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REVIEW

RESPIRATORY AND FUNCTIONAL TESTS IN THE ASSESSMENT AND PROGNOSIS OF PATIENTS WITH CHAGAS DISEASE

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ABSTRACT

Chagas disease causes an important impact on cardiorespiratory system, functional and working capacity of the patient. Performing a functional assessment on these individuals becomes essential, since the impact of physical limitation is an important factor that is related with other life domains, such as risk of cardiovascular events in a brief period and risk of death. The goal of this work was to perform a literature review to present the evaluative and prognostic value of main valid respiratory and functional tests in patients with Chagas disease, as well as their applicability and reproducibility. A literature search was performed from 1981 to 2020 in Scielo, Pubmed/Medline, Science Direct, Scopus and Web of Science databases. Only complete studies published in English, Portuguese or Spanish were analyzed which specifically discussed the respiratory and functional tests used in patients with Chagas disease. In total, 544 articles were retrieved of which 35 were eligible. The main functional tests approached were Cardiopulmonary Exercise Testing, Incremental Exercise Testing and Six-Minute Walk Test. Several studies show themselves as useful markers for predicting quality of life, mortality and functional impairment, in addition to other patients' characteristics. Several tests can be used to assess the respiratory and functional impact to patients' health, as well as its relationship with important domains of their lives.

KEY WORDS: Chagas disease; Chagas cardiomyopathy; exercise test; respiratory function tests; prognosis.

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INTRODUCTION

Chagas disease (ChD) occurs due to infection by the protozoan *Trypanosoma cruzi* and it is estimated that almost 7 million people are infected worldwide, with a predominance in Latin America, mainly in Argentina, Brazil and Mexico (WHO, 2015; Dias et al., 2016). The disease affects the economically productive population, interfering in the working life of about 300,000 people, in addition to causing around 12,500 deaths annually (WHO, 2015; Nunes et al., 2013).

The chronic phase of ChD begins around 4 to 8 weeks after infection, and may remain asymptomatic or impair several organs, especially the heart, the esophagus and the colon (Rassi Jr et al., 2010; Prata, 2001). Among all the clinical complications, the most common is chronic Chagas cardiomyopathy, and when in its most severe form, presents myocarditis, lymphomononuclear cell infiltration, interstitial fibrosis and cardiomyocyte hypertrophy, which can lead to dilated cardiomyopathy, heart failure (HF) and death (Ribeiro et al., 2012).

The main symptoms of HF in ChD are dyspnea and exercise intolerance due to low cardiac output and systemic congestive phenomena caused by right ventricular dysfunction (Simões et al., 2000; Braga et al., 2006a). It is also associated with a significant impairment of cardiorespiratory function and higher rates of morbidity and mortality when compared with other etiologies (Nishimura et al., 1994; Costa et al., 2017a; Chua et al., 1995; Daganou et al., 1999; Baião et al., 2013). It plays an important role in patients' functional capacity and directly impacts their quality of life and prognosis (Sousa et al., 2008).

Functional capacity (FC) may be defined as the extent to which a person can increase the exercise intensity and maintain these high levels (Eng et al., 2002) or even the ability to manage the physical demand of daily activities (Solway et al., 2001). In this context, performing a functional assessment on this population is essential, as the impact of physical constraint is an important factor related to other areas of patients' life, such as increased risk of cardiovascular events and death (Rassi Jr et al., 2010). Measuring FC, including pulmonary, cardiac and peripheral musculature evaluation, is essential for guiding diagnosis and treatment, with orientation about physical activities applied to each situation (Solway et al., 2001).

Studies using several methodologies have been conducted to evaluate the FC of patients with HF associated to ChD (Mady et al., 2000; Oca et al., 2004; Mady et al., 2005; Oliveira & Pedrosa, 2006). However, few studies have performed an integrative analysis of the results found. In this context, the present study aimed to perform a literature review to present the evaluative and prognostic importance of main valid respiratory and functional tests in patients with Chagas disease, as well as their applicability and reproducibility.

MATERIAL AND METHODS

This study is an integrative review, a tool which allows to identify and gather scientific information about a subject, helping the construction of theoretical and practical knowledge. The question guiding the study was: Which are the main functional tests to the assessment and prognosis of patients with Chagas disease, as well as its purposes and importance?

A literature search was performed from November 2020 to April 2021 in the Scielo, Pubmed/Medline, Science Direct, Scopus, and Web of Science databases, using the following descriptors which were selected considering the Medical Subject Headings (MeSH): "Chagas disease", "exercise tests", "Chagas cardiomyopathy", "heart failure", "mortality", "quality of life", "pulmonary gas exchange" and "prognosis".

All search terms were linked by the Boolean operator AND in different research strategies, always including "Chagas disease" and "exercise tests", as follows: "Chagas disease" AND "exercise test" AND "Chagas cardiomyopathy"; "Chagas disease" AND "exercise test" AND "heart failure"; "Chagas disease" AND "exercise test" AND mortality; "Chagas disease" AND "exercise test" AND "quality of life"; "Chagas disease" AND "exercise test" AND "pulmonary gas exchange"; "Chagas disease" AND "exercise test" AND prognosis.

