**UNIVERSIDADE FEDERAL DOS VALES DO JEQUITINHONHA E MUCURI**
**Programa de Pós-Graduação em Reabilitação e Desempenho Funcional**

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# A ACURÁCIA DA FORÇA MUSCULAR RESPIRATÓRIA NA IDENTIFICAÇÃO DA DISFUNÇÃO SISTÓLICA EM PACIENTES COM CARDIOMIOPATIA CHAGÁSICA

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Dissertação apresentada ao programa de Pós-Graduação em Reabilitação e Desempenho Funcional da Universidade Federal dos Vales do Jequitinhonha e Mucuri, como requisito para obtenção do título de Mestre em Reabilitação e Desempenho Funcional.

Orientador: Prof. Dr. Henrique Silveira Costa

Coorientadora: Profª. Dra. Alessandra de Carvalho Bastone

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Dissertação apresentada ao MESTRADO EM REABILITAÇÃO E DESEMPENHO FUNCIONAL, nível de MESTRADO como parte dos requisitos para obtenção do título de MESTRAEM REABILITAÇÃO E DESEMPENHO FUNCIONAL

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*Aos meus avós que são a expressão do amor genuíno.*

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## RESUMO

**Introdução:** A doença de Chagas é uma doença tropical prevalente em regiões com alta vulnerabilidade social. Dos pacientes acometidos, 30% dos podem evoluir para a forma cardíaca da doença, denominada de cardiomiopatia chagásica (CCh). A CCh apresenta-se clinicamente de forma heterogênea, sendo a disfunção sistólica, caracterizada ela redução expressiva da fração de ejeção do ventrículo esquerdo (FEVE), um marcador importante de gravidade. Concomitantemente com a deterioração da função cardíaca, o paciente com CCh pode evoluir com redução da capacidade funcional, alteração na proporção das fibras musculares e fraqueza musculoesquelética generalizada, inclusive fraqueza dos músculos respiratórios. Dessa forma, tanto a disfunção sistólica como a fraqueza muscular respiratória acompanham a progressão da doença. Nesse cenário, a avaliação das pressões respiratórias máximas surge como alternativa para a triagem dos pacientes onde a ecocardiografia não estiver disponível. **Objetivo:** Verificar a acurácia da força muscular respiratória na identificação de disfunção sistólica em pacientes com CCh. **Métodos:** Cinquenta e sete pacientes com CCh (53,2±9,0 anos, 61,4% mulheres, NYHA I-III) foram recrutados e submetidos a ecocardiografia e avaliação da força muscular respiratória por manovacuometria. A força muscular inspiratória e expiratória foi definida pela pressão inspiratória máxima (PImáx) e pressão expiratória máxima (PEmáx), respectivamente. A disfunção sistólica foi definida por valores de FEVE abaixo de 52% (para homens) ou 54% (para mulheres). **Resultados:** Trinta e sete pacientes (64,9%) apresentavam disfunção sistólica e 20 (35,1%) pacientes apresentavam função cardíaca preservada. O grupo com disfunção sistólica apresentou PImáx reduzida quando comparado ao grupo com função cardíaca preservada (66,5±34,5 $cmH_2O$ *versus* 85,3±29,2 $cmH_2O$, p=0,044). Não houve diferença na PEmáx (89,9±43,9 $cmH_2O$ *versus* 87,3±22,3 $cmH_2O$, p=0,812). Na curva ROC, a PImáx apresentou acurácia adequada para identificar pacientes com disfunção sistólica (AUC=0,71). A PEmáx não apresentou acurácia satisfatória na identificação desses pacientes. O ponto de corte ótimo da PImáx para identificar disfunção sistólica em pacientes com CCh foi ≤62 cmH2O, com valor preditivo positivo de 85%. **Conclusão:** A PImáx tem valor potencial na identificação de disfunção sistólica em pacientes com CCh. Esse achado pode auxiliar na triagem e na estratificação de risco quando a ecocardiografia não está disponível.



**Palavras-chave:** Doença de Chagas; cardiomiopatia chagásica; ecocardiografia; músculos respiratórios, testes diagnósticos.

