 35)$ 67.3 (±12.8)72.0 (±9.4)66.1 (±13.4)0.28DP max (mmHg,bpm) $(n = 32)$ 12904.3 (±4578.1)16266.0 (±4563.7)12128.5 (±4299.5)0.04 Δ SBP (mmHg) $(n = 35)$ 5.7 (±19.3)13.4 (±14.7)3.7 (±20.0)0.24 Δ HR _{1min} (bpm) -15.7 (±12.7) -9.7 (±5.5) -17.2 (±13.6)0.17Dysautonomia58.3 (21)28.6 (2)65.5 (19)0.10No58.3 (21)71.4 (5)34.5 (10)	HR max (bpm)	1.1 (±0.14) 109.1 (±24.0)	1.0 (±0.1) 111.0 (±14.1)	1.1 (±0.2) 108.7 (±26.0)	0.20				
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	SBP max (mmHg) ($n = 35$)	115.6 (±27.3)	142.9 (±19.4)	108.9 (±24.8)	0.002				
UP max (mmHg.ppm) $(n = 32)$ 12904.3 (±45/8.1) 16266.0 (±4563.7) 12128.5 (±4299.5) 0.04 Δ SBP (mmHg) $(n = 35)$ 5.7 (±19.3) 13.4 (±14.7) 3.7 (±20.0) 0.24 Δ HR _{1min} (bpm) -15.7 (±12.7) -9.7 (±5.5) -17.2 (±13.6) 0.17 Dysautonomia 58.3 (21) 28.6 (2) 65.5 (19) 0.10 Vor 41.7 (15) 71.4 (5) 34.5 (10) 0.10	DBP max (mmHg) $(n = 35)$	67.3 (±12.8)	72.0 (±9.4)	66.1 (±13.4)	0.28				
ΔHR_{1min} (bpm) $-15.7 (\pm 12.7)$ $-9.7 (\pm 5.5)$ $-17.2 (\pm 13.6)$ 0.17 Dysautonomia No 58.3 (21) 28.6 (2) 65.5 (19) 0.10 Vor 41.7 (15) 71.4 (5) 34.5 (10) 0.17	UP max (mmHg.bpm) ($n = 32$) ASBP (mmHq) ($n = 35$)	12904.3 (±45/8.1) 5 7 (+19 3)	16266.0 (±4563./) 13 4 (+14 7)	12128.5 (±4299.5) 3.7 (+20.0)	0.04				
Dysautonomia S8.3 (21) 28.6 (2) 65.5 (19) 0.10 Vor 41.7 (15) 71.4 (5) 34.5 (10)	ΔHR_{1min} (bpm)	–15.7 (±12.7)	-9.7 (±5.5)	-17.2 (±13.6)	0.17				
No 58.3 (21) 28.6 (2) 65.5 (19) 0.10	Dysautonomia								
	NO Yes	58.3 (21) 41.7 (15)	28.6 (2) 71.4 (5)	65.5 (19) 34.5 (10)	0.10				

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; VO₂ peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO₂ 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.

	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
Δ SBP (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)		

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

CPET: cardiopulmonary exercise test; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO₂ peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO₂ 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.

^aUnstandardized beta values from linear mixed model adjusted by age and sex (stage C vs. B2).

peak was $16.4 \pm 4.7 \text{ ml.kg}^{-1}$.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. $105.0 \pm 13.8 \text{ mmHg}$; p < 0.001), resting DBP (81.4 ± 11.4 vs. $68.0 \pm 8.9 \text{ mmHg}$; p = 0.002), maximum SBP (142.9 ± 19.4 vs. $108.9 \pm 24.8 \text{ mmHg}$; p = 0.002), DP (16266.0 ± 4563.7 vs. $12128.5 \pm 4299.5 \text{ mmHg.bpm}$; 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. $44.9 \pm 14.5\%$; 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 VO₂ peak (β =+2.4 ml.kg⁻¹.min⁻¹; p < 0.001), FAI (β =-7.8%; p=0.001), MET max (β =+0.7; p < 0.001), VE max (β =+6.0 ml/min; p < 0.001), resting SBP (β =-12.6 mmHg; p < 0.001), and resting DBP (β =-8.0 mmHg; p < 0.001). The median interval from the initial to the third CPET was 6.6 months, with significant improvements in VO₂ peak (β =+1.6 ml.kg⁻¹.min⁻¹; p=0.03), FAI (β =-5.6%; p=0.04), MET max (β =+0.5; p=0.03), VE max (β =+7.5 ml/min; p < 0.001), and resting SBP (β =-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 (β =+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 (<i>n</i> = 4)	C (n = 22)	β^{a}	p Value	B2 (n = 4)	C (<i>n</i> = 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
Δ SBP (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
Δ HR _{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; VO₂ peak: oxygen consumption at peak exercise; MET: metabolic equivalent; VE: pulmonary ventilation; VE/VCO₂ 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.

^aUnstandardized 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.