The articles were analyzed through the initial reading of their titles and abstracts by two reviewers, considering the specific discussion on the use of respiratory and functional tests in patients with ChD. Once they were selected, the complete articles were read for screening according to the inclusion and exclusion criteria, namely: were included only complete studies, published in English, Portuguese or Spanish and the ones that discussed the application of studies to evaluate patients with ChD; studies repeated in the databases and/or published in another language were excluded.

RESULTS

In total, 544 articles were retrieved, of which 35 were eligible by the inclusion and exclusion criteria (Figure). The publication date ranged from 1981 to 2020. Regarding the recovered studies, 9 were prospective and 26 were cross-sectional studies. All articles included a population above 18 years old, with a mean working time ranging from 33±6 (Mady et al., 2000) to 66±10.4 (Menezes Junior et al., 2015) years. Regarding gender, 23 of the 35 retrieved articles used both men and women, of which 22 had predominance of males. Among the others, seven had a female predominance and six had exclusively male participants.

From the 35 studies retrieved, most analyzed ChD patients with heart conditions, with the exception of five of them which assessed asymptomatic patients without heart failure and patients with an indeterminate form (Mady et al., 2000; Alencar et al., 2014; Costa et al., 2015; Suman et al., 2017; Vargas et al., 1987). All articles included echocardiograms and electrocardiograms to evaluate the sample and, serology was used as diagnostic criteria, except for one case that it was not sufficiently clarified (Mady et al., 2000).

In most of the studies, heart failure degree was classified according to the New York Heart Association (NYHA) criteria (Yazbek Júnior et al., 1998), except for one (Silva et al., 2020). Eighteen studies had very heterogeneous patients' classification, ranging from I to IV. Four studies that used NYHA also used the Goldman classification to assess the severity of patients' symptoms (Ritt et al., 2012; Vieira et al., 2014; Lima et al., 2010a; Nascimento et al., 2014). Two studies also used the Los Andes clinical and hemodynamic classification (Oliveira & Pedrosa, 2006; NYHA, 1994).

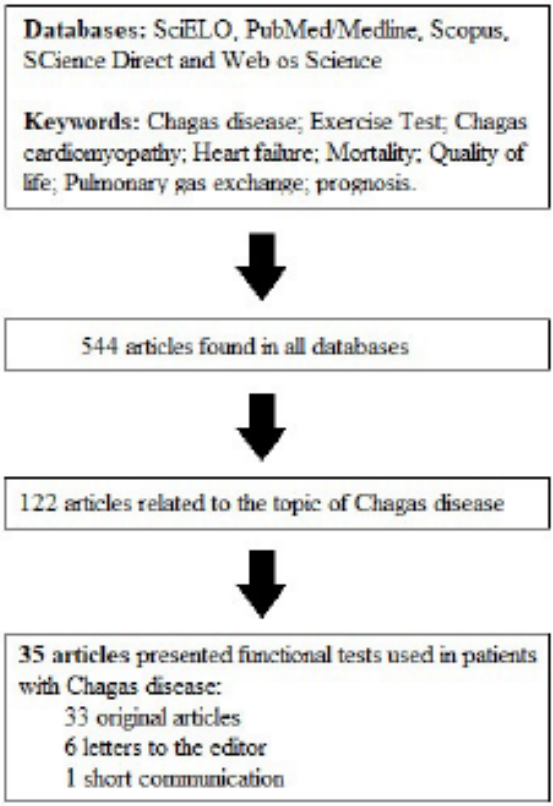

Figure. Methodology flowchart describing the research steps and results.

DISCUSSION

Functional capacity can be assessed by exercise tests that measure maximal oxygen consumption (VO_{2max}), which is the best way to measure cardiovascular fitness throughout changes between myocardial oxygen availability and requirement (Fletcher et al., 2001); it is also able to evaluate arrhythmias and blood pressure (BP) behavior with and without the use of medication (Yazbek Júnior et al., 1998).

The main exercise tests which allows to determine the VO_{2max} are the symptom-limited ones, and it allows an indirect and stipulated measurement of VO_{2max}. The Cardiopulmonary Exercise Test (CPET), which performs direct measurement is considered the gold standard for evaluating functional capacity. However, the high costs and the demand for specialized professionals makes the CPET unfeasible to be performed at some services (Pulz et al., 2008; ACSM, 2010).

Another way to assess FC is by submaximal exercise level determined by complex interactions between lungs, heart, circulation and muscle groups (Olsson et al., 2005; Pereira et al., 2014); it can also measure the functional status of patients, assess the effectiveness of treatment and establish a probable diagnosis (Solway et al., 2001; Oliveira Jr et al., 1996). Among the submaximal tests are the Six-Minute Walk Test (6MWT), which is limited by time, and the Incremental Shuttle Walk Test (ISWT), which is limited by symptoms. These tests are widely used in cardiac patients (Solway et al., 2001; ATS/ERS, 2002) and in patients with ChD (Sousa et al., 2008; Dourado et al., 2010; Lima et al., 2010a) and they have shown good correlation with VO_{2max} measures (Cahalin et al., 1996).