## ABSTRACT

**Purpose:** Chagas disease is a tropical disease prevalent in areas with high social vulnerability. Of the affected patients, 30% may progress to the cardiac form of the disease, called Chagas cardiomyopathy (ChC). ChC is clinically heterogeneous, with systolic dysfunction, characterized by a significant reduction in left ventricular ejection fraction (LVEF), an important marker of severity. Concomitantly with the deterioration of cardiac function, the patient with ChC may evolve with reduced functional capacity, alteration in the proportion of muscle fibers and generalized musculoskeletal weakness, including weakness of the respiratory muscles. Thus, both systolic dysfunction and respiratory muscle weakness accompany disease progression. In this setting, the assessment of maximal respiratory pressures emerges as an alternative for screening patients where echocardiography is not available. **Methods:** Fifty-seven patients with ChC (53.2±9.0 years, 61.4% females, NYHA I-III) were recruited and underwent echocardiography and assessment of respiratory muscle strength by manovacuometry. Inspiratory and expiratory muscle strength was defined by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), respectively. Systolic dysfunction was defined by LVEF values below 52% (for men) or 54% (for women). **Results:** Thirty-seven patients (64.9%) had systolic dysfunction and 20 (35.1%) patients had preserved cardiac function. The group with systolic dysfunction had reduced MIP when compared to the group with preserved cardiac function (66.5±34.5 $cmH_2O$ versus 85.3±29.2 $cmH_2O$, p=0.044). There was no difference in MEP (89.9±43.9 $cmH_2O$ versus 87.3±22.3 $cmH_2O$, p=0.812). In the ROC curve, the MIP showed adequate accuracy in identifying patients with systolic dysfunction (AUC=0.71). The MEP did not show satisfactory accuracy in identifying those patients. The optimal MIP cutoff point to identify systolic dysfunction in patients with ChC was ≤62 $cmH_2O$, with a positive predictive value of 85%. **Conclusion:** MIP has potential value in identifying systolic dysfunction in patients with ChC. This finding may aid in screening and risk stratification when echocardiography is not available.



**Keywords:** Chagas disease; Chagas cardiomyopathy; echocardiography; respiratory muscles, diagnostic tests.

**SUMÁRIO**

# 1 INTRODUÇÃO

## 1.1 Doença de Chagas

A doença de Chagas (DC) é uma doença infecciosa causada pelo protozoário *Trypanossoma cruzi (T. cruzi)* (CHAGAS, 1909). Endêmica na América Latina, a DC é considerada um problema de saúde pública negligenciado e estigmatizado (PEREZ-MOLINA; MOLINA, 2018; LIDANI *et al.*, 2019) por acometer população com considerável vulnerabilidade social e dependente de cuidados básicos de saúde (PINHEIRO *et al.*, 2017) sendo um resultado da pobreza humana (DIAS *et al.*, 2016).

Cerca de 6 a 8 milhões de pessoas são infectadas nas Américas (OMS, 2021) prioritariamente por transmissão oral ou vetorial, através fezes dos triatomíneos, popularmente conhecidos como barbeiros, hospedeiro do protozoário *T. cruzi* (ANDRADE *et al.*, 2011; DIAS *et al.*, 2016). Entretanto, aumento expressivo da prevalência já foi documentada em regiões não endêmicas da doença, como Estados Unidos e Europa (BERN *et al.*, 2019), em decorrência dos movimentos migratórios. No Brasil, a estimativa é de que pelo menos um milhão de pessoas estejam infectadas (DIAS *et al.*, 2016; MINISTÉRIO DA SAÚDE, 2022) e que 80% delas não possuem tratamento específico (DIAS *et al.*, 2016; PINHEIRO *et al.*, 2017), o que realça o impacto social expressivo da DC. O diagnóstico para DC deve ser realizado através da história clínica e exames parasito ou sorológicos, dependendo da fase da infecção (MINISTÉRIO DA SAÚDE, 2014).

O curso clínico da DC compreende a fase aguda e crônica (PÉREZ-MOLINA, MOLINA, 2018). A fase aguda é caracterizada pelo surgimento de sintomas generalizados e pouco específicos, como febre, dor de cabeça, edema facial e edema nos membros inferiores (SHIKANAI-YASUDA; CARVALHO, 2012; SANTOS *et al.*, 2020), que pode durar de 4 a 8 semanas com redução da parasitemia em 90 dias (RIBEIRO, ROCHA 1998; PÉREZ-MOLINA, MOLINA, 2018). A fase aguda da doença apresenta, em muitas vezes, resolução espontânea. Porém, se não diagnosticados e tratados em tempo hábil, a DC evolui para fase crônica (PÉREZ-MOLINA, MOLINA, 2018).

Na fase crônica, cerca de 50% dos indivíduos apresentam a forma indeterminada da DC, primeiro estágio dessa fase. Na forma indeterminada observa-se ausência de sinais e sintomas, eletrocardiograma convencional normal ou com mínimas alterações, além dos exames radiológicos do coração, esôfago e cólon normais (RIBEIRO, ROCHA, 1998).

Duas a três décadas após a contaminação, os pacientes podem evoluir com sinais relacionados ao acometimento de órgãos e vísceras, como a cardiomiopatia e megavísceras (megacólon e megaesôfago), além de possíveis alterações do sistema nervoso (PRATA, 2001; PÉREZ-MOLINA, MOLINA, 2018). O acometimento cardíaco é o mais comum e grave na evolução clínica da DC (ROCHA; TEIXEIRA; RIBEIRO, 2007), afetando a estrutura do miocárdio e o sistema de condução cardíaco (PÉREZ-MOLINA, MOLINA, 2018). A forma cardíaca da doença é denominada de cardiomiopatia chagásica (CCh).

