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Inspiratory muscle weakness in patients with Chagas heart disease: Echocardiographic and functional predictors

Henrique S. Costa [a,*], Marcia Maria O. Lima [b], Maria Carmo P. Nunes [a], Giovane Rodrigo Sousa [a], Fernanda R. de Almeida [a], Pedro Henrique S. Figueiredo [b], Manoel Otavio C. Rocha [a]

[a] Postgraduate Course of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Medical School and Hospital das Clinicas of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil

[b] Healthy and Biological Sciences Faculty, Physical Therapy School, Federal University of the Jequitinhonha and Mucuri Valleys, Diamantina, Brazil

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ABSTRACT

Background: Patients with Chagas heart disease (CHD) usually present progressive fatigue and dyspnea. The inspiratory muscle weakness (IMW) may be a marker of exercise intolerance during disease progression. However, the factors related to IMW in CHD patients still remain unknown.

Methods: Forty-eight CHD patients aged 56.4 (53.3–59.5) years were selected and underwent respiratory muscle strength, echocardiography, Cardiopulmonary Exercise Testing and International Physical Activity Questionnaire (IPAQ). The sample was stratified according to the percentage (%) of maximum inspiratory pressure (MIP) achieved in preserved muscle strength (MIP > 70%) or IMW (MIP ≤ 70%). Chi-square and Poisson regression analysis was performed to verify the predictors of IMW.

Results: The %MIP predicted correlated with left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd) and minute ventilation-carbon dioxide production slope (VE/VCO_2 slope). Significant differences in the IPAQ scores ($p = 0.036$), LVEF ($p = 0.020$) and VE/VCO_2 slope ($p = 0.008$) were found between groups with preserved inspiratory muscle strength and with IMW. In multivariate analysis, sedentary patients and those with reduced LVEF and impaired VE/VCO_2 slope had 6.3, 5.5 and 1.2-fold increased risk for IMW, respectively.

Conclusion: The sedentary lifestyle, reduced LVEF and impaired VE/VCO_2 slope showed to be independent predictors of IMW, probably by the association between these variables and the presence of inflammation in CHD patients. The detection of IMW may be helpful in identifying patients at high risk based on echocardiographic and functional aspects without much operating costs.

1. Introduction

Chagas disease continues to be an important cause of cardiac disease in many countries of Latin America [1] and it is now an increasing worldwide problem due to the migration of infected patients to more developed regions [2]. Approximately 30% of infected patients will have cardiac damage and 15% will develop severe ventricular dysfunction [3]. The mortality rate of Chagas heart disease (CHD) with cardiac dysfunction is approximately 50% in five years [4]. Moreover, patients with CHD usually presents with various degrees of heart failure (HF), fatigue, dyspnea and exercise intolerance [5].

Exercise intolerance, recognized as one of the factors of poor prognosis in HF [6], can be assessed by New York Heart Association (NYHA) functional class, one of the main prognostic markers in CHD [7], or by exercise testing, such as Cardiopulmonary Exercise Testing (CPET). The evaluation of respiratory muscle strength, especially inspiratory muscle strength, can be a new assessment tool of exercise intolerance in HF, considering the role of respiratory system during exercise [8].

The inspiratory muscle strength is determined by the maximum inspiratory pressure (MIP) during contraction of the inspiratory muscles, particularly the diaphragm. Inspiratory muscle weakness (IMW) is defined when MIP is significantly reduced compared to the predicted value by gender and age [9].

In HF patients, the prevalence of IMW is estimated in 30–50% [10] and MIP has been correlated with peak oxygen uptake (VO_{2peak}) [11] and NYHA functional class [12]. Furthermore, the IMW is considered an independent predictor of poor prognosis in this population [13]. In Chagas disease, the predictors and factors related to IMW in the disease remain unknown.

The evaluation of inspiratory muscle strength is simple, inexpensive and can be easily implemented in resource-limited areas, especially in endemic regions of Chagas disease. Therefore, the present study was

* Corresponding author at: Rua dos Timbiras, 2505/903, Santo Agostinho, 30.180-100, Belo Horizonte, Minas Gerais, Brazil.
E-mail address: henriquesilveira@yahoo.com.br (H.S. Costa).