Moreover, the specific functionality of respiratory system can be evaluated by measuring pulmonary flow and volumes using the Pulmonary Function Test (Cahalin et al., 1996), which establishes restrictive or obstructive airflow patterns. Another form of evaluation is through manovacuometry, which indirectly evaluates inspiratory and expiratory muscle strength through maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) (Pereira et al., 2014).

Cardiopulmonary Exercise Testing

CPET is a gradually-increasing intensity exercise limited by exhaustion or symptoms and it is established as the gold standard for cardiorespiratory functional evaluation. The main parameters evaluated are VO_{2max}, ventilation efficiency (VE/VCO_2), O_2 pulse rate, among other variables (ATS/ERS, 2002; Yancy et al., 2013), and the joint analysis of the results allows evaluating cardiovascular, respiratory, muscular and metabolic parameters throughout exercise (Francis et al., 2000).

Moreover, the test also allows to identify mechanisms involved in functional capacity reduction and it associates with changes in cardiorespiratory and musculoskeletal disorders. In addition, it can be used to help prescribe exercise routines for healthy individuals, athletes and patients with cardiopulmonary diseases, besides guiding the definition of prognosis (SBC, 2010).

Table 1 shows several studies which have evaluated the test applicability in ChD, reporting several markers and parameters well correlated with patients' mortality and quality of life prognosis (Menezes Junior et al., 2015; Ritt et al.,2012; Ritt et al., 2013; Fialho et al., 2012). Due to high operational and logistical costs, efforts have been made to find other functional tests with the same effectiveness, which can be used when CPET cannot be performed. Among those, 6MWT and ISWT have been shown to be alternatives, reproducing reliably data.

Table 1. Studies that used Cardiopulmonary Exercise Test to evaluate patients with Chagas Disease.

Characteristics of the study	Findings	Reference
Forty-eight ChD patients were subjected to respiratory muscle strength test, echocardiography, CPET and International Physical Activity Questionnaire. Patients were classified according to MIP achieved. The aim was to evaluate the correlation between inspiratory muscle weakness with other functional variables in ChD patients.	ChD patients presented lower physical levels ($p=0.036$), LVEF ($p=0.020$) and ventilatory efficiency ($p=0.008$) as independent predictors of inspiratory muscle weakness.	Costa et al., 2017a
Eighteen asymptomatic ChD patients with electrocardiographic changes typical of the disease were selected. This group and the control group were submitted to CPET for evaluation of exercise functional capacity.	When compared to healthy individuals, patients with ChD showed a significant impairment of the exercise functional capacity ($p<0.001$), showing lower VO_{2max}, PO_{2max}, VE_{max}, VO_2-AT and HR_{max}. Electrocardiographic changes typical of the ChD are capable of altering the functional capacity of patients.	Mady et al., 2000;

Nineteen ChD patients and eleven healthy volunteers were subjected to exercise testing and peripheral muscle biopsies. The aim was to evaluate metabolic and structural characteristics of peripheral muscle in patients with severe ChD, and its relation with the exercise performance.	ChD patients presented VO_{2max} and PO_{2max} correlated with the muscle/fiber ratio ($p<0.01$), capillary contacts to type I fibers ($p<0.05$) and the cross-sectional area of the fibers ($p<0.01$).	Oca et al., 2004.
One hundred and four patients with ChD cardiomyopathy were assessed. LVEF and VO_{2max} were both classified into 3 degrees and the aim was to evaluate the relation of VO_{2max}, LVEF, and NYHA functional class in those patients.	The functional capacity, mainly VO_{2max}, had good association with LVEF and NYHA functional class in patients with ChD ($p<0.001$).	Mady et al., 2005
Forty-eight ChD patients were divided into four groups according to the Los Andes classification and VO_{2max} and the results were compared with a control group. A cycle ergometer was used with increasing loads (12.5 watts/min) and VO_{2max}, VE/VCO_2 and VE/VCO_2 slope were recorded at different times. The aim was to evaluate the ventilatory response of patients with chronic Chagas' heart disease.	VO_{2max} ($p<0.001$), VE/VCO_2 ($p=0.698$) and VE/VCO_2 slope ($p=0.394$) showed to be functional for classifying cardiopulmonary conditions in ChD patients. The VE/VCO_2 parameters did not require maximum exercise levels.	Oliveira & Pedrosa, 2006
Forty-four patients with functional class I or II and LVEF 58±7 were evaluated. The sensor's HR_{max} was scheduled by age. The aim was to assess the cardiorespiratory response of the accelerometer when compared to the blended sensor to exercise in ChD patients undergoing CPET.	The HR_{max} rate and VO_{2max} of ChD patients who were subjected to the CPET were not achieved in both sensors. Metabolic equivalent, the oxygen consumption and the HR_{max} were greater than expected in the blended sensor ($p<0.001$).	Menezes Junior et al., 2015
Thirty-five ChD patients were assessed based on the FC and HRQoL. FC was evaluated by CPET, 6MWT and ISWT. HRQoL was measured by the SF-36 and MLWHFQ. The aim was to associate the travelled distance in the ISWT and 6MWT tests as well as the VO_{2max} by CPET and HRQoL.	The VO_{2max} evaluated by CPET was correlated with the distance walked by ISWT ($p<0.001$) and 6MWT ($p=0.003$) in the ChD patients.	Costa et al., 2014a.

