Factors related to the discontinuation and mortality rates of a cardiac rehabilitation programme in patients with Chagas disease: a 6-year experience in a Brazilian tertiary centre

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Abstract

OBJECTIVES   To describe the clinical and sociodemographic characteristics of participants as well as discontinuation and mortality rates in a cardiac rehabilitation programme (CRP) tailored to Chagas disease (CD).

METHODS   Participants underwent functional capacity, anthropometry and cardiac function evaluations before beginning a CRP. Univariate and multivariate Cox proportional hazards models were performed to investigate the associations between clinical and sociodemographic characteristics at baseline with discontinuation rates and deaths.

RESULTS   Forty-two patients were enrolled in the CRP (61.9% men, mean age of 58.1 ± 11.8 years). During a median follow-up period of 10.8 months, 74% discontinued and 14% died while enrolled in CRP. 34% of the patients who discontinued CRP died during follow-up. White race (HR = 0.09; 95% CI 0.01–1.00), right ventricular systolic dysfunction (HR = 10.54; 95% CI 1.24–89.50) and oxygen pulse (HR = 0.69; 95% CI 0.48–0.99) were independently associated with death while enrolled in CRP. Married status (HR = 0.44; 95% CI 0.21–0.95) was independently associated with discontinuation rates from CRP. VO_2 peak (HR = 0.85; 95% CI 0.74–0.98) and CRP discontinuation due to CD-related reasons (HR = 8.33; 95% CI 1.91–36.27) were the variables independently associated with death after discontinuation of CRP.

CONCLUSION   In this population, sociodemographic aspects and severity of CD were important determinants of CRP discontinuation and mortality.

keywords Chagas disease, Chagas cardiomyopathy, cardiac rehabilitation, exercise, heart failure, survival analysis

Sustainable Development Goals (SDGs): 3.4

Introduction

Chronic Chagas disease (CD) is caused by the protozoan *Trypanosoma cruzi* and affects approximately 6 million people worldwide, with around one million of them living in Brazil [1]. In the last three decades, migratory movement from Latin America to non-endemic regions has transformed CD into a global public health problem [2]. About 20%–30% of patients with chronic CD may develop Chagas cardiomyopathy (ChC), and the most common cardiac complications are arrhythmias,

ventricular aneurysms, thromboembolism, heart failure (HF) and cardiac sudden death [3].

Exercise-based cardiac rehabilitation has emerged as an important strategy for the treatment of ChC [4,5]. In fact, exercise-based cardiac rehabilitation programme (CRP) is a safe and effective strategy for the treatment of several cardiomyopathies, improving clinical symptoms and quality of life as well as decreasing hospitalisations and mortality rates [6–8]. However, the few studies that evaluated CRP in CD included only short-term and surrogate outcomes, such as functional capacity, leaving

uncertainty about the effects of CRP on long-term and hard outcomes such as mortality [5,9–11]. Moreover, discontinuation from CRP is usually high, making the implementation of this strategy a challenge in clinical practice [12,13]. To our knowledge, no previous study evaluated the discontinuation rates from CRP in patients with CD.

In 2013, the Evandro Chagas National Institute of Infectious Disease (INI/Fiocruz) pioneered a CRP tailored exclusively to patients with CD with cardiac complications directly related or not to CD. The present study aimed to describe the clinical and sociodemographic characteristics of the participants enrolled in this CRP, their discontinuation rates and their mortality rates.

Methods

Study design

The present study is a longitudinal observational retrospective study with data obtained from medical records of all patients enrolled in the CRP of INI/Fiocruz from May 2013 to November 2019. Patients with CD diagnosis confirmed by two simultaneously positive serological tests (enzyme-linked immunosorbent assay and indirect immunofluorescence) [14,15], who presented cardiac complications directly related to CD or not, were eligible to participate in the CRP. Patients who were unable to attend 3-week exercise training sessions or had neuromuscular or clinical absolute contraindications to exercise were not eligible to participate in the CRP [16].

The study was performed according to the revised Helsinki Declaration and was approved by the Institutional Ethics Committee of INI/Fiocruz (CAAE: 0055.0.009.000-11) for the implementation of CRP.

