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Heart failure associated with chronic Chagas cardiomyopathy increases the risk of impaired lung function and reduced submaximal functional capacity

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ABSTRACT

Background: With the evolution of chronic Chagas cardiomyopathy (CC) and the progression towards heart failure (HF), patients may show a decline in inspiratory muscle strength, lung function, and functional capacity.
Objective: We compared respiratory function and submaximal functional capacity in patients with CC with versus without HF.
Methods: This observational, cross-sectional study was carried out with CC patients divided into CCG, a group without HF ($n = 28$), and HFG, a group with HF ($n = 27$). Spirometry (percent predicted forced vital capacity (ppFVC), forced expiratory volume in one second of FVC (ppFEV$_1$), forced expiratory flow between 25 % and 75 % of FVC (ppFEF$_{25–75\ \%}$), and maximum voluntary ventilation (ppMVV)) and submaximal functional capacity (six-minute step test: 6MST) were evaluated. Mann-Whitney (comparison of pulmonary function and functional capacity between groups) and linear regression (association between the presence of HF and other variables) were performed.
Results: We included 55 participants, with median age of 67 years (56.25–71.75) and 54.55 % males. Dyslipidemia was the most recurrent comorbidity (49.09 %). HFG presented lower ppFVC ($P = 0.000$), ppFEV$_1$ ($P = 0.011$), ppFEF$_{25–75\ \%}$ ($P = 0.017$), and ppMVV ($P = 0.003$) than the CCG. The ppFVC ($B = -18.95$; $P = 0.000$), ppFEV$_1$ ($B = -16.29$; $P = 0.021$), ppFEF$_{25–75\ \%}$ ($B = -19.57$; $P = 0.014$), ppMVV ($B = -16.59$; $P = 0.003$), and 6MST ($B = -17.13$; $P = 0.034$) were negatively associated with the presence of HF.
Conclusion: Our data suggest that impaired lung function, compatible with a restrictive pulmonary pattern, is present among adults with CC and HF.

Introduction

Great efforts have been made to control Chagas disease transmission during the last decades. However, the intense human geographic mobility over the years, socioeconomic vulnerability, and the emerging importance of non-vector transmission routes of disease make it difficult

List of abbreviations: 6MST, 6-minute step test; BMI, body mass index; CC, chronic Chagas cardiomyopathy; CCG, group composed of participants with CC without heart failure; CPET, cardiopulmonary exercise tests; FEF$_{25–75\ \%}$, forced expiratory flow between 25 % and 75 % of FVC; FEV$_1$/FVC, ratio between FEV$_1$ and FVC; FEV$_1$, forced expiratory volume in one second of FVC; FVC, forced vital capacity; HF, heart failure; HFG, group composed of participants with CC with heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MVV, maximum voluntary ventilation; NYHA, New York Heart Association; ppFEF$_{25–75\ \%}$, percent predicted of forced expiratory flow between 25 % and 75 % of FVC; ppFEV$_1$/FVC, percent predicted of ratio between FEV$_1$ and FVC; ppFEV$_1$, percent predicted of forced expiratory volume in one second of FVC; ppFVC, percent predicted of forced vital capacity; ppMVV, percent predicted of maximum voluntary ventilation; UDS, number of up-and-down step cycles; VO_2, oxygen uptake.

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to effectively control Chagas disease,[1] which remains included in the group of neglected diseases of the World Health Organization.[2] Chagas disease affects about 6 to 8 million people worldwide and is considered endemic in 21 countries of the Latin American continent.[3] In Brazil, an estimated 1.9 to 4.6 million people are infected with *T. cruzi*,[1,4] the organism that causes Chagas disease, and this accounts for a high number of deaths.[2,4]

During the chronic phase of Chagas disease, which can last for decades, approximately 20 % to 30 % of patients will develop cardiac complications,[5] also known as chronic Chagas cardiomyopathy (CC). Cardiac involvement in CC includes a range of manifestations, from the presence of electrocardiographic abnormalities without symptoms to severe manifestations, such as heart failure (HF), thromboembolic complications, ventricular arrhythmias, and sudden death.[6] According to the Brazilian Society of Tropical Medicine, CC classification includes three stages without HF (Stage A, with no global left ventricular (LV) systolic dysfunction or LV wall motion abnormalities; Stage B1, LV wall motion abnormalities with or without mild LV systolic dysfunction (LV ejection fraction (LVEF) $\geq$ 45 %); Stage B2, moderate or severe LV systolic dysfunction with LVEF $<$ 45 %), and two stages with HF (Stage C, compensated HF; and Stage D, refractory HF).[1]