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addressed to verify the echocardiographic and functional predictors of IMW in CHD patients.

2. Methods

2.1. Study design

This cross-sectional study was conducted between February 2015 and March 2016 at the Referral Outpatient Center for Chagas Disease at the Clinical Hospital of the Federal University of Minas Gerais (UFMG), Brazil. The research was carried out in accordance with the declaration of Helsinki [14] and was approved by the institutional ethics committee. All patients gave their written informed consent prior to participating in the study.

Criteria for inclusion were the diagnosis of Chagas disease determined by positive specific serology for *Trypanosoma cruzi*, clinical, electrocardiographic or echocardiographic findings compatible with CHD [15] and stable clinical condition. Exclusion criteria were being smokers or ex-smokers, the presence of systemic or heart disease by any other causes and associated comorbidities that could influence the performance in functional evaluations.

The overall study population comprised patients within a wide spectrum of CHD presenting different degrees of cardiac involvement. The previously selected patients underwent clinical evaluation, respiratory muscle strength testing, echocardiography and Cardiopulmonary Exercise Testing. The evaluations were performed at the same time on each day. After all blinded evaluations, patients were stratified according to the presence of IMW.

2.2. Respiratory muscle strength testing

Respiratory muscle strength was determined with a previously calibrated aneroid vacuum manometer (GERAR, São Paulo, Brazil) and values expressed in cmH_2O. MIP was evaluated through a mouthpiece in deep inspiration from functional residual capacity [9,16]. To determine the maximal expiratory pressure (MEP), subjects were instructed to perform a maximal expiratory effort from the total lung capacity [9]. In both MIP and MEP evaluation, the highest value of three measurements was considered.

The values are shown in absolute and relative values by the percentage achieved compared to the predicted by age and gender [17]. Patients were classified as with IMW when MIP was less than 70% of predicted [10,16].

2.3. Functional and echocardiography evaluation

The Cardiopulmonary Exercise Testing (CPET), the gold-standard in functional capacity evaluation, was carried out on a treadmill (Centurion 200, Micromed®, Brasilia, Brazil) by ramp protocol with the metabolic analysis system (MetaLyzer® 3B Cortex-Leipzig, Germany). The VO_{2peak}, peak oxygen uptake at anaerobic threshold (VO_{2peak} at AT), minute ventilation-carbon dioxide production slope (VE/VCO_2 slope) and percentage of maximal heart rate achieved (%HR) were considered for functional evaluation according to current guidelines [18].

To assess the physical activity level, the International Physical Activity Questionnaire (IPAQ) was applied. Validated in 12 countries [19], IPAQ is a questionnaire that allows estimating the time spent weekly in physical activity and classify the physical level in sedentary (score 1), moderate active (score 2) or physically active (score 3) individuals.

The echocardiography techniques and calculations of different cardiac dimension and volumes were performed according to the recommendations of the American Society of Echocardiography [20]. Left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson's rule.

2.4. Statistical analysis

G Power software (G*Power for Windows, version 3.1.7) was used to detect a prevalence ratio of 1.7 increased risk of sedentary patients in develop IMW, based on a pilot study. Considering an alpha error of 0.05 and statistical power of 95%, a total of 48 patients was obtained.

Data were analyzed with SPSS (SPSS for Windows, version 17.0). The data distribution was verified by Kolmogorov-Smirnov test. The descriptive analysis was shown as mean and 95% confidence interval and categorical variables are presented as absolute number (percentage). Spearman Rank correlation test, Chi-square, Independent T-test and Mann-Whitney were performed for data analysis, with significance levels at 0.05.