CRP for CD

The CRP consisted of exercise training sessions performed three times a week, for 60 min each session, divided into 30 min of aerobic exercise on a treadmill or cycle ergometer, 20 min of strength training comprising two sets of 12 repetitions for the major muscle groups (sit-ups, push-ups and pull-ups) and 10 min of stretching exercises. Aerobic exercise was performed at moderate intensity set according to the heart rate at anaerobic threshold obtained during a maximal progressive cardiopulmonary exercise test (CPET) (90%–100% of heart rate at anaerobic threshold in the first month of exercise training and 100%–110% of heart rate at anaerobic threshold thereafter). For those patients whose anaerobic threshold was not identified during the CPET, training

intensity was prescribed according to the Hellerstein formula [HR = (102 + maximum metabolic equivalents achieved)/1.41] [17]. In this case, the target HR ranged 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.

All training sessions were performed in the morning under medical supervision. In order to monitor intensity and guarantee patient safety, vital signs including blood pressure, oxygen saturation levels and heart rate were measured before, during aerobic exercise and at the end of each training session using an aneroid sphygmomanometer, a pulse oximeter and a heart rate monitor, respectively. Individuals with severe arrhythmias were monitored with an electrocardiogram monitor (CM5 or D2 derivations) during the aerobic exercise. Patients with diabetes had their glucose levels monitored before and after each session, as did those patients who had any symptoms of hypoglycaemia. A more detailed description of exercise training sessions can be found elsewhere [10,18].

Follow-up

Participants enrolled in the CRP underwent assessments of functional capacity (maximal progressive CPET), anthropometric evaluation and cardiac function (left ventricular ejection fraction [LVEF] from 2-dimensional echocardiography and right ventricular [RV] systolic dysfunction) before beginning the CRP (baseline assessment). CPET comprised measures of heart rate, blood pressure, oxygen uptake at peak exercise (VO$_2$ peak), oxygen pulse, ventilatory equivalent slope for carbon dioxide output (VE/VCO$_2$ slope), oxygen uptake efficiency slope (OUES) and functional aerobic impairment (FAI) [19]. The anthropometric evaluation consisted of measurements of height and weight according to Lohman et al (1988) [20]. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2). Echocardiographic studies were performed in accordance with the American Society of Echocardiography recommendations using phased-array ultrasound system (Vivid 7, GE Medical Systems, Milwaukee, WI) equipped with an M4S phased-array transducer [21]. LVEF was determined using the modified Simpson's rule. RV systolic function was evaluated by measurement of the peak systolic myocardial velocity (RVS') of the lateral tricuspid annulus.

Clinical (essential hypertension, diabetes mellitus, dyslipidaemia, stroke, chronic obstructive pulmonary disease, presence of non-chagasic heart disease, New York Heart Association [NYHA] functional class and kidney function) and sociodemographic (age, sex, schooling, race and

marital status) variables were obtained from medical records. Overweight and obesity were classified using BMI according to the WHO definition [22]. Schooling included the years of formal study, stratified into two categories (<5 years and ≥5 years). Race was self-reported and further clustered into white and non-white (black, mulatto and others). Marital status was categorised as single/widowed or married. Patients were asked about their smoking habits and classified as non-smoker (currently does not use any tobacco product that emits smoke, even occasionally, even if have experienced) or former/current smoker (regular use of tobacco, regardless of how long or past occasional use of tobacco for at least 3 months or daily use for a period of at least 1 month) [23]. Functional class was determined using the NYHA criteria and stratified into two categories (I–II and III–IV) [24]. Kidney function was assessed by serum creatinine levels [25].

Participants were closely followed during their participation in the CRP. In case of missing three consecutive training sessions, the CRP staff contacted the patient by phone to ask about their clinical status and the reasons for their nonattendance. Information obtained during the phone contacts was included in patient's medical records. CRP discontinuation was considered when the patient missed CRP sessions for more than a month in a row, and deaths were identified by reviewing the medical records. The CRP discontinuation was classified according to their reasons into two categories: CD-related reasons, which comprised clinical alterations related to CD; and non-CD-related reasons, which comprised clinical alterations not related to CD, lack of interest to continue in the CRP and sociodemographic issues. Clinical alterations related to CD were any clinical abnormality that precluded the participation into the CRP, such as decompensated heart failure, stroke or the need to implant a cardiac device. Clinical alterations not related to CD were clinical conditions such as orthopaedic injuries, ophthalmologic complaints, depression and other infectious conditions that unrelated to CD abnormalities. Sociodemographic issues included lack of family support, distance from CRP, employment issues and lack of money for transportation.

Data analysis

Data were analysed with Stata 13.0 software. Descriptive analysis for clinical and sociodemographic characteristics of patients enrolled in the CRP consisted of mean and standard deviation for continuous variables and number of observations and percentage for categorical variables.