### 1.2 Cardiomiopatia chagásica

Cerca de 30 a 40% dos pacientes na forma indeterminada vão evoluir para a CCh (BOTONI *et al.*, 2013). Na CCh, a infecção tem como consequência a miocardite crônica, com característica fibrosante, de baixa intensidade e incessante (SIMÕES *et al.*, 2018). É a manifestação clínica mais grave e ao mesmo tempo mais comum da DC, relacionada à limitação das atividades laborais e pior prognóstico dos pacientes (ROCHA; TEIXEIRA; RIBEIRO, 2007).

Entretanto, a expressão clínica dos pacientes com CCh é heterogênea, podendo variar desde distúrbios de condução elétrica à tríade insuficiência cardíaca, arritmias malignas e tromboembolismo (ROCHA; TEIXEIRA; RIBEIRO, 2007; BOTONI *et al.*, 2013). Inicialmente, podem apresentar alguns achados no eletrocardiograma e pequenas alterações no ventrículo esquerdo, porém, mantém a função sistólica preservada (NUNES *et al.*, 2018; SIMÕES *et al.*, 2018). Um marco na transição entre a forma indeterminada e a CCh é a detecção do bloqueio completo de ramo direito, associado ou não ao hemibloqueio anterior esquerdo (NUNES *et al.*, 2018).

No seguimento dos pacientes, é bem estabelecido que a redução da fração de ejeção do ventrículo esquerdo (FEVE) é um marcador de progressão da doença (NUNES *et al.*, 2018) e de mortalidade dos pacientes com CCh (RASSI; RASSI; RASSI, 2007; NUNES *et al.*, 2012; RIBEIRO *et al.*, 2012).

Sendo assim, a redução da função sistólica em decorrência do declínio da FEVE é um dos principais parâmetros de estratificação de risco dos pacientes com CCh, estando relacionada, inclusive, à redução da capacidade ao exercício físico e intolerância ao esforço.

### 1.3 Alterações funcionais da CCh

Dentre as alterações funcionais características da CCh, a dispneia e a fadiga são achados comuns. Em decorrência disso, o comprometimento funcional está presente desde os estágios iniciais da cardiopatia (COSTA *et al.*, 2018). Pacientes com CCh e função sistólica preservada já apresentam alterações funcionais quando comparados à saudáveis (COSTA *et al.*, 2018) e pacientes na forma indeterminada (SILVA *et al.*, 2021). A funcionalidade do paciente com CCh assume um papel central uma vez que a capacidade funcional do paciente, representada pelo pico do consumo de oxigênio (VO2pico), é um potencial marcador prognóstico nessa população (COSTA *et al.*, 2020). Além disso, estudo prévio (MONTES DE OCA *et al.*, 2004) também demonstrou redução significativa das fibras do tipo I e um aumento de fibras do tipo II (IIb), associado ao aumento de atividade glicolítica e capacidade oxidativa dos músculos periféricos. Diante disso, a alteração na proporção de fibras pode ser um dos mecanismos responsáveis pelo comprometimento funcional.

Alterações na força muscular esquelética também foram reportadas. Apesar do aumento de fibras do tipo IIb, a maioria dos pacientes com CCh apresenta atrofia das fibras musculares, pois também ocorre, simultaneamente, lesões em capilares, gerando um declínio de força generalizado (MONTES DE OCA *et al.*, 2004). Fonseca *et al* (2020), demonstraram que a força muscular, avaliada à dinamometria por preensão palmar, estava reduzida em pacientes com insuficiência cardíaca de etiologia chagásica em relação aos pacientes com insuficiência cardíaca isquêmica e não isquêmica.

Em pacientes com insuficiência cardíaca, a redução da força muscular respiratória pode ser encontrada em aproximadamente 30 a 50% dos pacientes, sendo observada correlação importantes entre capacidade funcional e força muscular respiratória nesses pacientes (RIBEIRO *et al.*, 2009). Além disso, a manovacuometria é um método simples e acessível de avaliação da força muscular respiratória através da pressão inspiratória máxima (PImax) e pressão expiratória máxima (PEmax). A PImax destacou-se ainda mais no contexto da insuficiência cardíaca quando foi reportado o importante valor prognóstico dessa variável, sendo considerada um marcador independente de sobrevida nessa população (MEYER *et al.*, 2001).

Na doença de Chagas, Baião *et al* (2013), demonstraram que, de fato, a força muscular inspiratória e expiratória eram menores em pacientes com insuficiência cardíaca de etiologia chagásica em relação aos saudáveis. Em uma amostra de 48 pacientes com CCh, Costa

*et al*. (2017) encontraram que 35% apresentavam fraqueza muscular inspiratória. Finalmente, Vieira *et al* (2014) verificaram, em pacientes com CCh, a correlação entre a força muscular inspiratória e a fração de ejeção do ventrículo esquerdo (r=0,524, p=0,037).