Thirty ChD patients were classified into 2 groups according to the presence of dilated cardiomyopathy based on the echocardiographic findings. They were assessed by CPET, echocardiography and blood sampling for quantifying serum BDNF.	The reduction in serum BDNF depended on exercise intensity. Patients who were subjected to CPET of high intensity showed an important depletion in BDNF serum levels ($p<0.001$), unlike those of moderate intensity. It reinforces the importance of monitoring ChD patients during the exercise test and of cautiously prescribing high-intensity exercises for patients with chagasic heart disease. These data are specific for patients with ChD.	Costa et al., 2014b
The HFSS was calculated in fifty-five ChD patients with severe left ventricular systolic dysfunction. The correlations were evaluated between the HFSS and the variables derived from echocardiography, CPET, measures the quality of life and tests of distance traveled in 6MWT.	There was correlation between the HFSS index, VO_{2max}, VE/VCO_2 slope, VO_2-AT and efficiency of oxygen uptake in patients with HF due to ChD ($p<0.01$). Patients with smaller values of HFSS had significantly lower score of $VO_{2max.}$	Ritt et al., 2012
Fifty-five patients with HF due to ChD were assessed by echocardiograms, CPET and 6MWT in order to predict quality of life and mortality.	There was significant correlation between quality of life with higher VO_{2max} ($p=0.03$) and EF ($p=0.04$); VO_{2max} less than 18 mL/kg/min and VE/VCO_2 slope more than 32.5 has been associated with significantly worse survival. After adapting it for age, Rassi score and EF, only VE/VCO_2 slope had association with mortality. These data are specific for patients with ChD.	Ritt et al., 2013

Thirty-two patients with ChD were subject to clinical evaluation, echocardiography, CPTE by ramp protocol and ISWT. The aim was measuring the FC by ISWT with direct assessment of VO_{2max} and to compare these findings with results from CPET.	Patients with ChD had good correlation between VO_{2max} and distance walked in ISWT ($p<0.001$), suggesting that ISWT is a good alternative test to assess the FC of ChD patients.	Alves et al., 2016
Eighteen patients were followed to evaluate the impact of exercising on the FC of ChD patients. The program lasted 6 months and FC was assessed by comparing the measurement of VO_{2max} by CPET pre and post exercise.	The assessment of patients with chronic ChD pre and post exercise program showed significant difference on the VO_{2max}, O_2 pulse rate and VO_2-AT ($p=0.01949$).	Fialho et al., 2012
One hundred and four ChD patients with heart failure and VO_{2max} greater than 20mL/kg/min were evaluated and compared with a control group. VO_{2max} was reached using a Beckman metabolic measurement cart and LVEF by transthoracic echocardiography.	Although patients with ChD may show normal $VO_{2max,}$ they had VO_{2max} and EF significantly lower than normal individuals ($p<0.0001$). These data are specific for patients with ChD.	Mady et al., 1996
Eighteen asymptomatic ChD patients with suggestive electrocardiographic alterations were evaluated and compared with a control group. They were subjected to the assessment of functional capacity by measurement of several respiratory variables and the ventricular dysfunction was evaluated by echocardiography. The aim was to diagnose early cardiac dysfunctions in asymptomatic patients.	When compared with normal individuals, asymptomatic ChD patients had significantly lower $VO2_{max}$, PO_{2max}, VE_{max}, HR_{max} and VO_2-AT ($p<0.001$). These data are specific for patients with ChD.	Mady et al., 1997
Fifteen healthy volunteers and fifty-two ChD patients were classified according to Los Andes classification. Several respiratory variables were analyzed in order to compare gas exchange at rest and while exercising.	Variables such as VO_{2max}, maximum VCO_2, maximum expiratory and inspiratory current volume and maximum load were meaningly altered in the groups with more severe stages, which demonstrate the reduction in FC due to ChD progression ($p<0.05$).	Oliveira et al., 2000