Patients with CC could present symptoms associated with a reduction in functional capacity, such as exercise intolerance and difficulty in performing daily living activities, with a significant impact on quality of life.[7] Changes in lung function suggest a worse prognosis in patients with heart disease from different etiologies,[8] including CC.[9] Detection of changes in lung function in the early stages of CC may suggest specific and individualized therapeutic approaches, including cardiac and respiratory rehabilitation.[7-12] Therefore, the present study aimed to compare respiratory function and submaximal functional capacity in patients with CC with and without HF.

Methods

Study design

This observational cross-sectional study was conducted with CC patients followed at the outpatient clinic of the Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (Fiocruz). Ethical approval was obtained from the institutional ethics committee (CAAE: 55959422.9.0000.5262) on June 13th, 2022. All patients were invited to participate and voluntarily gave their written informed consent before the evaluation, following Brazilian Ministry of Health Resolution 466, December 12, 2012.[13]

Population

Adult patients (over 18 years) of both sexes with regular follow-up at the INI/Fiocruz outpatient clinic and diagnosed with chronic Chagas disease (confirmed by at least two different reactive serological tests) with CC confirmed by a clinical cardiologic evaluation were eligible for the study. According to the Brazilian Society of Tropical Medicine, CC classification includes three stages without HF (Stages A, B1 and B2), and two stages with HF (Stages C and D), as previously detailed.[1]

We excluded patients who had refractory HF (stage D of CC), patients with HF decompensation in the past three months (presence of hemodynamic instability and the need for hospitalization), acute infectious processes, neuromuscular limitations, cognitive and systemic conditions that prevented or limited the performance of the evaluation tests, other etiologies of heart disease, obstructive and/or restrictive disease of respiratory origin, participation in respiratory muscle training or cardiac rehabilitation, and lack of complete immunization for the coronavirus.

Recruitment and data collection occurred between January and June 2023. Patients with CC were identified according to previously scheduled medical appointments accessed via electronic medical records. On the day of the medical appointment, those identified as eligible were invited and, in case of acceptance, signed consent and had their data collected. This strategy was adopted to avoid further displacement and movement of volunteers in the aftermath of the peak of the COVID-19 pandemic. Participants were divided according to their clinical characteristics into CCG, a group composed of participants with CC without HF, and HFG, a group composed of participants with CC with HF (advanced phase and with compensated HF - stage C).

Assessment of outcomes

The hemodynamic assessment was performed by analyzing vital signs (blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation). Heart rate and peripheral oxygen saturation were analyzed by pulse oximetry. Anthropometrics included measurements of height and weight. Height was measured using a stadiometer graduated in centimeters, and the weight of the volunteers was measured using an anthropometric platform scale (Welmy® W 200, Brazil). Body mass index (BMI) was calculated by dividing weight by the squared height.

Using an aneroid sphygmomanometer, blood pressure was measured by the indirect method with the auscultatory technique and Korotkoff noise assessments.[14] All patients performed electrocardiogram and echocardiogram evaluation as their regular clinical evaluation, with analysis of the LVEF, preferably using the Simpson method. The attending physician classified CC using clinical, electrocardiographic, and echocardiographic data. For patients with HF, the current functional class (assessed in the medical record) was identified according to the New York Heart Association (NYHA) classification as Class I (absence of symptoms and limitation in routine activities), Class II (mild symptoms and limitations in routine and comfortable activities at rest), Class III (significant limitation in activities less than routine with the development of symptoms) or Class IV (severe limitations and symptoms present even at rest).[15]