Diante disso, sugere-se que tanto a força respiratória como a função cardíaca tendem a piorar com a evolução da doença. Considerando que 1) a avaliação da musculatura respiratória é simples, de fácil acesso e baixo custo e pode ser realizada em regiões com poucos recursos, além disso, 2) que a DC é endêmica em regiões com alta vulnerabilidade e que 3) os exames de diagnóstico requerem recursos financeiros dispendiosos, a avaliação respiratória surge como uma alternativa para rastreio de pacientes com disfunção sistólica.

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# 2 OBJETIVOS

## 2.1 Objetivo geral

Identificar o papel da força muscular respiratória na identificação de pacientes com disfunção sistólica em pacientes com CCh.

## 2.2 Objetivos específicos

- Avaliar os paciente com CCh quanto à força muscular respiratória e ecocardiografia;

- Verificar a acurácia da PImáx e PEmáx na identificação da disfunção sistólica de pacientes com CCh;

- Estabelecer um ponto de corte ideal da PImáx e PEmáx para triagem dos pacientes com CCh e disfunção sistólica.

## 3 ARTIGO CIENTÍFICO

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da UFVJM (ANEXO A) e o artigo seguiu a formatação textual recomendada pela Revista Disability and Rehabilitation (ANEXO B).

# The accuracy of respiratory muscle strength in identifying systolic dysfunction in patients with Chagas cardiomyopathy

**Purpose**: To verify the accuracy of respiratory muscle strength in identifying systolic dysfunction in patients with Chagas cardiomyopathy (ChC). **Methods**: Fifty-seven patients with ChC (53.2±9.0 years, 61.4% females, NYHA I-III) were recruited and underwent echocardiography and assessment of respiratory muscle strength by manovacuometry. Inspiratory and expiratory muscle strength was defined by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), respectively. Systolic dysfunction was defined by LVEF values below 52% (for men) or 54% (for women). **Results**: Thirty-seven patients (64.9%) had systolic dysfunction and 20 (35.1%) patients had preserved cardiac function. The group with systolic dysfunction had reduced MIP when compared to the group with preserved cardiac function (66.5±34.5 $cmH_2O$ versus 85.3±29.2 $cmH_2O$, p=0.044). There was no difference in MEP (89.9±43.9 $cmH_2O$ versus 87.3±22.3 $cmH_2O$, p=0.812). In the ROC curve, the MIP showed adequate accuracy inidentifying patients with systolic dysfunction (AUC=0.71). The MEP did not show satisfactory accuracy in identifying those patients. The optimal MIP cutoff point to identify systolic dysfunction in patients with ChC was ≤62 $cmH_2O$, with a positive predictive value of 85%. **Conclusion**: MIP has potential value in identifying systolic dysfunction in patients with ChC. This finding may aid in screening and risk stratification when echocardiography is not available.

**Keywords**: Chagas disease; Chagas cardiomyopathy; echocardiography; respiratory muscles, diagnostic tests.

## Introduction

Chagas disease is an infectious disease caused by the parasite *Trypanosoma Cruzi*, which remains a public health problem in Latin America [1,2] and with potential for expansion to non-endemic countries [3,4]. Among infected patients, about 30% will develop the cardiac form of the disease [5], denoted Chagas cardiomyopathy (ChC). ChC has a broad spectrum of clinical expression, ranging from electrical conduction disturbances to thromboembolic events, malignant arrhythmias, ventricular dysfunction [6], and severe functional impairment [7].

Many reviews [8-10] reported the prognostic value of left ventricular dysfunction in patients with ChC. A reduced left ventricular ejection fraction (LVEF) is a well-established marker of poor outcomes in these patients. For this reason, echocardiography is required for clinical management, follow-up, and risk stratification [5]. However, Chagas disease is endemic in areas with social-cultural vulnerability regarding aspects influencing health [11], and echocardiography is not always available [5]. Therefore, it is necessary to identify low-cost methods to screen those patients at higher risk for ventricular dysfunction.

Respiratory muscle strength is the ability to produce a maximal force and is assessed by maximal inspiratory and expiratory pressures, MIP and MEP, respectively [12]. A previous study [13] demonstrated the association between LVEF and MIP ($r=0.524$; $p=0.037$) in patients with ChC. Furthermore, it has also been shown that patients with ChC and left ventricular dysfunction had a 5.5-fold increased risk for inspiratory muscle weakness than patients with preserved function [14]. Thus, both the reduction in respiratory muscle strength and left ventricular dysfunction are detectable in the disease progression.