To verify the predictors of IMW, the Chi-square test was used in the univariate analysis. The following variables were categorized: gender (male and female); NYHA (I, II and III); IPAQ score (1, 2 and 3); expiratory muscle weakness [17] (MEP ≤ 70% of predicted); LVEF [21] in normal (≥50%) and reduced (<50%); left ventricular end-diastolic diameter (LVDd) in normal (≤50 mm) and abnormal (>50 mm); VO_{2peak} [22] in normal (>20 mL.kg.min) and functional impairment (≤20 mL.kg.min); %HR achieved in low-to-moderate (<80% of maximum HR) and high intensity effort (≥80% of maximum HR) and, finally, VE/VCO_2 slope [23] in normal (<32.5) and impaired (≥32.5).

For the multivariate analysis, Poisson regression was performed to determine the prevalence ratio (PR) with the variables that showed a p-value <0.15 in the univariate analysis.

3. Results

3.1. Characteristics of the sample

A total of 108 CHD patients were selected. Of these, fifty patients (46%) were excluded for having a comorbid condition, such as systemic arterial hypertension (n = 26), diabetes mellitus (n = 7), thyroid dysfunction (n = 9) and lower extremity osteoarthritis (n = 8). Another 10 patients (9%) were excluded because they were smokers or ex-smokers. Thus, 48 patients fulfilled the inclusion criteria of the present study. Clinical and demographic characteristics, echocardiographic parameters and functional variables in the overall study population are shown in Table 1.

The %MIP predicted correlated weakly with LVEF ($r = 0.423$; $p = 0.007$), LVDd ($r = -0.380$; $p = 0.017$) and VE/VCO_2 slope ($r = -0.446$; $p = 0.004$) as demonstrated in Fig. 1.

The inspiratory muscle weakness was verified in 17 patients (35%). Significant differences in IPAQ score, LVEF and VE/VCO_2 slope were found between groups with preserved inspiratory muscle strength and with IMW (Table 2).

In the univariate model, the IMW was significantly associated with lower IPAQ score ($p = 0.036$), reduced LVEF ($p = 0.007$) and abnormal LVDd ($p = 0.029$) but not with age ($p = 0.900$), gender ($p = 0.489$), worse NYHA functional class ($p = 0.132$), expiratory muscle weakness ($p = 0.193$), functional impairment by VO_{2peak} ($p = 0.846$), impaired VE/VCO_2 slope ($p = 0.135$) and %HR achieved ($p = 0.757$). In the multivariate model, it was found that patients with sedentary lifestyle, reduced LVEF and impaired VE/VCO_2 slope had, respectively, a 4.3, 5.5 and 1.2-fold increased risk for IMW (PR 4.3, 95% CI 2.3 to 6.6, $p < 0.001$; PR 5.5, 95% CI 1.9 to 11.9, $p = 0.002$, PR 1.2, 95% CI 1.1 to 1.5, $p = 0.001$, respectively) (Table 3).

4. Discussion

To the best of our knowledge, the present study is the first that showed the functional differences in CHD patients with IMW when compared to those with preserved strength. Our results demonstrated that the sedentary lifestyle, reduced LVEF and impaired VE/VCO_2 slope were independent predictors of IMW in CHD patients. The coexistence

Table 1
Characteristics of the patients (n = 48).

Variables	Mean (95% CI) or n (%)
Age (years)	56.4 (53.3–59.5)
Female gender, n (%)	34 (71%)
Medication, n (%)	
Amiodarone	26 (55%)
β-blockers	12 (25%)
ACE-inhibitor	37 (82%)
Diuretics	31 (65%)
Digitalis	6 (12%)
Anticoagulants	3 (6%)
NYHA functional class, n (%)	
I	27 (56%)
II	17 (36%)
III	4 (8%)
IPAQ score, n (%)	
1	10 (21%)
2	18 (37%)
3	20 (42%)
LVEF (%)	54.3 (48.6–59.9)
LVDd (mm)	55.7 (51.9–59.5)
VO_{2peak} (mL.kg.min)	20.4 (18.8–22.0)
VO_2 at AT (mL.kg.min)	15.9 (14.7–17.0)
VE/VCO_2 slope	22.8 (19.7–25.9)
Peak HR (% predicted)	81.9 (77.3–86.6)