The follow-up time was measured from the time of CRP entry until the occurrence of study outcomes (CRP discontinuation or death) or the time of administrative censoring on November 2019, when the study observation period ended. Cox proportional hazards models were performed to investigate the associations between clinical and sociodemographic characteristics at baseline with discontinuation rates and death during and after CRP discontinuation. For each outcome, clinical (functional capacity, body composition, cardiac function, comorbidities, functional class and kidney function) and sociodemographic variables (age, sex, schooling, race and marital status) were included as exposure variables in the survival models. The discontinuation reason (CD-related vs. non-CD-related) was also considered as an exposure variable in the survival model for death after CRP discontinuation. The analyses were performed in two steps. Univariate models were fitted to evaluate the associations between each outcome (discontinuation, death while enrolled in CRP and death after discontinuation of CRP) and the exposure variables. Variables which presented a *P*-value < 0.20 in the univariate analysis were included in the multivariate model that maintained only those with $P \leq 0.05$ through the backwards method in the final model. Cumulative event rates were also calculated using the Kaplan–Meier method, and a log-rank test was used to verify whether there was a difference in mortality after CRP discontinuation between non-CD-related reasons vs. CD-related reasons.

Results

Baseline characteristics

The baseline characteristics of the 42 patients included in this study are presented in Table 1. Briefly, most were men (61.9%), non-white (59.5%), with low educational level (<5 years; 57.1%) and with a mean age of 58.1 ± 11.8 years. The majority had HF (76.2%). There was also one patient who presented the indeterminate form of CD but with ischaemic heart disease, a formal indication of cardiac rehabilitation programme.

Most patients were receiving beta-blockers (95.2%, *n* = 40), 92.8% were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 83.3% used diuretics, and 61.9% used an aldosterone antagonist (spironolactone). The compliance rate to exercise training sessions was high (>70%).

Follow-up

Table 2 shows the characteristics of patients stratified by their outcomes while enrolled in CRP. Of the 42 patients that initiated CRP, 74% (*n* = 31) discontinued, 14%

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Table I Characteristics of participants included in the study (*n* = 42)

Variable	Percentage (frequency) or Mean (standard deviation)
Age (years)	58.1 (11.8)
Sex (%)	
Male	61.9 (26)
Female	38.1 (16)
Schooling (%)	
0–5 years	*57.1 (24)*
>5 years	42.9 (18)
Race (%)	
Non-white	59.5 (25)
White	40.5 (17)
Marital status (%)	
Married	59.5 (25)
Single or widowed	40.5 (17)
Heart failure (%)	
No	23.8 (10)
Yes	76.2 (32)
Hypertension (%)	
No	71.4 (30)
Yes	28.6 (12)
Diabetes mellitus (%)	
No	85.7 (36)
Yes	14.3 (6)
Dyslipidaemia (%)	
No	73.8 (31)
Yes	26.2 (11)
Stroke (%)	
No	78.6 (33)
Yes	21.4 (9)
Chronic obstructive pulmonary disease (%)	
No	95.2 (40)
Yes	4.8 (2)
BMI classification (%)	
Underweight or eutrophic	50.0 (21)
Overweight or obese	50.0 (21)
Smoking (%)	
Non-smoker	76.2 (32)
Former or current smoker	23.8 (10)
Chagas disease classification	
Indeterminate	2.4 (1)
Cardiac stage A	2.4 (1)
Cardiac stage B1	2.4 (1)
Cardiac stage B1	16.7 (7)
Cardiac stage C	69.0 (29)
Cardiac stage D	7.1 (3)
Cardiac device (%)	
No	57.1 (24)
Yes	42.9 (18)
Non-chagasic heart disease (%)	
No	92.9 (39)
Yes	7.1 (3)

Table I (*Continued*)

Variable	Percentage (frequency) or Mean (standard deviation)
Functional class (NYHA)	
I or II	40.5 (17)
III or IV	59.5 (25)
Medications (%)	
Beta-blockers	95.2 (40)
Diuretics	83.3 (35)
Aldosterone antagonist	61.9 (26)
Anticoagulants	52.4 (22)
Angiotensin-converting enzyme inhibitors	47.6 (20)
Angiotensin receptor blockers	45.2 (19)
Amiodarone	31.0 (13)
Digital	31.0 (13)
Acetylsalicylic acid	16.7 (7)
Isosorbide	11.9 (5)
Ivabradine	2.4 (1)
BMI (Kg/m^2)	25.6 (5.3)
LVEF (%)[†]	33.0 (9.3)
RV systolic dysfunction (%)[‡]	
No	72.5 (29)
Yes	27.5 (11)
Resting SBP (mmHg)	107.6 (17.7)
Resting DBP (mmHg)	68.7 (11.6)
VO$_2$ peak (ml/kg/min)	16.1 (4.9)
VE/VCO$_2$ slope	27.9 (6.5)
OUES	1367.5 (550.6)
FAI	45.6 (15.0)
Oxygen pulse	10.2 (4.3)
Heart rate recovery ≤ 12 bpm (%)	40.5 (17)
Creatinine (mg/dL)	1.2 (0.3)