The evaluation of respiratory muscle strength is simple, low-cost, and easy to perform in resource-limited areas. Due to the association between the LEVF and the respiratory muscle strength, it is necessary to verify the accuracy of respiratory muscle strength, assessed by MIP

and MEP, in identifying patients with systolic dysfunction. The present study aimed to investigate the role of MIP and MEP in the identification of systolic dysfunction in patients with ChC. Establishing an optimal cutoff point based on MIP and MEP can help screening for patients at risk when echocardiography is not available.

## Material and methods

### *Study design*

This is a cross-sectional study with patients with ChC recruited in an endemic area, in Brazil, from August 2019 to February 2020. All patients were submitted to functional evaluation to verify the accuracy of MIP and MEP in identifying systolic dysfunction. Patients were invited to participate in the research after the approval of the Research Ethics Committee (CAAE 16379719.5.0000.5108). The procedures were performed according to the Helsinki Declaration [15]. When applicable, the present study followed the recommendations of the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guideline [16].

### *Subjects*

The sample size calculation was based on that proposed for sensitivity studies [17]. Considering the minimum area under the Receiver Operating Characteristic Curve (ROC) curve of 0.7, the ratio of 1:2 between patients with preserved systolic function and systolic dysfunction, and 10% attrition, a sample of 57 patients was required.

To be included, patients should have at least two positive serological tests for Chagas disease and present electro and/or echocardiographic signs compatible with ChC [18]. The exclusion criteria were cardiomyopathies of other etiologies, in addition to the inability to perform the respiratory muscle strength measurements. Smokers and patients with acute conditions that could change the results of respiratory muscle strength, such as flu, were also

excluded. The researchers were unaware of the results of the other assessments. The entire evaluation was performed in the same week.

***Procedures***

The echocardiography was the reference standard test and was performed according to the guidelines of the American Society of Echocardiography [19] to quantify the cardiac function of patients. Images were acquired using Philips HDI 5000-ATL echo machine (Bothell, Washington, USA). LVEF was obtained by the modified Simpson rule. Systolic dysfunction was defined by LVEF values below 52% (for men) or 54% (for women) [19].

Respiratory muscle strength was used as the index test. It was measured using a previously calibrated aneroid vacuum manometer (MV-150/300, Ger-Ar, São Paulo, Brazil). MIP was evaluated based on residual volume while the volunteers were seated, and the highest value of three valid measurements was retained [20,21]. MEP was evaluated based on the total lung capacity [21]. The measurements were satisfactory if the variance between them was at most 10%. The predicted values for age and sex were calculated as proposed by Neder et al. [22] for the healthy Brazilian population.

***Statistical analysis***

Statistical analysis was performed using the Software SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data distribution was verified by the Kolmogorov-Smirnov test and described as mean and standard deviation or median and interquartile range. Categorical variables were presented as absolute and relative frequency.

The association between LVEF, MIP and MEP was verified by Pearson or Spearman Correlation tests, as appropriate. Differences between patients with preserved systolic function

and systolic dysfunction were verified by T-test for independent samples, Mann-Whitney or chi-square test, with the significance level set at 5%.

The ROC curve was performed to verify the accuracy of the MIP and MEP in identifying systolic dysfunction. The optimal cutoff point was chosen by the value with the best sensitivity and specificity (Youden index). The sensitivity, specificity, positive and negative predictive values, and their respective 95% confidence intervals were obtained using the software MedCalc version 13.1.2.0 (MedCalc Software, Ostend, Belgium).

**Results**

Seventy-five patients were recruited in this study. After the clinical examination, 18 patients were excluded due to comorbidities (n=16) and lack of interest to participate in the study (n=2). A total of 57 patients were enrolled in the study. There were no missing data. The mean value of the MIP and MEP were 73.1±33.7 and 89.0±37.5 $cmH_2O$, respectively. Patients with systolic dysfunction (65%; n=37) were younger, most male, with lower body mass index, systolic blood pressure, MIP, and LVEF, and higher left ventricular end-diastolic diameter (LVDd). The demographic, clinical, echocardiographic, and functional characteristics of the patients are presented in table 1.