Data presented as mean and 95% confidence interval (95% CI) or number (percentage). NYHA = New York Heart Association functional class; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; VO_{2peak} = peak oxygen uptake; VO_2 at AT = oxygen uptake at anaerobic threshold; VE/VCO_2 slope = minute ventilation-carbon dioxide production slope; Peak HR = percentage of maximum heart rate achieved.

of IMW with physical inactivity and mortality-related factors in CHD patients emphasizes the need to evaluate inspiratory muscle strength in the periodic assessment of these patients and the stimulation of early change of lifestyle. In addition, the presence of IMW may be helpful in identifying patients at high risk based on echocardiographic and functional parameters without many operating costs.

We hypothesize that the inflammatory process present in CHD can be the central role of interaction among IMW, physical inactivity and systolic dysfunction. In heart failure patients, there was an increase in proportion of fibers type I and IIa and a decrease in fibers type IIb in diaphragm [24], which are easily fatigued. In fact, diaphragmatic work is increased in HF patients both at rest and during exercise compared to healthy individuals, leading to an exaggerated ventilatory response and consequent increase in the physiological dead space [25,26].

The presence of inflammatory process, especially the higher expression of tumor necrosis factor alpha (TNF-α) seems to be the main factor of modification of diaphragmatic muscle fibers. The increase of myocardial overload stimulates TNF-α release [27], which will act on the diaphragm, leading to atrophy of myosin fibers and, consequently, to a decrease in diaphragmatic contractility [26,28]. Thus, it is expected that patients with systolic dysfunction may also develop IMW, especially in CHD, characterized by intense inflammatory process.

Sousa et al. [29] verified that asymptomatic Chagas disease patients had significantly higher inflammatory cytokine expression, such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) compared to healthy individuals. Moreover, they also reported that patients with Chagas cardiomyopathy with dilated left ventricle and impaired ventricular systolic function had higher concentrations of inflammatory cytokine compared with both healthy individuals and asymptomatic Chagas disease patients. To confirm our hypothesis, further studies are necessary to compare the inflammatory cytokine expression and MIP in CHD patients.

We also demonstrated that the sedentary lifestyle is a strong predictor of IMW, independently of other clinical variables. It is well established that exercise at moderate to high intensity significantly reduces the circulating levels of TNF-α [30], one responsible for IMW. A recent systematic review [31] reported that exercises with frequency