BMI, body mass index; DBP, diastolic blood pressure; FAI, functional aerobic impairment; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RV, right ventricular; SBP, systolic blood pressure; VE/VCO$_2$ slope, ventilatory equivalent slope for carbon dioxide output; VO$_2$ peak, oxygen intake at peak exercise.
[†] *n* = 38.
[‡] *n* = 40.

(*n* = 6) died while enrolled in CRP, and 12% (*n* = 5) were administratively censored. No deaths occurred during the exercise training sessions. The median length of permanence in CRP was 10.8 months (Figure 1a). The main reason for discontinuation was clinical alterations related to CD (48.4%; *n* = 15), followed by sociodemographic issues (19.3%; *n* = 6), lack of interest (16.1%; *n* = 5) and clinical alterations not related to CD (16.1%;

Table 2 Baseline characteristics of participants stratified by outcomes while enrolled in CRP (*n* = 42)

Variable	Percentage (frequency) or Mean (standard deviation)			
	Continued (*n* = 5)	Discontinued		Deceased (*n* = 6)
		Non-CD-related reasons (*n* = 16)	CD-related reasons (*n* = 15)	
Age (years)	60.6 (13.0)	56.3 (11.8)	59.9 (12.3)	56.5 (11.3)
Sex (%)				
Male	80.0 (4)	68.8 (11)	66.7 (10)	16.7 (1)
Female	20.0 (1)	31.3 (5)	33.3 (5)	83.3 (5)
Schooling (%)				
0–5 years	20.0 (1)	56.3 (9)	66.7 (10)	66.7 (4)
>5 years	80.0 (4)	43.7 (7)	33.3 (5)	33.3 (2)
Race (%)				
Non-white	40.0 (2)	75.0 (12)	40.0 (6)	83.3 (5)
White	60.0 (3)	25.0 (4)	60.0 (9)	16.7 (1)
Marital status (%)				
Married	80.0 (4)	31.3 (5)	73.3 (11)	83.3 (5)
Single or widowed	20.0 (1)	68.8 (11)	26.7 (4)	16.7 (1)
Heart failure (%)				
No	40.0 (2)	31.3 (5)	13.3 (2)	16.7 (1)
Yes	60.0 (3)	68.8 (11)	86.7 (13)	83.3 (5)
Hypertension (%)				
No	40.0 (2)	62.5 (10)	80.0 (12)	100.0 (6)
Yes	60.0 (3)	37.5 (6)	20.0 (3)	0.0 (0)
Diabetes mellitus (%)				
No	80.0 (4)	81.3 (13)	86.7 (13)	100.0 (6)
Yes	20.0 (1)	18.8 (3)	13.3 (2)	0.0 (0)
Dyslipidaemia (%)				
No	40.0 (2)	75.0 (12)	73.3 (11)	100.0 (6)
Yes	60.0 (3)	25.0 (4)	26.7 (4)	0.0 (0)
Stroke (%)				
No	80.0 (4)	81.3 (13)	86.7 (13)	50.0 (3)
Yes	20.0 (1)	18.8 (3)	13.3 (2)	50.0 (3)
COPD (%)				
No	100.0 (5)	93.8 (15)	100.0 (15)	83.3 (5)
Yes	0.0 (0)	6.3 (1)	0.0 (0)	16.7 (1)
BMI classification (%)				
Underweight or normal	0.0 (0)	43.8 (7)	73.3 (11)	50.0 (3)
Overweight or obese	100.0 (5)	56.3 (9)	26.7 (4)	50.0 (3)
Smoking (%)				
Non-smoker	60.0 (3)	75.0 (12)	93.3 (14)	50.0 (3)
Former or current smoker	40.0 (2)	25.1 (4)	6.7 (1)	50.0 (3)
Cardiac device (%)				
No	80.0 (4)	75.0 (12)	33.3 (5)	50.0 (3)
Yes	20.0 (1)	25.0 (4)	66.7 (10)	50.0 (3)
Non-chagasic heart disease (%)				
No	100.0 (5)	81.3 (13)	100.0 (15)	100.0 (6)
Yes	0.0 (0)	18.8 (3)	0.0 (0)	0.0 (0)
Functional class (NYHA)				
I or II	20.0 (1)	37.5 (6)	53.3 (8)	33.3 (2)
III or IV	80.0 (4)	62.5 (10)	46.7 (7)	66.6 (4)
BMI (kg/m^2)	30.8 (3.3)	26.3 (5.9)	26.3 (5.9)	26.5 (5.4)
LVEF (%)	43.0 (10.8)	32.7 (5.8)[†]	28.1 (10.1)[‡]	36.5 (4.1)
RV systolic dysfunction (%)				
No	100.0 (5)	92.9 (13)	60.0 (9)	33.3 (2)
Yes	0.0 (0)	7.1 (1)	40.0 (6)	66.7 (4)