**Table 1**: Characteristics of the patients (n=57).

| VARIABLE | | Total (n=57) | Preserved systolic function (n=20) | Systolic dysfunction (n=37) | p-value |
|---|---|---|---|---|---|
| Age (years) | | 53.2 ± 9.0 | 59.5 ± 9.0 | 49.9 ± 7.5 | **<0.001** |
| Sex, n (%) | Female | 35 (61.4) | 17 (85.0) | 18 (48.6) | **0.007** |
| | Male | 22 (38.6) | 03 (15.0) | 19 (51.4) | |
| NYHA class, n (%) | I | 36 (63.2%) | 14 (70.0) | 22 (59.4) | 0.311 |
| | II / III | 21 (33.3%) | 06 (20.0) | 15 (40.6) | |
| BMI ($kg/m^2$) | | 24.3 (22.1 – 28.0) | 26.5 (23.6 – 29.7) | 23.6 (21.9 – 26.8) | **0.029** |
| HR (bpm) | | 67.4 ± 10.6 | 68.8 ± 8.8 | 66.7 ± 11.5 | 0.522 |
| SBP (mmHg) | | 120.0 (110.0 – 130.0) | 135.0 (117.5 – 140.0) | 120.0 (105.0 – 120.0) | **0.006** |
| DBP (mmHg) | | 80.0 (70.0 – 80.0) | 80.0 (70.0 – 82.5) | 75.0 (70.0 – 80.0) | 0.326 |
| MIP ($cmH_2O$) | | 73.1 ± 33.7 | 85.3 ± 29.2 | 66.5 ± 34.5 | **0.044** |
| % of predicted MIP | | 78.5 ± 36.2 | 102.4 ± 35.2 | 65.6 ± 29.8 | **<0.001** |
| MEP ($cmH_2O$) | | 89.0 ± 37.5 | 87.3 ± 22.3 | 89.9 ± 43.9 | 0.812 |
| % of predicted MEP | | 88.9 ± 39.6 | 97.5 ± 36.9 | 84.4 ± 40.7 | 0.236 |
| LVEF (%) | | 43.0 (35.0 – 58.8) | 63.5 (58.0 – 73.7) | 36.0 (31.0 – 43.0) | **<0.001** |
| LVDd (mm) | | 59.1 ± 9.3 | 48.5 ± 5.3 | 64.2 ± 5.7 | **<0.001** |

*Data presented as mean and standard deviation, median and interquartile range or absolute number and percentage. Abbreviations: NYHA = New York Heart Association; BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter.*

There was a significant correlation between MIP and LVEF (r=0.320; p=0.017). There was no correlation between MEP and LVEF (r=0.239; p=0.079). The area under the ROC curve (AUC) to identify the patients with systolic dysfunction by the MIP and MEP were 0.72 (95% CI: 0.56 – 0.83) and 0.51 (95% CI: 0.36 – 0.66), respectively (Figure 1). The cutoff points of MIP and MEP with the best combination of sensitivity and specificity are shown in table 2.

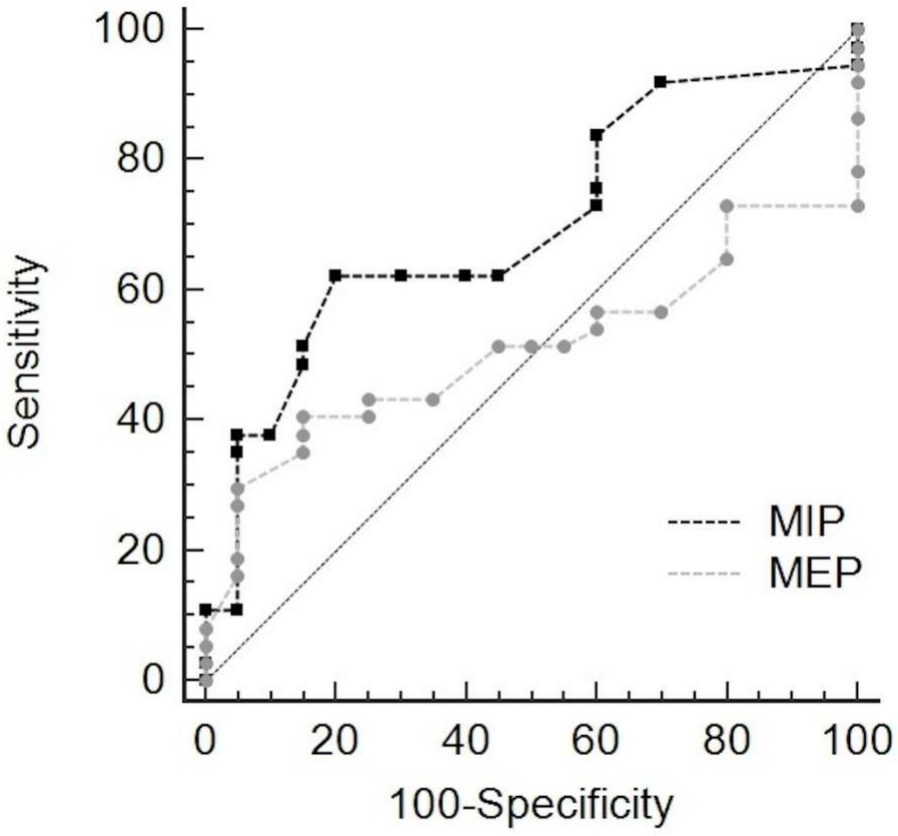




**Figure 1:** Area under the receiver operating characteristic curve demonstrating the accuracy of the MIP (black line) and MEP (gray line) in identifying systolic dysfunction in patients with CC.