Thirty-five patients with Chagas cardiomyopathy were evaluated by echocardiography, CPET, 6MWT, Mini-Mental State Examination and other tests. CPET was performed on a treadmill, and peak oxygen and minute ventilation-carbon dioxide production slope were used to functional assessment. The aim was to check the prevalence of depressive symptoms and its determinants.	Female gender, NYHA functional class, mental summary of SF-36, peak oxygen uptake and 6MWT walking distance were some variables related to depressive symptoms ($p<0.1$).	Silva et al., 2020
One hundred and thirty patients were followed up and were subjected to the CPET until reaching the anaerobic threshold (measured by VO_2 value). The aim was to verify the prevalence of EIVA in chronic Chagas' cardiomyopathy patients and to found out if it would be a good indicator of mortality.	The results showed a prevalence of EIVA of 43.1%, with mortality rates around 3.5 per 100 patients/year (against 1.9 in the control group). A radiography interaction between EIVA and cardiomegaly was observed, which can be established as an important marker of cardiovascular mortality ($p=0.05$).	Pedrosa et al., 2011

ChD: Chagas Disease; CPET: Cardiopulmonary Exercise Test; MIP: maximal inspiratory muscle pressure; LVEF: left ventricular ejection fraction; VE/VCO_2: ventilation efficiency; VO_{2max}: maximal oxygen consumption; PO_{2max}: O_2 pulse rate; VE_{max}: maximal ventilation; VO_2-AT: O_2 consumption at anaerobic threshold; HR_{max}: maximal heart rate; NYHA: New York Heart Association; FC: functional capacity; HRQoL: health-related quality-of-life; 6MWT: Six-minute Walk Test; ISWT: Incremental Shuttle Walk Test; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; BDNF: Brain-derived neurotrophic factor; HFSS: Heart Failure Survival Score; HF: heart failure; EF: ejection fraction; SF-36: generic short-form health survey; EIVA: exercise-induced ventricular arrhythmia.

Incremental Exercise Testing

The Incremental Exercise Testing performs an extensive evaluation of the cardiovascular system. In this test, the patient is submitted to a gradually increased physical effort on a treadmill. Symptoms, heart rate, blood pressure and electrocardiogram behavior are observed before, during and after the exercise test, in addition to estimate the maximum VO_2 achieved. It is usually used to diagnose coronary artery disease, however it also evaluates the presence of arrhythmias, abnormalities in blood pressure and cardiorespiratory function, among other uses (Herdy et al., 2016; ACSM, 2010). As patients with ChD, especially with the cardiac form, present some of the described changes, we have found some studies that evaluated its applicability to this type of patient (Table 2).

Table 2. Studies that used the Incremental Exercise Testing to evaluate patients with Chagas Disease.

Characteristics of the study	Findings	Reference
One hundred and forty-nine subjects were divided into 3 groups, including patients in the indeterminate form ChD, patients with complete RBBB but normal ventricular systolic function and a control group. The aim was to compare the heart rate recovery after Incremental Exercise Test between the groups.	Patients with RBBB had major prevalence of chronotropic incompetence, lower exercise capacity and lower heart rate recovery compared with patients in indeterminate form and controls ($p<0.001$). There were no differences between the other groups. These data are specific for patients with ChD.	Alencar et al., 2014
Seventy-five ChD patients with no cardiac involvement and thirty-eight healthy individuals were evaluated using echocardiography, Incremental Exercise Testing and autonomic function tests. The aim was to compare the occurrence of EIVA and the rates of autonomic maneuvers between the groups.	ChD patients had higher occurrence of EIVA ($p=0.010$) and more vagal dysfunction by respiratory sinus arrhythmia when subjected to Incremental Exercise Testing ($p<0.001$). These data are specific for patients with ChD.	Costa et al., 2015
Eighty-one ChD patients were subjected to clinical evaluation, echocardiography, Incremental Exercise Testing and 6MWT. The aim was to determine the VO_{2max} assessed by 6MWT through a regression equation and patients' clinical variables and to compare the values assessed by Incremental Exercise Testing with a regression equation with observed VO_{2max}.	The VO_{2max} assessed by Incremental Exercise Testing can be easily predicted by 6MWT and clinical data in patients with ChD. The equation obtained had a good performance to predict VO_{2max} without additional information ($p<0.001$).	Costa et al., 2017b
Respiratory function, muscle strength and endurance of ChD patients were compared with patients with HF for other etiologies as well as the relation with the functional capacity. Forty-five subjects were evaluated, including a control group. VO_{2max} was assessed by Incremental Exercise Testing and MEP and MIP using manovacuometer.	Patients with ChD presented correlation between smaller VO_{2max} and worse MEP and MIP as well as muscular endurance ($p<0.0001$), though no relation to left ventricular function. These data are specific for patients with ChD.	Baião et al., 2013