Respiratory function was analyzed using spirometry (Spirobank II), during which the values of the expiratory variables forced vital capacity (FVC), forced expiratory volume in one second of FVC (FEV_1), FEV_1/FVC ratio, and forced expiratory flow between 25 % and 75 % of FVC ($FEF_{25–75\ \%}$) were quantified. In addition, maximum voluntary ventilation (MVV), an inspiratory variable, was also analyzed. The predicted values of the expiratory and inspiratory variables were provided by the software (Medical International Research) of the spirometer based on requested anthropometric information such as sex, height, age, and number of cigarette packs used per day (for smokers) and expressed in BTPS (Body Temperature Pressure Standard) conditions. For the clinical evaluation of each group individually, the following standards and cutoff points were used: (1) normal pattern, characterized by FVC and FEV_1 above 80 % predicted and FEV_1/FVC ratio above 70 % predicted; (2) restrictive pattern, characterized by normal or minimally reduced FEV_1, FVC below 80 % predicted, and FEV_1/FVC ratio normal or above 70 % predicted; (3) obstructive pattern, characterized by FEV_1 below 80 % predicted, normal or reduced FVC, and FEV_1/FVC ratio below 70 % predicted.[16] Additionally, $FEF_{25–75\ \%}$ below 65 % of predicted were considered abnormal spirometry values.[17] Technical procedures and acceptability and reproducibility criteria were performed according to the standards recommended and updated by the American Thoracic Society[18] and Brazilian standards.[19,20] The data were transported and stored in a microcomputer for later analysis.

Submaximal functional capacity was assessed using the 6-minute step test (6MST), performed on top of a platform 20 cm high, 75 cm wide, and 40 cm deep. The volunteers were instructed to get on and off the platform and could start climbing the step with the lower limb, which they felt most comfortable, without the help of their hands. The evaluator used no words of encouragement, only the standard phrase was used: “You are doing well” and it was informed how many minutes remained until the end of the test as recommended by the ATS for the 6-minute walk test (6MWT).[21] When necessary, the volunteer could reduce the speed of ascent and descent, stop or sit, or lean on, but

without interrupting the timer.[22,23] The number of up-and-down step cycles (UDS) was quantified [going up and down = 1 step], as well as the number of stops, for all participants during the 6 min of the test to estimate the VO_2 (oxygen uptake) peak through the equation proposed by Ritt et al..[24] The 6MST previously demonstrated to be a reliable and valid functional capacity test in patients with heart failure.[22] The most accurate cutoff point for the 6MST to predict VO_2 peak $\geq$ 20 mL/kg/min was above 105 steps. The equations used to estimate VO_2 peak were: [19.6 + (0.075 * UDS) – (0.10 * age)] for men and [19.6 + (0.075 * UDS) – (0.10 * age) – 2] for women.[24]

Bias

To control observation and measurement bias, a trained professional used a systematized protocol and calibrated instruments for data collection. A second and blinded researcher conducted the data analysis.

Sample size calculation

Sample size calculation was based on the study published by De Morais et al.,[9] that evaluated the difference in FVC percentage (p = 0.005) between patients with Chagas disease with (82.89±13.83) and without CC (94.16±14.79). The sample was calculated for the primary outcome considered in the present study (percentage of predicted forced vital capacity). Calculating a type I of 5 %, a type II of 10 %, and increasing the size by 20 % due to possible losses to follow-up and refusals, 27 individuals in each group were required to carry out this study.

Statistical analysis

Descriptive data analysis comprised estimating medians (25–75 % interquartile range) for the continuous variables and absolute frequency (percentages) for categorical variables. The medians of sex, age, BMI, spirometry variables (FVC, FEV_1, FEV_1/FVC, $FEF_{25–75\ \%}$, MMV and their respective percent predicted ppFVC, $ppFEV_1$, $ppFEV_1$/FVC, $ppFEF_{25–75\ \%}$, ppMMV) and 6MST between the CCG and HFG groups were compared using the Mann-Whitney test, while the frequencies were compared using Fisher's exact test. An analysis of each group separately was also performed for clinical purposes to understand the behavior of the spirometry variables of each group about the predicted values, as well as the interpretation of the pulmonary function patterns (normal, restrictive, and obstructive). We also compared groups on the functional capacity variables.

Linear regression (continuous variables) analysis was performed to verify associations between the presence of HF (independent variable) and respiratory and submaximal functional capacity (dependent variables), adjusted for age. All analyses were performed by Stata 13.0 software, considering a significance level of $P \leq 0.05$.