Table 2 (*Continued*)

| Variable | Percentage (frequency) or Mean (standard deviation) | | | |
| | Continued (*n* = 5) | Discontinued | | Deceased (*n* = 6) |
		Non-CD-related reasons (*n* = 16)	CD-related reasons (*n* = 15)	
SBP (mmHg)	116.8 (16.5)	112.2 (16.9)	101.9 (15.4)	101.7 (23.2)
DBP (mmHg)	74.4 (6.1)	71.9 (11.9)	64.4 (10.0)	66.0 (15.2)
VO$_2$ peak (ml/kg/min)	13.9 (3.0)	16.6 (5.6)	17.1 (4.7)	13.7 (4.8)
VE/VCO$_2$ slope	25.5 (4.8)	28.2 (5.4)	28.1 (7.7)	28.2 (8.0)
OUES	1541.1 (604.6)	1443.8 (610.9)	1222.8 (300.1)	1444.4 (838.6)
FAI	43.7 (9.5)	47.2 (17.3)	41.6 (14.2)	53.2 (13.3)
Oxygen pulse	11.0 (3.1)	11.6 (5.7)	9.4 (2.3)	7.6 (3.4)
HR recovery ≤ 12 bpm (%)	60.0 (3)	31.3 (5)	53.3(8)	16.7 (1)
Creatinine (mg/dl)	1.3 (0.4)	1.2 (0.3)	1.3 (0.3)	1.2 (0.5)

BMI, body mass index; CD, Chagas disease; COPD, chronic obstructive pulmonary disease; CRP, cardiac rehabilitation program; DBP, diastolic blood pressure; FAI, functional aerobic impairment; HR recovery, heart rate recovery; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RV, right ventricular; SBP, systolic blood pressure; VE/VCO$_2$ slope, ventilatory equivalent slope for carbon dioxide output; VO$_2$ peak, oxygen intake at peak exercise.
†*n* = 13.
‡*n* = 14.

n = 5). All deaths that occurred while enrolled in CRP (*n* = 6) were due to clinical complications of CD: five due to decompensated heart failure and one due to sudden death (Figure 1b).

Of the 31 patients who discontinued CRP, 34% (*n* = 11) died after CRP discontinuation, all from clinical complications of CD, ten due to decompensated HF and one due to sudden cardiac death. The median length between discontinuation and death was 12.0 months (Figure 1c). Kaplan–Meier survival curves depict a higher mortality after discontinuation of CRP among those who discontinued CRP due to CD-related reasons ((53.3% [*n* = 8]) than among those who discontinued CRP due to non-CD-related reasons (18.8% [*n* = 3]; *P* = 0.006) (Figure 1d).

The results of the univariate and multivariate Cox survival analysis are shown in Tables 3 and 4, respectively. White race (HR = 0.09; 95% CI 0.01–1.00) and oxygen pulse (HR = 0.69; 95% CI 0.48–0.99) were independently associated with lower mortality rates while enrolled in CRP, whereas the presence of RV systolic dysfunction (HR = 10.54; 95% CI 1.24–89.50) was independently associated with higher mortality rates while enrolled in CRP. Married status (HR = 0.44; 95% CI 0.21–0.95) was independently associated with lower discontinuation rates from CRP. For mortality rates after CRP discontinuation, VO$_2$ peak (HR = 0.85; 95% CI 0.74–0.98) was independently associated with lower deaths, whereas CRP discontinuation due to CD-related

reasons (HR = 8.33; 95% CI 1.91–36.27) was associated with higher death rates.