Sixty-five patients were evaluated by Incremental Exercise Testing. Standard and tissue Doppler echocardiography were performed to evaluate right ventricular peak annular diastolic and systolic velocities. The study aimed to estimate if tissue Doppler has potential to predict functional capacity in ChD patients based on right ventricular function.	Tissue Doppler imaging of right ventricular systolic annular velocity showed an important association with VO_{2max} assessed by Incremental Exercise Testing ($p<0.001$), regardless of parameters such as age, sex and echocardiographic characteristics. These data are specific for patients with ChD.	Nunes et al., 2010
Forty sedentary patients with ChD were assessed by Incremental Exercise Testing, 6MWT, SAS, HQoL and BNP levels. They were divided into two groups: exercise training group, which were subjected to 12 weeks of exercise, and inactive control group. The aim was to define the influence of exercise on functional capacity, HQoL and BNP levels in ChD patients.	VO_{2max} ($p=0.001$) and exercise time ($p<0.001$) were improved after exercise training in ChD patients. They were also improved in vitality, emotional and mental health aspects of HQoL. However, there was no difference in BNP levels.	Lima et al., 2010a
Thirty-seven sedentary patients with chagasic heart disease were organized into two groups: the intervention group, which were subjected to a 12-week exercise program, and a control group. This study aimed to measure heart rate changes due to physical activity using Incremental Exercise Testing.	VO_{2max}, Incremental Exercise Testing time ($p<0.001$) and functional class of Goldman ($p<0.008$) were improved after physical training, but no significant changes were found in heart rate variability in ChD patients.	Nascimento et al., 2014
Forty patients with dilated cardiomyopathy due to ChD were studied by two-dimensional Doppler and tissue Doppler imaging. Furthermore, exercise testing was fulfilled by a Bruce protocol and BNP levels were measured. The aim was to identify the association between left ventricular diastolic parameters and exercise capacity using Incremental Exercise Testing in ChD patients.	Functional capacity was related to increase on the left ventricular filling pressures, independently on systolic function in patients with ChD.	Lima et al., 2010b

Sixty-nine patients with chronic chagasic cardiomyopathy and ventricular arrhythmias were evaluated by treadmill exercise test. Peak heart rate and the presence of sustained ventricular tachycardia were limiting factors. The aim was to verify the prognostic value of EIVA in ChD patients.	Forty-four patients developed ventricular tachycardia during exercise testing, of which seven had sudden cardiac death after 24 months. None of the other 25 patients had neither arrhythmias or cardiac death, what indicates EIVA as an important cardiac death marker ($p<0.05$).	Paola et al., 1995

ChD: Chagas Disease; RBBB: right bundle-branch block; EIVA: exercise-induced ventricular arrhythmia; 6MWT: Six-minute Walk Test; VO2max: maximal oxygen consumption; HF: heart failure; MEP: maximal expiratory muscle pressure; MIP: maximal inspiratory muscle pressure; SAS: Goldman Specific Activity Scale; HRQoL: health-related quality-of-life; BNP: brain natriuretic peptide.

We noticed that all studies used the Bruce protocol, and the estimated VO_{2max} was important, it related to respiratory muscle strength, left and right ventricular functions, and it was valid in evaluating the effectiveness of exercise programs, thereby consolidating the Incremental Exercise Testing as a good tool for evaluating patients with ChD.

Incremental Shuttle Walk Test

The ISWT is a functional test limited by patients' effort, performed within a 10-meter space in which the patient has their walking rhythm dictated by the sound signals. It was originally developed for individuals with chronic obstructive pulmonary disease (COPD); however, it can also be applied for functional evaluation of other health conditions, including HF of several etiologies, as well as for ChD (Arena et al., 2007).

Only two studies using the Shuttle Test in patients with ChD were found: one of them aimed to perform a direct measurement of maximum VO_2 in patients submitted to the test, and later analyzed its equivalence with the results obtained on the Cardiopulmonary exercise testing. A similar hemodynamic response and a direct and positive relationship with the maximal VO_{2max} measured in both tests were observed, which validates the Shuttle test as an alternative method to evaluate the functional capacity of patients with chagasic cardiomyopathy. In addition, the study formulated an equation to indirectly measure the VO_{2max} measurement on the ISWT (Alves et al., 2016). The other study found correspondence between the distance covered in ISWT and VO_{2max}, distance walked in 6MWT, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores and physical capacity and domains of the SF-36 scores (Costa et al., 2014a).

Six-Minute Walk Test

The 6MWT is a submaximal exertion test that resembles the energy of patients' daily activities, enabling a quickly evaluation of physical condition. It is limited by time and carried out on a 30-meter path with maximum walking pace - the patient walks for 6 minutes and a standardized incentive phrase is given each minute. The test was initially developed and used on patients with COPD.

Its effectiveness is currently well-established, particularly in patients with heart failure, showing a moderate to high relation with VO_2 peak assessed by CPET, and it has been applied to estimate mortality risk in patients with symptoms of heart failure of various etiologies (Cahalin et al., 1996; Houchen-Wolloff et al., 2015; ATS, 2002). Some studies have compared their findings with other tests considered as more specific (Table 3). The importance of the test is noteworthy, since it had important correlations with quality of life, mortality, and with CPET, in addition to being valid for evaluating the effectiveness of exercise programs in patients with ChD.

Table 3. Studies that used the Six-minute walk test to evaluate patients with Chagas Disease.