**Table 2**: Cutoff points, area under the receiver operating characteristic (ROC) curve, sensitivity, specificity, and positive and negative predictive values of MIP and MEP in identifying patients with CC and systolic dysfunction.

| Variable | AUC (95% CI) | Cutoff point | Sensitivity (95% CI) | Specificity (95% CI) | NPV (95% CI) | PPV (95% CI) |
|---|---|---|---|---|---|---|
| MIP | 0.71 (0.56 – 0.83) | ≤62 $cmH_2O$ | 62% (45 – 77%) | 78% (52 – 93%) | 50% (38 – 62%) | 85% (70 – 93%) |
| MEP | 0.51 (0.36 – 0.66) | ≤69 $cmH_2O$ | 40% (25 – 58%) | 85% (62 -97%) | 43% (36 – 52%) | 83% (62 – 94%) |

Abbreviations: MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure AUC = area under the ROC curve; NPV = negative predictive value; PPV = positive predictive value.

## Discussion

To our best knowledge, the present study was the first that verified the accuracy of respiratory muscle strength in identifying systolic dysfunction in patients with ChC. Our findings demonstrate that MIP, rather than MEP, can be used as an alternative to identify patients with systolic dysfunction, especially when echocardiography is not available. In heart failure from other etiologies, the role of MIP in the functional and prognostic assessment has already been reported [23]. However, few studies addressed the respiratory muscle strength in patients with ChC. The main findings of the present study were: 1) MIP was reduced in ChC patients with systolic dysfunction compared to those with preserved systolic function; 2) MIP showed good accuracy in identifying systolic dysfunction in patients with ChC; 3) the optimal cutoff point for MIP to identify systolic dysfunction in patients with ChC was 62 cmH2O; 4) ChC patients with MIP below or equal to 62 cmH2O have an 85% probability of having systolic dysfunction.

A prior study [24] demonstrated that both MIP and MEP were reduced in patients with dilated ChC (n=15) compared to healthy individuals (n=15) ($p<0.05$ for both). Muscle fiber abnormalities in patients with ChC, such as lower oxidative capacity [25], may contribute to the generalized weakness observed in this population. A recent study [26] verified that muscle

strength was reduced in patients with Chagas disease compared to patients with ischemic and nonischemic dilated cardiomyopathy. These muscle abnormalities may also be present in respiratory muscles and partially explain the reduction in MIP and MEP in ChC. In the present study, there was a significant difference in MIP between the groups with systolic dysfunction and preserved systolic function. There was no difference between groups regarding MEP. Similarly, Vieira et al. [13] also found that patients with ChC had lower MIP compared to Chagas disease patients without apparent cardiopathy, with no difference between groups in MEP.

The reduction in MIP in patients with Chagas disease and systolic dysfunction is expected, mainly due to the inflammatory profile of the disease. In general, the myocardial overload stimulates the release of tumor necrosis factor-alpha (TNF-alpha) [27], a potent inflammatory marker [28]. A previous study [29] showed a significantly higher concentration of TNF-alpha in patients with ChC compared to asymptomatic patients with Chagas disease and healthy individuals. An experimental study with murine animal models showed that the TNF-alpha compromised the contractile function of the diaphragm and decreased force by blunting the response of muscle myofilaments to calcium activation [30]. Therefore, patients with systolic dysfunction may present greater atrophy of myosin fibers, reduced diaphragm contractility [31,32], and consequently reduced MIP. On the other hand, MEP values are similar among patients with systolic dysfunction and preserved cardiac function, which can be explained by the use of expiratory muscles during exercise or in forced breathing [33].

Furthermore, MIP, unlike MEP, showed good accuracy in identifying systolic dysfunction in patients with ChC. The optimal cutoff point was 62 $cmH_2O$, with a positive predictive value of 85%, which means that patients with MIP equal to or below 62 $cmH_2O$ have an 85% probability of having systolic dysfunction. Considering the unavailability of echocardiography in the disease endemic areas, as mentioned above, this result has important

clinical meaning. Of course, the assessment of inspiratory muscle strength should not replace echocardiography. The MIP showed its usefullness in screening and risk stratifying patients with ChC. Nonetheless, the negative predictive value was low, and the presence of systolic dysfunction cannot be rejected when the MIP is greater than 62 $cmH_2O$. As a recommendation, the respiratory muscle strength results should be interpreted in association with the cardiological examination. In contrast, by the ROC curve, MEP did not demonstrate good accuracy in identifying patients with systolic dysfunction. Therefore, the use of MEP is not recommended for screening systolic dysfunction in this population.

The present study has limitations and strengths. As a limitation, the sample may be small for clinical implications, despite adequate statistical power and alpha error. In addition, most patients were in a preserved NYHA functional class, even those with systolic dysfunction. As a strength, the results suggest that MIP, a simple and low-cost evaluation, can complement the screening and risk stratification of patients with ChC.

## Conclusion

ChC patients with systolic dysfunction have reduced MIP compared to those with preserved systolic function. A MIP value equal to or less than 62 $cmH_2O$ is the optimal cutoff point to identify systolic dysfunction in those patients. It may be a valuable alternative to screen systolic dysfunction in ChC patients and stratify their risk in settings where echocardiography is unavailable.