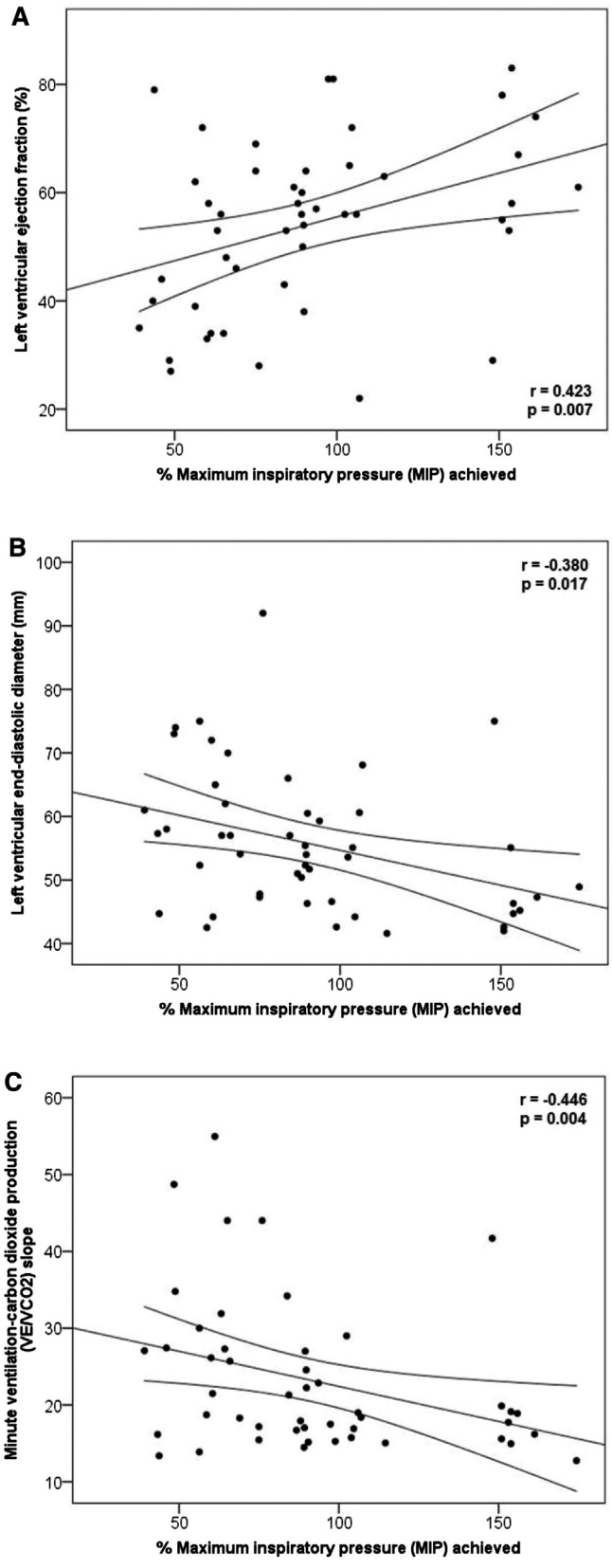

Fig. 1. Correlation analysis between percentage of maximum inspiratory pressure (MIP) achieved and A) left ventricular ejection fraction, B) left ventricular end-diastolic diameter and C) minute ventilation-carbon dioxide production slope.

Table 2
Differences in variables between groups stratified according to the inspiratory muscle strength.

Variables	Patients with preserved inspiratory muscle strength (n = 31)	Patients with inspiratory muscle weakness (n = 17)	p-value
Age (years)	56.4 (52.7–60.1)	56.9 (51.3–63.5)	0.889
Gender (F/M)	23/8	11/6	0.489
NYHA	I (20); II (10); III (1)	I (7); II (7); III (3)	0.132
IPAQ	1 (3); 2 (13); 3 (15)	1 (7); 2 (5); 3 (5)	**0.036**
%MEP predicted	83.4 (68.5–98.3)	72.38 (63.7–81.0)	0.154
LVEF (%)	58.5 (55.1–64.4)	46.9 (38.6–52.7)	**0.020**
LVDd (mm)	53.4 (49.2–57.5)	59.0 (53.6–64.4)	0.097
VO_{2peak} (mL.kg.min)	21.1 (18.9–23.4)	20.2 (17.5–22.8)	0.459
VO_2 at AT (mL.kg.min)	16.5 (15.1–17.8)	15.7 (13.4–17.9)	0.517
VE/VCO_2 slope	20.4 (17.7–23.2)	28.2 (22.1–34.3)	**0.008**
Peak HR (%predicted)	83.5 (78.3–88.7)	84.0 (75.4–92.7)	0.900

Data presented as mean and 95% confidence interval (95% CI) or number (percentage). NYHA = New York Heart Association functional class; %MIP predicted = percentage of maximal inspiratory muscle strength achieved; %MEP predicted = percentage of maximal expiratory muscle strength achieved; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; VO_{2peak} = peak oxygen uptake; VO_2 at AT = oxygen uptake at anaerobic threshold; VE/VCO_2 slope = minute ventilation-carbon dioxide production slope; Peak HR = percentage of maximum heart rate achieved. The values highlighted in bold are statistically significant ($p < 0.05$).

equal or higher than five times a week significantly reduced circulating levels of TNF-α in HF patients. In the present study, sedentary CHD patients have similar risks of developing IMW compared to those moderately active and the risk in sedentary patients is almost threefold elevated than in physically active patients.

The expiratory muscle strength was also lower than the predicted, which is consistent with generalized muscle weakness presented by CHD patients, especially in those with dilated cardiomyopathy [32].