Characteristics of the study	Findings	Reference
Thirty-eight ChD patients with left ventricular dilatation were evaluated. 6MWT, monocyte chemoattractant protein-1 and natriuretic peptide type B were measured in order to find the correlation between submaximal functional capacity and the hemodynamic, humoral and inflammatory markers.	Submaximal functional capacity is associated to heart disease severity, as showed by hemodynamic, immunological and inflammatory markers (p=0.04). 6MWT may be a helpful tool to assess clinical status of patients with ChD.	Sousa et al., 2008
Nineteen patients completed the study. At baseline and after 12 weeks, all patients were subjected to 6MWT, analyses of serum BDNF concentrations and 24-hour Holter monitoring. The aim was to investigate aerobic exercise training effects on BDNF levels and the association of those variables with cardiac autonomic modulation in patients with ChD.	Improvement of the 6MWT exhibited a positive correlation with the changes in BDNF (p=0.002). At baseline, the correlation between the 6MWT was negative with BDNF and positive with chronotropic response and heart rate variability indexes in patients with ChD.	Lima et al., 2013

Thirty-five patients with ChD were evaluated. The functional class was assessed by CPET, ISWT and 6MWT and HRQoL by the MLWHFQ and SF-36. The aim was to compare the distance walked in the ISWT and 6MWT, and VO_{2max} by CPET and HRQoL.	The distance walked by 6MWT was significantly correlated with distance walked by ISWT ($p<0.001$) and with the values of VO_{2max} assessed by CPET ($p=0.003$), in patients with ChD.	Costa et al., 2014a
Eighty-one ChD patients were subjected to clinical evaluation, echocardiography, Incremental Exercise Testing and 6MWT. The aim was to determine the VO_{2max} assessed by 6MWT through a regression equation and patients' clinical variables and to compare the values assessed by Incremental Exercise Testing with a regression equation with observed VO_{2max}.	The VO_{2max} assessed by Incremental Exercise Testing can be easily predicted by 6MWT and clinical data in patients with ChD ($p<0.001$). The equation obtained had a good performance to predict VO_{2max} without additional information.	Costa et al., 2017b
The HFSS was calculated in fifty-five ChD patients with severe left ventricular systolic dysfunction. The correlations were evaluated between the HFSS and the variables derived from echocardiography, CPET, measures of quality of life and tests of distance traveled in 6MWT.	There was correlation between the HFSS index, VO_{2max}, VE/VCO_2 slope, VO_2-AT and efficiency of oxygen uptake in patients with HF due to ChD ($p<0.01$). Patients with smaller values of HFSS had significantly lower score of $VO_{2max.}$	Ritt et al., 2012
Ninety-eight patients were recruited, sixty of them had ChD and thirty-eight had ChD and SAH. Functional capacity was evaluated by 6MWT. The aim was to compare physical capacity of patients with chagasic chronic heart failure associated with SAH.	Coexistence with SAH does not seem to interfere on functional capacity of patients with ChD and chronic heart disease ($p>0.05$). No correlation was also observed between the score of the MLWHFQ and the 6MWT in patients with ChD and with SAH. These data are specific for patients with ChD.	Dourado et al., 2010
Forty-nine ChD patients were divided into two groups: patients with normal heart dimensions and function and patients with dilated left ventricle and systolic dysfunction. They were subjected to CPET and 6MWT in order to evaluate the association between the 6MWT distance and CPET, and also to identify a minimum distance from the 6MWT capable of indicating functional impairment.	The 6MWT seems to be an efficient test to assess functional capacity in patients with ChD and also identify functional commitment, what is useful to help patients' management ($p<0.001$).	Costa et al., 2014c

Thirty-two patients were organized into groups with and without heart dysfunction. It was measured by the MLWHFQ, maximal inspiratory and expiratory pressures, distance walked and rating of perceived exertion over the 6MWT, vitals, oxygen saturation and ejection fraction. The aim was to evaluate respiratory muscle strength and its relationship to functional capacity, quality of life and rate of perceived exertion in patients with Chagas cardiomyopathy.	No significant difference was observed in distance walked between the two groups, but it was observed that a smaller distance in the 6MWT associated to worse quality of life measured by the MLWHFQ ($p<0.001$). These data are specific for patients with ChD.	Vieira et al., 2014
Forty sedentary ChD patients were divided into two groups (inactive control group and exercise training group) and evaluated by Incremental Exercise Testing, 6MWT, HQoL, Goldman Specific Activity Scale and serum BNP levels. The exercise training group patients followed a 12-weeks exercising program and the aim was to measure the influence of physical activity on functional capacity, HQoL and BNP levels of patients.	There was a substantial improvement in the distance covered in the 6MWT after the training program in patients with ChD ($p=0.001$).	Lima et al., 2010a
One hundred and seven ChD patients were organized into three groups based on the presence or absence of pulmonary hypertension. Patients were subjected to clinical evaluation, 6MWT, respiratory tests, the Hospital Anxiety and Depression Scale and SF-36 questionnaire.	Patients with the indeterminate form of ChD associated with pulmonary hypertension completed significantly smaller distances than the control group ($p<0.005$). It demonstrates smaller exercise tolerance when the two conditions affect the patient. These data are specific for patients with ChD.	Suman et al., 2017
Forty patients with ChD and heart failure were included. NYHA functional class, echocardiogram, BNP serum levels, 6MWT, MLWHFQ and SF-36 questionnaires were performed. The aim was to measure the association between the distance covered in the 6MWT and heart function and quality of life in these patients.	The distance covered during the 6MWT was related with BNP levels ($p=0.02$), quality of life ($p=0.002$) and left ventricular diastolic function ($p=0.03$).	Chambela et al., 2017