Discussion

To the best of our knowledge, this is the first study that evaluates the discontinuation and mortality rates of a CRP tailored for patients with CD. Our results demonstrated high discontinuation rates, in which 74% of the participants discontinued after a median length of permanence equal to 10.8 months. This discontinuation rate is much higher than that found in other studies for CRP [26,27], although another study described rates of 82% in middle-income countries [28]. These conflicting results can be attributed to differences in the severity of heart disease and cardiac function between study populations, in which 76.2% of our patients presented HF, with low LVEF (33.0% ± 9.3%) and low functional class (NYHA III–IV; 59.5%), representing a very severe disease.

Marital status was the only variable that remained independently associated with CRP discontinuation, with being married a protective factor in comparison to being single/widowed. This is in accordance with previous results in the literature, since living alone may lead to less social support and consequently to less commitment with medical treatment [29,30] and many studies indicated that being single or widowed was associated with higher non-participation or discontinuation rates from CRP [27,31,32], although others did not find any association
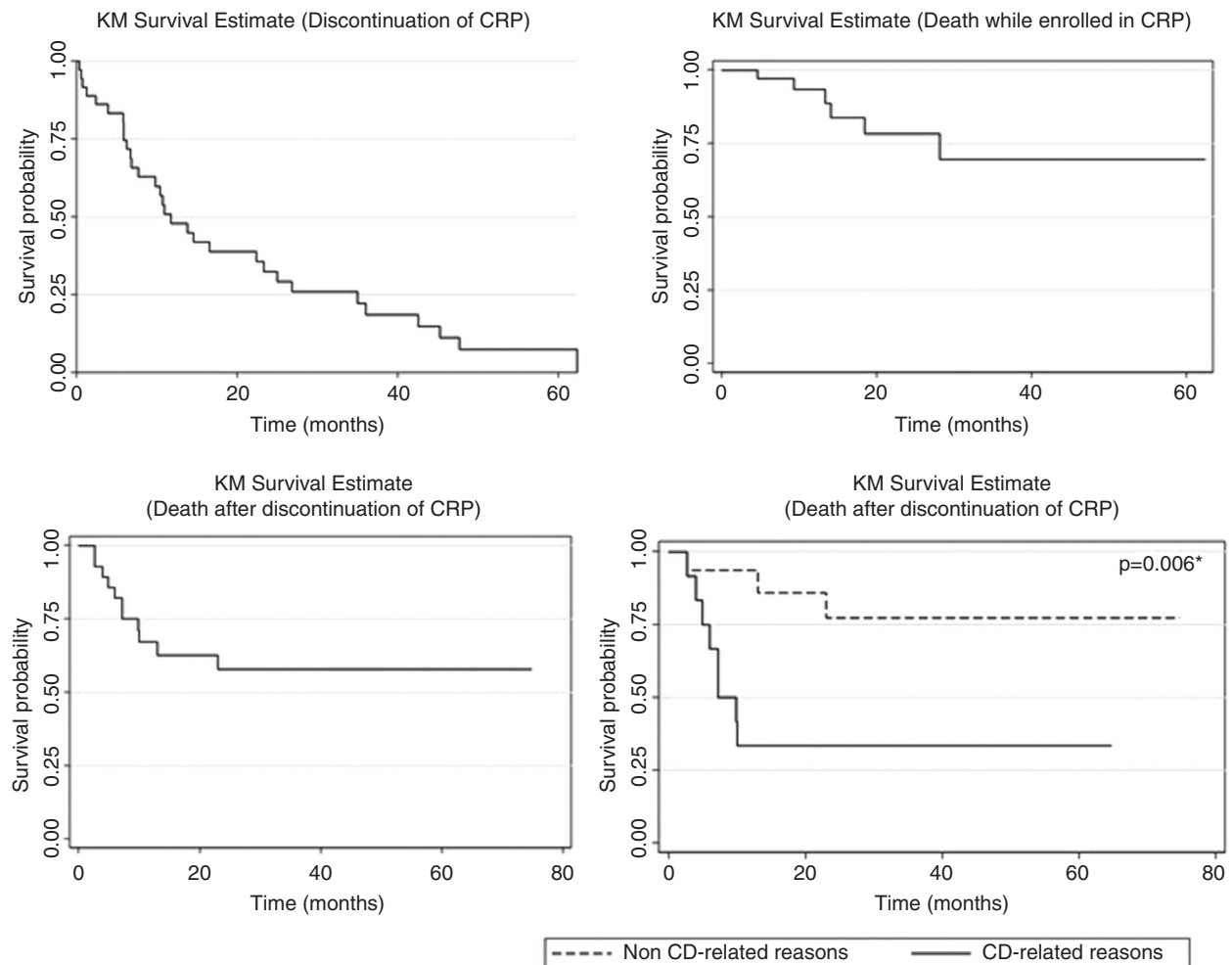
Figure 1 Kaplan–Meier survival curves for discontinuation and mortality in patients with CD enrolled in cardiac rehabilitation programme. CD, Chagas disease; CRP, cardiac rehabilitation programme; KM, Kaplan–Meier survival curves. *$P < 0.05$