**Acknowledgements**

None

## Disclosure statement

No potential conflict of interest was reported by the authors.

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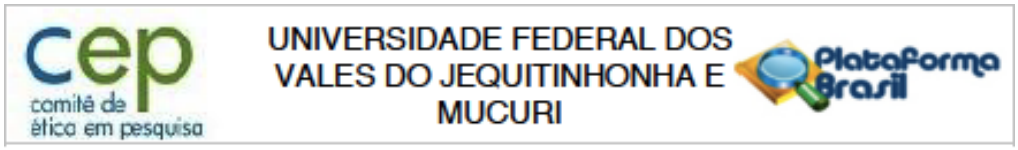
# 4 CONSIDERAÇÕES FINAIS

O presente estudo surge como possível ferramenta para prática clínica no manejo da CCh, uma vez que essa população necessita avaliação periódica para reduzir agravos, prevenir novos casos e promover saúde por ser um método de avaliação de fácil acesso e reprodutível. A avaliação da força respiratória como alternativa de rastreio da disfunção sistólica, também auxilia no conhecimento dos profissionais para melhor rastreio e manejo da condição de saúde, para que o tratamento seja elaborado de forma eficaz garantindo melhores condições de tratamento para população.

A importância também se aplica no âmbito da saúde pública, uma vez que, considerando a escassez de recursos da população de regiões endêmicas, os exames ficam à cargo das instituições públicas, sobrecarregando o serviço e dificultando o acesso da população que muitas vezes possuem no SUS a segurança do diagnóstico e tratamento da condição.

# ANEXO

## ANEXO A – APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA




**PARECER CONSUBSTANCIADO DO CEP**

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Avaliação clínica e funcional de pacientes com cardiopatia chagásica em área endêmica: análise clínica, da capacidade funcional, força muscular periférica e respiratória e qualidade de vida

**Pesquisador:** Henrique Silveira Costa

**Área Temática:**

**Versão:** 2

**CAAE:** 16379719.5.0000.5108

**Instituição Proponente:** Universidade Federal dos Vales do Jequitinhonha e Mucuri

**Patrocinador Principal:** Financiamento Próprio

**DADOS DA NOTIFICAÇÃO**

**Tipo de Notificação:** Envio de Relatório Final

**Detalhe:**

**Justificativa:** Envio do relatório final.

**Data do Envio:** 17/11/2021

**Situação da Notificação:** Parecer Consubstanciado Emitido

**DADOS DO PARECER**

**Número do Parecer:** 5.150.638

**Apresentação da Notificação:**

Relatório final do projeto de pesquisa intitulado: Avaliação clínica e funcional de pacientes com cardiopatia chagásica em área endêmica: análise clínica, da capacidade funcional, força muscular periférica e respiratória e qualidade de vida.

**Objetivo da Notificação:**

Apresentar relatório final de pesquisa

**Avaliação dos Riscos e Benefícios:**

Não se aplica

**Comentários e Considerações sobre a Notificação:**

O relatório foi apresentado após o prazo estipulado pelo CEP.

**Endereço:** Rodovia MGT 367 - Km 583, nº 5000
**Bairro:** Alto da Jacuba **CEP:** 39.100-000
**UF:** MG **Município:** DIAMANTINA
**Telefone:** (38)3532-1240 **Fax:** (38)3532-1200 **E-mail:** cep.secretaria@ufvjm.edu.br

O relatório apresenta todas as informações devidas.

**Considerações sobre os Termos de apresentação obrigatória:**

O relatório foi apresentado conforme modelo do CEP.

**Recomendações:**

Não se aplica.

**Conclusões ou Pendências e Lista de Inadequações:**

Relatório deferido.

**Considerações Finais a critério do CEP:**

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Envio de Relatório Final | relatorio_final_cep_ufvjm.docx | 17/11/2021 16:38:01 | Henrique Silveira Costa | Postado |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

DIAMANTINA, 07 de Dezembro de 2021

**Assinado por:**
**FABIO LUIZ MENDONÇA MARTINS**
**(Coordenador(a))**

## ANEXO B – FORMATAÇÃO DA REVISTA DISABILITY AND REHABILITATION

# Preparing your paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

We also refer authors to the community standards explicit in the American Psychological Association's (APA) Ethical Principles of Psychologists and Code of Conduct.

We encourage authors to be aware of standardised reporting guidelines below when preparing their manuscripts:

- Case reports - CARE
- Diagnostic accuracy - STARD
- Observational studies - STROBE
- Randomized controlled trial - CONSORT
- Systematic reviews, meta-analyses - PRISMA

Whilst the use of such guidelines is supported, due to the multi-disciplinary nature of the Journal, it is not compulsory.

## Structure

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