Previous study [33] demonstrated the significant correlation between MIP and VO_{2peak} in cardiac patients. But in the present study, among the functional variables evaluated by CPET, the only one that was significantly different between the groups with and without IMW was the VE/VCO_2 slope, also an independent predictor of IMW. The VE/VCO_2 slope represents the patient's ventilatory inefficiency, especially the difficulty in removing carbon dioxide and is related to the ventilation-perfusion abnormalities [34], such as the presence of inflammation and tissue fibrosis, common clinical findings in CHD [5, 35]. Recently, other functional variables evaluated by CPET have gained prognostic significance [36] and the relationship between IMW and these variables should be investigated.

Baiao et al. [37] evaluated 15 patients with Chagas cardiomyopathy (50.27 ± 5.68 years; NYHA II/III) and lower values in the %MIP predicted compared to the healthy group ($p = 0.005$) were observed. The authors also reported the correlation between MIP and VO_{2peak} ($r = 0.52$; $p < 0.001$). In contrast, the present study did not find a significant correlation between MIP and VO_{2peak} and two points can explain the difference. First, the functional capacity in our study was directly evaluated by gas analysis, which is the most accurate tool for determining the VO_{2peak}, while Baiao et al. [37] used the estimated VO_2. Second, the present study verified the physical level of the patients and Baiao et al. [37] did not mention the patient's physical activity profile.

The study limitations include the small number of patients with severe functional impairment, since most of the patients were in functional class I. In addition, patients were on medication that could improve the performance on functional tests and can influence some variables, such as the peak heart rate achieved during the CEPT. However, due to ethical reasons, we decided not to discontinue drug use during the study period, as these medications are essential for the management of patients with left ventricular dysfunction.

The results of the present study have great clinical importance because Chagas disease patients often come from resource-limited areas without sophisticated equipment, where echocardiography and CPET are generally not available. Left ventricular systolic function is a well-established prognostic marker of the risk of death in Chagas disease [38] and the VE/VCO_2 slope is considered the only independent predictor of mortality among functional variables measured at CPET [23]. The close relationship between IMW with reduced LVEF and impaired VE/VCO_2 slope can assist in risk stratification of patients using inexpensive methods. We also emphasize the early incentive to exercise in CHD and the need to evaluate the inspiratory muscle strength in this population.

Table 3
Independent predictors of IMW in the study population in multivariate model.

	N (%)	PR	95% CI	p-value
NYHA				
III	4 (8%)	1	Reference	
II	17 (36%)	0.997	0.297 to 3.339	0.996
I	27 (56%)	0.397	0.108 to 1.466	0.166
IPAQ				
Active	20 (42%)	1	Reference	
Moderate	18 (37%)	1.685	0.676 to 4.197	0.263
Sedentary	10 (21%)	4.319	2.271 to 6.581	<**0.001**
EMW				
Preserved	27 (56%)	1	Reference	
Weakness	21 (44%)	1.404	0.673 to 2.929	0.366
VE/VCO_2 slope				
Normal	40 (83%)	1	Reference	
Impaired	8 (17%)	1.178	1.062 to 1.515	**0.001**
LVEF				
Preserved	31 (64%)	1	Reference	
Reduced	17 (36%)	5.529	1.913 to 11.861	**0.002**
LVDd				
Normal	26 (54%)	1	Reference	
Abnormal	22 (46%)	0.587	0.169 to 2.033	0.401

PR = prevalence ratio; 95% CI = 95% confidence interval; NYHA = New York Heart Association; IPAQ = International Physical Activity Questionnaire; EMW = expiratory muscle weakness; LVEF= left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; VE/VCO_2 slope = minute ventilation-carbon dioxide production slope. The values highlighted in bold are with statistical significance ($p < 0.05$).

5. Conclusion

Lower physical levels, LVEF and higher ventilatory inefficiency by VE/VCO_2 slope were independent predictors of IMW in CHD patients, probably by the presence of intense inflammatory process in this population.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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