[33]. However, some authors indicate that personal characteristics may not be good predictors of adherence to medical treatments [34] and that organisational factors (e.g. time spent with the doctor, continuity of care by the doctor, communication style of the doctor and interpersonal style of the doctor) are more associated to adherence than sociodemographic variables [35].

Despite the severity of the heart disease the patients presented, no deaths occurred during the exercise training sessions, which confirm the safety of cardiac rehabilitation for this population, as previously demonstrated by others [9,36]. However, six patients died while enrolled in CRP, all of them due to CD-related causes.

The variables that were independently associated with death while enrolled in CRP were race, RV systolic

dysfunction and oxygen pulse. In terms of race, being white was a protective factor vs. being non-white. In this setting, black ethnicity is associated with a higher prevalence of heart failure [37] and mortality [38] and with a worse prognosis in ChC [39]. However, this result must be analysed with caution, since the Brazilian population presents a high degree of miscegenation that makes difficult an accurate race classification [40–42].

In our study, RV systolic dysfunction increased tenfold the risk of dying while enrolled in CRP. In CD, RV dysfunction is usually present only at late stages of ChC when patients present heart failure [43] and is probably related to the increased RV afterload imposed by high pulmonary venous pressure. This result is in line with

Table 3 Univariate associations between clinical and sociodemographic characteristics with CRP discontinuation and death while enrolled and after CRP discontinuation

Variable	Univariate Analysis HR (95% CI)		
	Death while enrolled in CRP (n = 42)	CRP discontinuation (n = 36[†])	Death after CRP discontinuation (n = 31[‡])
Age (years)	0.97 (0.91–1.03)	0.98 (0.95–1.00)	1.04 (0.98–1.11)
Sex			
Male	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Female	0.09 (0.01–0.79)	0.59 (0.27–1.28)	0.50 (0.15–1.65)
Schooling			
0–5 years	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>5 years	0.65 (0.12–3.58)	0.92 (0.44–1.91)	0.50 (0.13–1.89)
Race			
Non-white	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
White	0.16 (0.02–1.41)	0.55 (0.26–1.14)	0.54 (0.14–2.05)
Marital status			
Single or widowed	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Married	2.52 (0.29–21.67)	0.51 (0.24–1.06)	1.53 (0.46–5.09)
Heart failure			
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	2.41 (0.28–20.81)	2.21 (0.88–5.50)	3.65 (0.47–28.54)
Number of comorbidities	1.03 (0.18–5.80)	0.61 (0.29–1.27)	0.47 (0.12–1.77)
Stroke			
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	3.23 (0.65–16.03)	0.86 (0.33–2.26)	0.57 (0.07–4.45)
Smoking			
Non-smoker	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former or current smoker	2.68 (0.53–13.42)	0.45 (0.15–1.34)	0.40 (0.05–3.15)
Functional class (NYHA)			
I and II	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
III and IV	1.40 (0.26–7.65)	1.01 (0.50–2.15)	1.53 (0.45–5.25)
LVEF	1.02 (0.94–1.11)	0.97 (0.93–1.00)	0.92 (0.85–1.00)
RV systolic dysfunction			
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	5.73 (1.04–31.56)	1.32 (0.56–3.14)	0.95 (0.21–4.41)
VO$_2$ peak (ml/kg/min)	0.88 (0.72–1.08)	1.01 (0.93–1.09)	0.90 (0.80–1.01)
VE/VCO$_2$ slope	1.04 (0.92–1.19)	1.05 (0.99–1.10)	1.09 (1.02–1.18)
OUES	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
FAI	1.07 (0.99–1.17)	1.01 (0.98–1.04)	1.02 (0.98–1.07)
Oxygen pulse	0.76 (0.52–1.10)	1.03 (0.96–1.10)	0.78 (0.61–1.00)
HR recovery ≤ 12 bpm	0.29 (0.34–2.51)	0.78 (0.74–1.64)	2.10 (0.64–6.90)
Creatinine (mg/dl)	1.13 (0.09–14.89)	0.68 (0.19–2.44)	4.24 (0.74–24.31)
CRP discontinuation due to CD related reasons			
No	---	---	1.00 (Reference)
Yes	---	---	5.40 (1.41–20.71)