Results

A flowchart of the study is depicted in Fig. 1. During recruitment, we assed 140 patients for eligibility through an electronic medical record review. Among these, 79 had one or more exclusion criteria, and four declined to participate in the study. The remaining 57 were divided into two groups, according to the stages of CC (CCG and HFG groups). Of the 29 participants included in the HFG group, two were unable to complete

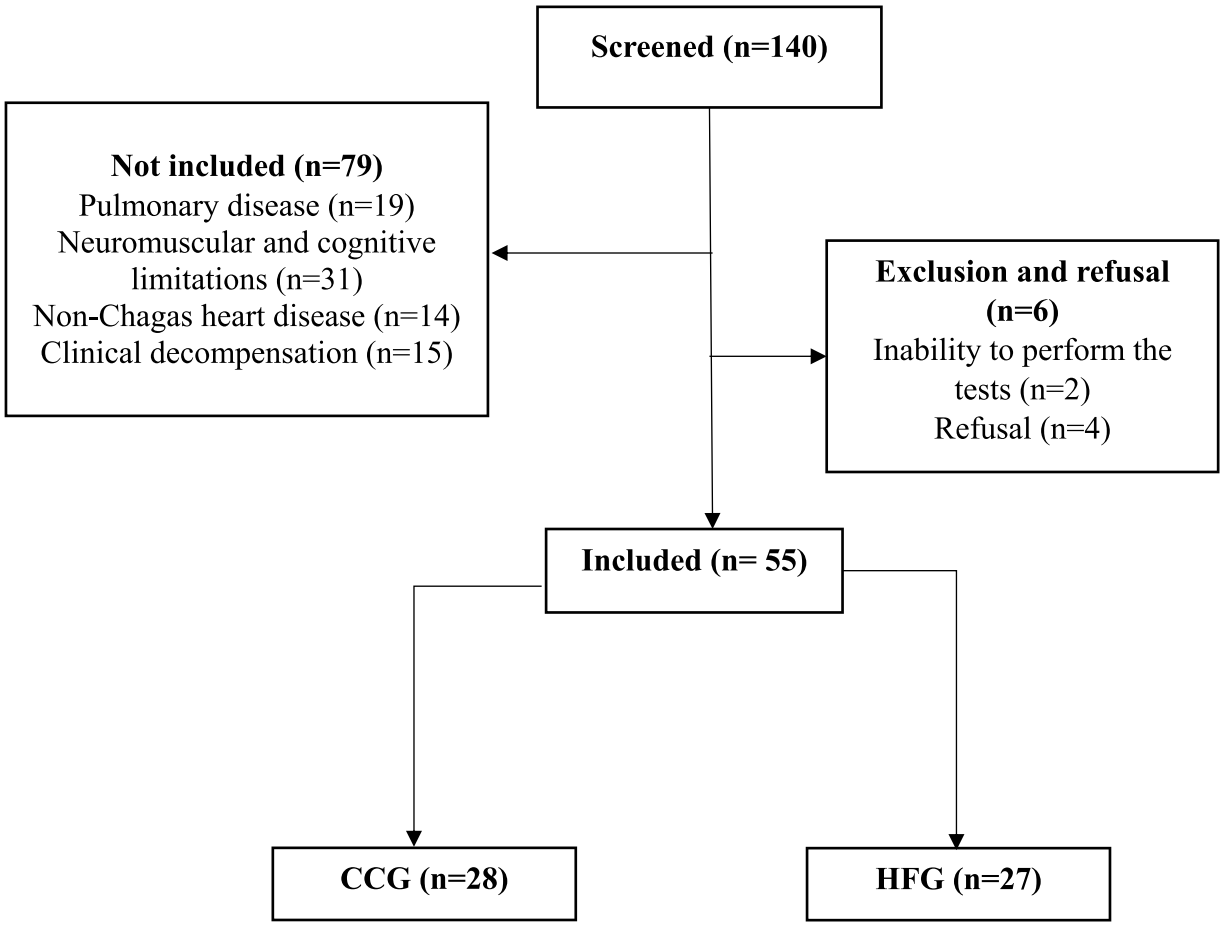

Fig. 1. Flowchart of patients throughout the study period. CCG: group composed of participants with chronic Chagas cardiomyopathy without heart failure; HFG: group composed of participants with chronic Chagas cardiomyopathy with heart failure.

the tests due to cognitive impairment (coordination). Thus, 27 participants in the HFG group and 28 in the CCG group were analyzed.