Disclosure statement

The authors report no conflicts of interest.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Aline Maria Nunes Viana () http://orcid.org/0000-0003-4112-9866 Marcelo Carvalho Vieira () http://orcid.org/0000-0002-6137-0246 Flavia Mazzoli-Rocha () http://orcid.org/0000-0003-0972-194X Rudson Santos Silva () http://orcid.org/0000-0002-8859-985X Aline Xavier Frota () http://orcid.org/0000-0003-4621-7267 Henrique Silveira Costa () http://orcid.org/0000-0002-1426-7246 Juliana Pereira Borges () http://orcid.org/0000-0002-3581-7251 Gilberto Marcelo Sperandio da Silva () http://orcid.org/0000-0002-0468-4417

Paula Simplício da Silva D http://orcid.org/0000-0002-7414-9698 Alejandro Marcel Hasslocher-Moreno D http://orcid.org/0000-0002-5430-7222

Roberto Magalhães Saraiva (b) http://orcid.org/0000-0002-2263-4261

Andrea Silvestre de Sousa i http://orcid.org/0000-0001-8266-4801

Fernanda de Souza Nogueira Sardinha Mendes (b) http://orcid.org/0000-0003-2033-1715

Mauro Felippe Felix Mediano (b) http://orcid.org/0000-0001-6369-3631

References

- [1] Pan American Health Organization. Guidelines for the diagnosis and treatment of Chagas disease. Washington (DC): PAHO; 2019.
- [2] Lidani KCF, Andrade FA, Bavia L, et al. Chagas disease: from discovery to a worldwide health problem. Front Public Health. 2019;7:166.
- [3] Pérez-Molina JA, Molina I. Chagas disease. Lancet. 2018; 391(10115):82–94.
- [4] Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. Circulation. 2018;138(12):e169–e209.
- [5] Dias JCP, Ramos AN Jr., Gontijo ED, et al. 2nd Brazilian consensus on Chagas disease, 2015. Rev Soc Bras Med Trop. 2016;49(Suppl. 1):3–60.
- [6] Lima MMO, Rocha MOC, Nunes MCP, et al. A randomized trial of the effects of exercise training in Chagas cardiomy-opathy. Eur J Heart Fail. 2010;12(8):866–873.
- [7] Mediano MFF, Mendes FDS, Pinto VLM, et al. Cardiac rehabilitation program in patients with Chagas heart failure: a single-arm pilot study. Rev Soc Bras Med Trop. 2016; 49(3):319–328.
- [8] Mediano MFF, Mendes FSNS, Pinto VLM, et al. Reassessment of quality of life domains in patients with compensated Chagas heart failure after participating in a cardiac rehabilitation program. Rev Soc Bras Med Trop. 2017;50(3):404–407.
- [9] Mendes FSNS, Mediano MFF, Souza FCC, et al. Effect of physical exercise training in patients with Chagas heart disease (from the PEACH study). Am J Cardiol. 2020;125.
- [10] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1): 1–39.e14.
- [11] Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191–225.

- [12] Herdy AH, Ritt LEF, Stein R, et al. Cardiopulmonary exercise test: fundamentals, applicability and interpretation. Arq Bras Cardiol. 2016;107:467–481.
- [13] Carvalho TD, Milani M, Ferraz AS, et al. Brazilian cardiovascular rehabilitation guideline – 2020. Arq Bras Cardiol. 2020;114(5):943–987.
- [14] Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021;28(5):460–495.
- [15] Fialho PH, Tura BR, Sousa AD, et al. Effects of an exercise program on the functional capacity of patients with chronic Chagas' heart disease, evaluated by cardiopulmonary testing. Rev Soc Bras Med Trop. 2012;45(2):220–224.
- [16] Mady C, Cardoso RH, Barretto AC, et al. Survival and predictors of survival in patients with congestive heart failure due to Chagas' cardiomyopathy. Circulation. 1994;90(6): 3098–3102.
- [17] Xavier SS, Sousa AS, Hasslocher-Moreno A. Aplicação da nova classificação da insuficiência cardíaca (ACC/AHA) na cardiopatia chagásica crônica: análise crítica das curvas de sobrevida [Application of the new classification of cardiac insufficiency (ACC/AHA) in chronic Chagas cardiopathy: a critical analysis of the survival curves]. Rev SOCERJ. 2005; 18:227–232.
- [18] Mendes MDF, Lopes WDS, Nogueira GÂ, et al. Exercício físico aeróbico em mulheres com doença de Chagas [Aerobic physical exercise in women with Chagas disease]. Fisioter Mov. 2011;24(4):591–601.
- [19] Oliveira CD, Sousa AD, Santos B, et al. Effects of an exercise program on blood pressure in patients with treated hypertension and chronic Chagas' heart disease. Rev Soc Bras Med Trop. 2012;45(6):727–731.
- [20] Costa HS, Lima MMO, Costa FD, et al. Reduced functional capacity in patients with Chagas disease: a systematic review with meta-analysis. Rev Soc Bras Med Trop. 2018; 51(4):421–426.