CRP, cardiac rehabilitation program; FAI, functional aerobic impairment; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RV, right ventricular; VE/VCO$_2$ slope, minute ventilation/carbon dioxide production relationship; VO$_2$ peak, oxygen intake at peak exercise.
[†] six patients that died while enrolled in the CRP were excluded from this analysis.
[‡] Eleven patients (six that died while enrolled in the CRP and five that were administrative censored) were excluded from this analysis.

previous studies which demonstrated that RV ejection fraction is an indicator of severity and an independent predictor of survival in mild [44] and advanced [45] heart failure and in ChC [46], besides being an independent determinant of exercise capacity in individuals with ChC [47].

Table 4 Clinical and demographic characteristics independently associated with CRP discontinuation and death while enrolled and after CRP discontinuation

	Multivariate Analysis HR (95% CI)	P-value
Death while enrolled in CRP (n = 42)		
Race		
Non-white	1.00 (Reference)	0.05
White	0.09 (0.01–1.00)	
RV systolic dysfunction		
No	1.00 (Reference)	0.03
Yes	10.54 (1.24–89.50)	
Oxygen pulse	0.69 (0.48–0.99)	0.04
CRP discontinuation (n = 36[†])		
Marital status		
Single or widowed	1.00 (Reference)	0.04
Married	0.44 (0.21–0.95)	
Death after CRP discontinuation (n = 31[‡])		
VO$_2$ peak (ml/kg/min)	0.85 (0.74–0.98)	0.03
CRP discontinuation due to CD-related reasons		
No	1.00 (Reference)	<0.01
Yes	8.33 (1.91–36.27)	

CRP, cardiac rehabilitation program; RV, right ventricular; VO$_2$ peak, oxygen intake at peak exercise.

[†] Six patients that died while enrolled in the CRP were excluded from this analysis.

[‡] Eleven patients (six that died while enrolled in the CRP and five that were administrative censored) were excluded from this analysis.

Oxygen pulse is a CPET variable that can be used as an indirect indicator of LV stroke volume [19], and its association with prognosis in ChC remains uncertain. While Souza et al. (2015) found no association between oxygen pulse and death in 2 years [48], Ritt et al. (2012) found a correlation between heart failure survival score (a validated prognostic score for HF patients) and oxygen pulse [49]. In our study, this variable presented an inverse association, decreasing the risk of death during the CRP in about 30%.

Among the patients who discontinued CRP, all deaths occurred due to causes related to CD. In the multivariate analysis, only VO$_2$ peak and CRP discontinuation due to CD-related reasons remained associated with the occurrence of death after discontinuation of CRP. VO$_2$ peak is an important predictor of long-term mortality in patients with heart failure due to different aetiologies [50] and specifically in ChC [51,52]. Accordingly, VO$_2$ peak was a protective factor for patients who discontinued CRP.

CRP discontinuation due to CD-related reasons was another variable independently associated with death after discontinuation of CRP. Taylor et al. (2017) [53] also found that long-term adherence (>36 months) to CRP was associated with a 33% lower mortality risk when compared to dropout at 3, 12 and 36 months. Moreover, in our study, those who discontinued CRP

due to CD-related reasons presented a higher mortality than those who discontinued CRP due to non-CD-related reasons. We hypothesise that these patients discontinued CRP due to the worsening of CD symptoms, precluding them to perform the exercise sessions [13,54]. Therefore, discontinuation of CRP seems to be a marker of poor prognosis in patients with CD.

The retrospective design and the small sample size are important limitations of the present study. Notwithstanding, this study is the first one examining discontinuation and mortality rates in a sample of patients with CD submitted to CRP; therefore, it can provide important information for future large studies in this area.

Conclusion

Although exercise-based cardiac rehabilitation seems to be an effective approach for the management of CD, discontinuation of CRP is a major concern. Our results indicate that sociodemographic variables and severity of CD are important determinants of discontinuation and mortality in patients with CD participating in a CRP. Since the benefits of CRP are remarkable, strategies tailored for patients with CD focusing on socioeconomic support and a close clinical follow-up must be implemented to decrease CRP discontinuation.

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