The total sample consisted of patients aged a median of 67 years (56.25–71.75), most of whom were men (54.55 %) and categorized as overweight with a median BMI of 26.56 kg/m^2 (23.89–30.86). The total sample had left ventricular ejection fraction (LVEF) of 49.00 % (33.00–64.00), with dyslipidemia being the most recurrent comorbidity (49.09 %). The groups were considered homogeneous in terms of age and sex. The CCG group was composed of patients with stage A (46.43 %) and stage B1 (53.57 %), with LVEF 64.00 % (54.50–71.50), while the HFG group consisted of 27 patients with CC stage C and LVEF of 33.00 % (29.00–44.00). NYHA class II was observed at 44.44 %, followed by class III at 33.30 %, and in sequence, class I was observed at 22.22 %. The LVEF of the HFG group was significantly lower compared to the CCG group ($P = 0.000$) (Table 1).

The comparison of pulmonary function and submaximal functional capacity variables between groups is depicted in Table 2. There was a significant reduction in ppFVC ($P = 0.000$), ppFEV$_1$ ($P = 0.011$), ppFEF$_{25–75\ \%}$ ($P = 0.017$), and ppMVV ($P = 0.003$) in the HFG group compared to the CCG group (Table 2). There was no significant difference between groups in relation to ppFEV$_1$/FVC and 6MST variables (Table 2). Evaluating each group separately, we observed the presence of normal ppFEV$_1$ (80.97 %), ppFVC below 80 % predicted (76.36 %), and increased ppFEV$_1$/FVC (99.60 %) in the HFG group, which suggests a restrictive pattern in these volunteers (Table 2). Additionally, ppFEF$_{25–75\ \%}$ was normal in the majority of participants in the CCG group (97.77 %) and HFG group (77.82 %), and in both groups, values of ppMVV were above 70 % of the predicted value. The HFG group showed, at the end of the 6MST, a median UDS (95 cycles) below the proposed cutoff point for reaching a VO_2 peak $\geq$ 20 mL/kg/min (105 cycles), despite reaching the median of estimated VO_2 peak of 20.13 mL/kg/min. The hemodynamic variables remained stable before and after the evaluation tests, and no complications were observed.

Table 1
Characteristics of participants included in the study.

	Overall ($n = 55$)	CCG ($n = 28$)	HFG ($n = 27$)	P value
Men (%)	54.55 (30)	50.00 (14)	59.26 (16)	0.591
Age (years)	67.00 (56.25–71.75)	68.00 (57.00–73.50)	65.00 (56.00–71.00)	0.550
Smokers (%)	9.09 (5)	10.71 (3)	7.41 (2)	1.000
BMI (kg/m^2)	26.56 (23.89–30.86)	27.59 (25.03–31.99)	26.23 (23.24–30.17)	0.178
CC classification (%)				
Stage A	23.64 (13)	46.43 (13)	–	–
Stage B1	27.27 (15)	53.57 (15)	–	–
Stage C	49.09 (27)	–	100.00 (27)	–
NYHA (%)				
I	–	–	22.22 (6)	–
II	–	–	44.44 (12)	–
III	–	–	33.30 (9)	–
LVEF (%)	49.00 (33.00–64.00)	64.00 (54.50–71.50)	33.00 (29.00–44.00)	**0.000**
Comorbidities (%)				
Dyslipidemia	49.09 (27)	53.57 (15)	44.44 (12)	0.593
SAH	41.82 (23)	53.57 (15)	29.63 (8)	0.102
Diabetes Mellitus	20.00 (11)	17.86 (5)	22.22 (6)	0.746
Cardioembolic event	10.91 (6)	10.71 (3)	11.11 (3)	1.000
Obesity	32.73 (18)	39.29 (11)	25.93 (7)	0.391

Data presented in median (25–75 % interquartile range) or percentage (absolute frequency), obtained from volunteers with CC. CCG: group composed of participants with chronic Chagas cardiomyopathy without heart failure; HFG: group composed of participants with chronic Chagas cardiomyopathy with heart failure; BMI: body mass index; CC: Chagas cardiomyopathy; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; SAH: systemic arterial hypertension. P values highlighted in bold represent a statistically significant difference between groups ($p \leq 0.05$).

Table 2
Pulmonary function and submaximal functional capacity variables.