Thirty-five patients with Chagas cardiomyopathy were evaluated by echocardiogram, CPET, 6MWT, Mini-Mental State Examination, among other tests. The aim was to identify the presence of depression symptoms and their clinical and functional determinants.	Several variables were related to depressive symptoms, such as gender, NYHA functional class, body mass index, SF-36 mental summary, peak oxygen consumption and distance walked in the 6MWT ($p<0.1$).	Silva et al., 2020

ChD: Chagas Disease; 6MWT: Six-minute Walk Test; BDNF: Brain-derived neurotrophic factor; HRQoL: health-related quality-of-life; CPET: Cardiopulmonary Exercise Test; ISWT: Incremental Shuttle Walk Test; SF-36: generic short-form health survey; SAH: Systemic Arterial Hypertension; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; VO_{2max}: maximal oxygen consumption; HFSS: Heart Failure Survival Score; BNP: brain natriuretic peptide.

Pulmonary function test

The pulmonary function test seeks to measure pulmonary volumes and flows through a forced expiratory test. Using this test data, it is possible to determine a functional diagnosis of the lung, in which the main data are Forced Vital Capacity (FVC), Forced Expiratory Volume in the First Second (FEV_1), Tiffenneau index and the Peak Expiratory Flow (PEF). The patient may present restrictive, obstructive or mixed respiratory disorders and they might be mild, moderate and severe (Pollentier et al., 2010).

Patients with ChD have dyspnea and physical limitations as symptomatology, which has increased the use of pulmonary function test in these patients. The studies found in the literature reported no significant difference in pulmonary flows and volumes when patients with cardiac form were compared to healthy individuals, or when undetermined Chagas patients were compared to their pairs with pulmonary hypertension. However, patients with chagasic cardiomyopathy had lower FVC values than those affected by other etiologies (Baião et al., 2013; Oca et al., 2004; Alves et al., 2016; Pollentier et al., 2010).

Despite being commonly used in pulmonary and cardiac pathologies with other etiologies, studies that focus on evaluating patients with ChD using the Pulmonary Function Test are scarce. Thus, new studies using other methodologies and larger samples are necessary to demonstrate the importance of this test as part of the functional evaluation of those patients.

Manovacuometry

Manovacuometry is a valid evaluation instrument used to measure the strength of respiratory muscles (Vargas et al., 1987; Duarte et al., 2007). This measurement is performed indirectly through MIP, it mainly involves the action of the external diaphragm and intercostal muscles, and MEP, which involves the use of the internal abdominal and intercostal muscles (Cook et al., 1964).

Muscle strength evaluation has already been used in patients with heart failure, where it was found that this parameter is related to other variables such as the correlation with VO_{2max} (Costa et al., 2017a; Black & Hyatt, 1969). Studies performed in patients with Chagas disease observed a decrease in respiratory muscle strength in relation to healthy individuals and cardiac patients due to other etiologies. An independent association between physical activity level by electrocardiographic findings, VE/VCO_2 slope and VO_{2max} measured indirectly with respiratory muscle weakness has also been reported. On the other hand (but undetermined), patients with ChD did not present an important difference in respiratory muscle strength when compared to their pairs who presented associated pulmonary hypertension (Costa et al., 2017a; Baião et al., 2013; Vieira et al., 2014; Alves et al., 2016).

Muscle strength measured by manovacuometry was a good predictor of functional capacity, being important in their functional diagnosis and prognosis. Nevertheless, more studies with larger samples are needed to reach more conclusive results.

CONCLUSIONS

The articles presented various methodologies in relation to the number of participants, gender, clinical form and severity of ChD, as well as the use of respiratory and functional tests, in which they noticed that in the evaluation as in the correlation of values with physiological variables and markers of clinical outcomes. Similar to heart diseases from other etiologies, respiratory and functional tests are useful markers for predicting quality of life, functional impairment and mortality, as well as other characteristics of patients with ChD such as echocardiographic data, blood markers and hemodynamic data.

Validity between the scores obtained by these tests has also been observed, thereby facilitating functional evaluation of patients with a simple or more complex instruments, contemplating the diverse sociodemographic contexts. Finally, we can conclude that a precise evaluation of functional capacity constitutes an important prognostic and an evaluative instrument in patients with ChD, since it directs more effectively therapeutics and prescription of exercises for these patients.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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