	CCG ($n = 28$)	HFG ($n = 27$)	P value
	Spirometry		
FVC (L)	2.81 (2.52–3.73)	2.81 (1.96–3.27)	0.256
ppFVC (%)	90.97 (80.45–105.35)	76.36 (61.36–85.78)	**0.000**
FEV$_1$ (L)	2.18 (1.89–2.87)	2.28 (1.42–2.58)	0.270
ppFEV$_1$ (%)	91.31 (83.91–104.10)	80.97 (61.36–94.44)	**0.011**
FEV$_1$/FVC	80.15 (76.20–82.90)	79.80 (74.80–82.60)	0.533
ppFEV$_1$/FVC (%)	100.61 (93.79–108.09)	99.60 (95.39–104.82)	0.614
FEF$_{25–75\ \%}$ (L/s)	2.41 (1.67–2.79)	1.86 (1.27–2.69)	0.119
ppFEF$_{25–75\ \%}$ (%)	97.77 (67.01–112.16)	77.82 (51.93–90.85)	**0.017**
MVV (L/min)	76.50 (69.50–97.15)	79.80 (47.30–90.30)	0.266
ppMVV (%)	75.19 (65.79–84.89)	62.15 (46.26–72.29)	**0.003**
	6MST		
UDS	106.00 (94.50 – 126.00)	95.00 (76.00–110.00)	0.077
Workload (watts)	253.67 (200.94–305.48)	193.93 (152.58–321.91)	0.123
Stops number	0.50 (0.00–2.50)	2.00 (0.00–3.00)	0.057
Estimated VO_2 peak (mL/kg/min)	20.00 (18.33–21.56)	20.13 (17.28–21.23)	0.556

Data presented as median (25–75 % interquartile range) obtained from volunteers with CC. CCG: group composed of participants with chronic Chagas cardiomyopathy without heart failure; HFG: group composed of participants with chronic Chagas cardiomyopathy with heart failure; FVC: forced vital capacity; ppFVC: percent predicted FVC; FEV$_1$: forced expiratory volume in the first second; ppFEV$_1$: percent predicted FEV$_1$; ppFEV$_1$/FVC: percent predicted FEV$_1$/FVC; FEF$_{25–75\ \%}$: forced expiratory flow between 25 and 75 % of FVC; ppFEF$_{25–75\ \%}$: percent predicted FEF$_{25–75\ \%}$; MVV: maximum voluntary ventilation; ppMVV: percent predicted MVV; UDS: up-and-down step cycles; 6MST: six-minute step test; Estimated peak VO_2: estimated maximum oxygen uptake. P values highlighted in bold represent statistically significant differences between groups ($p \leq 0.05$).

Linear regression analysis, using HF as a dependent variable adjusted for age, showed that HF of Chagas disease origin was negatively associated with the percentages achieved of predicted values of FVC ($B = -18.95$; $P = 0.000$), FEV$_1$ ($B = -16.29$; $P = 0.021$), FEF$_{25–75\ \%}$ ($B = -19.57$; $P = 0.014$), MVV ($B = -16.59$; $P = 0.003$), and UDS ($B = -17.13$; $P = 0.034$) (Table 3).

Discussion

The main finding of our study was a reduction of respiratory function but with no differences in submaximal functional capacity in the HFG group, a group of patients with chronic Chagas cardiomyopathy with heart failure. Moreover, respiratory function alterations in the HFG group suggest the presence of a restrictive pulmonary pattern. The presence of HF was associated with decreased respiratory function and submaximal functional capacity in patients with Chagas disease.

During CC progression, a high inflammatory response, with metabolic and structural changes, can occur, leading to reduced exercise tolerance and fatigue, that has a negative influence on functional capacity.[25] Inspiratory muscle weakness, which can be associated with reduced FVC, FEV$_1$, and FEV$_1$/FCV ratio, is also described in the literature in patients with CC and HF.[25,26] These modifications can contribute to a negative cycle in the CC. Therefore, the possibility of changes in functional capacity and inspiratory muscle weakness in CC with HF patients reinforces the need to understand and assess respiratory function in these patients, especially in those in the early stages of CC.

Table 3
Linear regression between the presence of HF (independent variable) with respiratory and submaximal functional capacity (dependent variables), adjusted for age.

	B	[95 % CI]	P value
FVC (L)	−0.40	−0.85 – 0.06	0.084
ppFVC (%)	−18.95	−28.56 – 9.34	**0.000**
FEV_1 (L)	−0.30	−0.67 – 0.66	0.105
ppFEV_1 (%)	−16.29	−30.00 – −2.58	**0.021**
FEV_1/FVC	−1.72	−8.25 – 4.82	0.600
ppFEV_1/FVC (%)	−2.00	−10.11 – 6.12	0.624
$FEF_{25–75\ \%}$ (L/s)	−0.39	−0.87 – 0.08	0.104
pp$FEF_{25–75\ \%}$ (%)	−19.57	−34.96 – −4.17	**0.014**
MVV (L/min)	−11.08	−23.64 – 1.47	0.082
ppMVV (%)	−16.59	−27.23 – −5.95	**0.003**
UDS	−17.13	−32.87 – −1.38	**0.034**
Workload (watts)	−41.32	−91.66 – 9.03	0.106
Stops number	+0.97	−0.11 – 2.05	0.077
Estimated VO_2 peak (ml/kg/min)	−1.10	−2.44 – 0.23	0.103

FVC: forced vital capacity; ppFVC: percent predicted FVC; FEV_1: forced expiratory volume in the first second; ppFEV_1: percent predicted FEV_1; ppFEV_1/FVC: percent predicted FEV_1/FVC; $FEF_{25–75\ \%}$: forced expiratory flow between 25 and 75 % of FVC; pp$FEF_{25–75\ \%}$: percent predicted $FEF_{25–75\ \%}$; MVV: maximum voluntary ventilation; ppMVV: percent predicted MVV; UDS: up-and-down step cycles; 6MST: six-minute step test; Estimated peak VO_2: estimated maximum oxygen uptake. Values highlighted in bold represents statistical significance ($p \leq 0.05$).

Respiratory function assessed by spirometry is the gold standard test according to the American Thoracic Society/European Respiratory Society (ATS/ERS).[18] Spirometry, a practical and fast-handling tool, can be well tolerated by patients with heart disease to detect lung flows and volumes and the presence of restrictive or obstructive patterns.[8,27] Regarding the characteristics of the pulmonary patterns diagnosed through spirometry, the normal pattern is presented with FVC and FEV_1 above 80 % predicted and FEV_1/FVC ratio above 70 % predicted.[16] Recently, the ATS/ERS Task Force published an update to the spirometry recommendation, which warned that spirometry alone should not be used to evaluate and diagnose a specific pathological condition. Instead, the lung function test should be used with biological variability associated with clinical and pathophysiological aspects, making the assessment more comprehensive.[28] In the present study, our intention was solely to evaluate the respiratory function and not diagnose any lung disease, justifying the use of spirometry alone. In our study, we chose to assess the cut-off points through the predicted value, considering the few studies on spirometry in the CC population, as well as other heart diseases of non-Chagas disease origin, used the predicted values for their analyses, allowing a direct comparison of our results with these few previous studies.

To the best of our knowledge, no previous studies compared respiratory function between volunteers with CC with and without HF. Two previous studies evaluated the lung function of CC patients.[9,30] De Morais et al.[9] observed reduced lung function (FVC and FEV_1) in the CC group compared to the Chagas disease group (without cardiac form). No detailed information regarding the CC group (stage or the presence of HF or LVEF values) was provided. In the study of Baião et al.,[29] the authors observed a reduced lung function only in the HF of other etiologies group, in relation to healthy control and CC groups, although LVEF values in the CC group were compatible with HF and control values in the normality range.

We observed reduced FVC and normal/increased FEV_1/FVC ratio in the HFG group, suggesting a restrictive pattern, according to the Global Initiative Group for Chronic Obstructive Pulmonary Disease (GOLD).[16] Unlike our results, a previous study observed normal spirometry variables in patients with CC, presenting a very low LVEF.[9] Unfortunately, De Morais et al. also observed normal lung function in the CC group but without detailed information regarding CC stage, HF diagnoses, or LVEF values.

The restrictive respiratory pattern is characterized by the inability to expand or lose the elastic recoil of the lungs.[30,31] It is associated with a higher risk of HF,[32] secondary to various etiologies related to respiratory system characteristics.[33] At present, no tropism has been described between *T. cruzi* and the lung parenchyma.[34] However, changes secondary to increases in intracardiac pressures can cause extravasation of interstitial fluids and pleural effusion with consequent reduction in lung compliance.[9] As a dilated inflammatory cardiomyopathy, CC can cause restriction of lung expansion as the cardiothoracic index increases. The inspiratory muscle strength has already been described as reduced in CC and HF in relation to patients without CC and health subjects,[10,27] and we hypothesize that these factors, grouped or not, can lead to a restrictive pulmonary pattern. This pattern is associated with an increased risk of hospitalization for HF patients[32] and an increased incidence risk for HF for patients without heart diseases compared to those with normal lung function and obstructive pulmonary pattern.[35] The presence of HF of any etiology and any LVEF is associated with an incidence of 51 % of restrictive pulmonary patterns.[33] However, more studies are needed to better understand the associations between restrictive pulmonary patterns and CC.

We observed no difference in submaximal functional capacity between groups. Although the HFG group presented a performance in the UDS (95 cycles) below the cut-off point of 105, both groups reached the minimum cut-off value of the estimated VO_2 peak for a good prognostic marker.[24] This cut-off value for the estimated VO_2 peak was described by Ritt et al. when they compared functional capacity through cardiopulmonary exercise tests (CPET) and 6MST in volunteers with non-Chagas disease cardiomyopathy by analyzing the association between VO_2 peak and UDS.[24] To our knowledge, no previous study evaluated submaximal functional capacity through 6MST in CC patients. In contrast, previous studies observed reduced functional capacity in CC patients with HF through 6MWT[26] and CPET,[7,10] which raised doubts about whether the 6MST is sufficiently sensitivity to detect reductions in functional capacity among CC patients. A previous study, which compared 6MST and CPET in non-Chagas disease HF patients, observed strong correlations between UDS and CPET workload, concluding that 6MST is a reliable and valid tool to assess functional capacity in this population.[22] However, more information is needed about the reliability of 6MST in assessing functional capacity in CC patients.

Spirometric abnormalities do not seem to be predicted by symptoms in patients with heart disease,[8] nor do they appear to precede the symptoms of respiratory disease.[36] In addition, the prevalence of pulmonary function changes appears to be high in patients with coronary artery disease[8] and HF by Chagas disease, as observed in this study, which reinforces the importance of screening for pulmonary disorders in patients with heart disease. Based on this, spirometry should be considered a simple and economical test for the clinical management of patients with Chagas disease, helping health professionals to systematically evaluate pulmonary function and understand the trajectory of the disease.[16] Spirometric evaluation can also be required to support the prescription of exercise once the presence of restrictive or obstructive pulmonary alterations would favor clinical decision-making in the rehabilitation program, improving the understanding of the need for prescription of respiratory exercise, such as lung expansion and clearance, and/or inspiratory muscle training. However, more studies are needed to understand the role of spirometry for individuals with CC in the rehabilitation program.

Finally, the presence of HF in patients with CC was associated with a reduction in lung function and functional capacity. Corroborating our results, a previous study demonstrated an association between the presence of heart disease from non-Chagas etiology (ischemic heart disease) and abnormal spirometry,[8] with no previous studies including patients with CC.

Study limitation

Firstly, the sample size calculation was based on the predicted FCV. It may have been adequate for detecting respiratory function variables, but more is needed to observe differences between groups in relation to 6MST variables. Secondly, as there are no spirometry and 6MST cut-off points for the CC population, the results were evaluated based on cut-off points validated for other populations, which may be very different from those for patients with CC.

Conclusion

Our data suggest that CC patients with HF may present impaired lung function, compatible with a restrictive pulmonary pattern. Additionally, HF in CC was associated with a reduction of lung function and submaximal functional capacity obtained by the 6-minute step test. Intervention strategies aimed to improve lung function among these patients should be tested in future intervention clinical studies.

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CRediT authorship contribution statement

Patrício Braz da Silva: Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Clara Pinto Diniz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources. **Mauro Felippe Felix Mediano:** Writing – review & editing, Visualization, Validation, Software, Resources, Formal analysis. **Fernanda de Souza Nogueira Sardinha Mendes:** Writing – review & editing, Visualization. **Alejandro Marcel Hasslocher-Moreno:** Writing – review & editing, Visualization, Validation. **Luis Felipe Fonseca Reis:** Writing – review & editing, Visualization, Validation. **Michel Silva Reis:** Writing – review & editing, Visualization, Validation. **Roberto Magalhães Saraiva:** Writing – review & editing, Validation, Supervision. **Marcelo Teixeira de Holanda:** Writing – review & editing, Visualization, Validation. **Flavia Mazzoli-Rocha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Andréa Silvestre de Sousa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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