Spirometric values associated with clinical form and risk of death and stroke in chagasic patients

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Abstract. The aim of the present study was to compare pulmonary function among patients with different clinical forms and scores for risk of death and stroke. Patients were recruited from the Chagas Disease Ambulatory Service at the University of Rio Grande do Norte State (Mossoró, Brazil). The evaluation of pulmonary function was performed through spirometry techniques using a digital spirometer, and information about the clinical forms (cardiac, cardiodigestive, digestive and undetermined) and scores for risk of death (Rassi's risk-of-death score) and stroke was subsequently collected. Upon completion of the evaluation, comparisons of the values obtained between the groups for different clinical forms, risk stratification of stroke and Rassi's risk-of-death were made. The study cohort consisted of 72 patients. Individuals with a low risk of death had significantly higher values in the Tiffeneau index and individuals with a low risk of stroke presented with higher percentage values for forced vital capacity and forced expiratory volume in 1 sec. In addition, individuals with heart disease had worse percentage values for FVC and FEV_1. In conclusion, the results showed that spirometry was an effective analytical technique and was associated with clinical forms, and death and stroke risk scores, in patients with Chagas disease, adding an important prognostic tool to those currently available.

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Introduction

Chagas disease is due to infection with the protozoan *Trypanosoma cruzi*. It is estimated that 6 to 7 million people are infected by the protozoan worldwide, with a predominance in Latin America, mainly in Argentina, Brazil and Mexico (1-3).

Chronic chagasic cardiomyopathy is the most common clinical complication in patients with Chagas disease; it is characterized by severe myocarditis, infiltration of the lymphomononuclear cells, interstitial fibrosis and cardiomyocyte hypertrophy, which may lead to dilated cardiomyopathy, end-stage heart failure (HF) and death (4).

Congestive heart failure, a characteristic of chagasic patients, is also associated with significant impairment of cardiac function and decreased inspiratory muscle strength (5,6), in addition to a restriction in pulmonary expandability, airway obstruction, increased dead space and respiratory rate, gas diffusion abnormalities and expiratory muscle weakness (7,8).

The interstitial congestion present in HF prevents alveolar distension, which contributes to the inefficiency of respiratory muscle function, a reduction in oxygen supply and pulmonary complacency. This set of changes results in a restrictive respiratory pattern that contributes to respiratory muscle overload and an uncontrolled breathing regulation mechanism (8).

Among the symptoms presented by affected patients, the sensation of exertion fatigue and dyspnea are notable, both of which restrict the activities of daily living (ADLs). The intensity of the dyspnea is disproportionate to the physical activity performed, which directly affects the quality of life and prognosis of the affected patient, thus having an important impact on the functional capacity of the individual (3,9).

In view of the aforementioned respiratory complications, the measurement of respiratory flows and volumes through spirometry becomes an important additional tool for a comprehensive evaluation of chagasic patients. The decrease in these parameters has an impact on the physical restriction, in addition to being associated with clinical outcomes of the

chagasic patient, such as the risk of cardiovascular events in a short period and the risk of death (10).

As the characteristics of the disease can lead to dysfunction and restriction of lung volumes, spirometric values become essential to assess the dysfunction present in patients with Chagas disease. Functional complications are already known to be associated with spirometric values in patients with Chagas disease. In the present study, the associations between pulmonary functional capacity values are expanded, and to the best of our knowledge, this is the first study to evaluate and compare the pulmonary flows and volumes of patients with Chagas disease according to their clinical characteristics, verifying the differences between the different risk groups of death and stroke, as well as different clinical forms of the disease.

Materials and methods

Study population. This study was a descriptive, cross-sectional study that included 72 individuals with Chagas disease, confirmed by a positive result in enzyme-linked immunoassays, indirect immunofluorescence assays and indirect hemagglutination assays. These individuals were treated clinically at the Chagas Disease Ambulatory Service of the Health Sciences College of the University of Rio Grande do Norte State (FACS-UERN; Mossoró, Brazil).

Inclusion and exclusion criteria. Patients with good cognition and understanding, those who were >18 years of age and those who agreed to participate in the survey were included in the study. Those patients who dropped out of the test protocol when already in progress, those who, due to physical limitation, were unable to complete one of the functional tests and those who had previously used bronchodilators were excluded.

Ethical considerations. The patients were initially informed about the objectives of the study and the methods to be applied, and were later questioned about their willingness to participate. After agreeing to participate, the patients were asked to sign an informed consent form. The research followed the criteria of the Declaration of Helsinki (1997) and respected the ethical principles of Resolution 466/2012 of the National Health Council in Brazil, which supports research involving human beings. The ethical aspects of the study were approved by the Research Ethics Committee of the University of Rio Grande do Norte State (approval nos. 1.510.620 and CAAE 53362316.8.0000.5294).

Data collection. An initial evaluation was performed at the FACS-UERN Chagas Disease Ambulatory Service, where the medical history and sociodemographic data of the patients were collected and a life habits assessment was performed through an evaluation form prepared for the study. Echocardiography, chest X-ray, contrast-enhanced radiography of the colon and esophagus, and subsequent classification of the clinical forms of Chagas disease were performed. Risk stratification of stroke and Rassi's risk-of-death were also analyzed, according to the criteria described in the literature (9,11). Finally, spirometry was performed. The sequence of actions performed from enrollment to statistical analysis is described in Fig. 1.

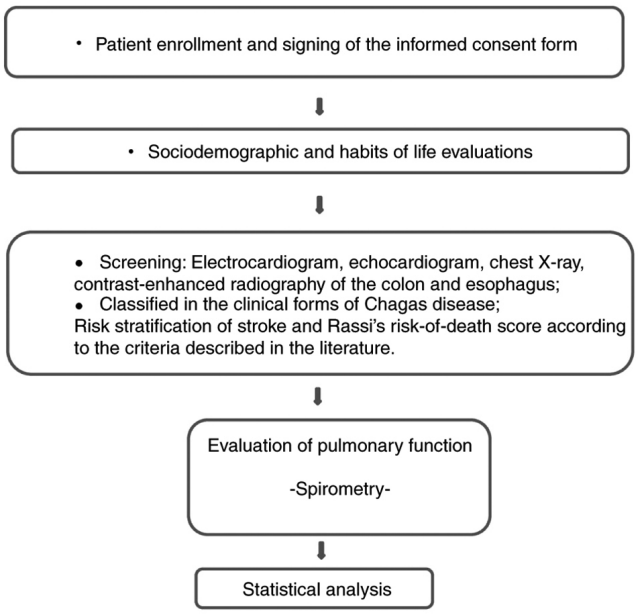

Figure 1. Study design flowchart.

The pulmonary function evaluation was performed by spirometry, using a USB digital spirometer from the CareFusion® brand (Becton, Dickinson and Company), to characterize the degree of obstructive pulmonary disorder as an evaluation parameter.

The entire procedure was performed as described by Pereira *et al* (12,13) and Miller *et al* (14). For spirometry, the volunteer was sitting, with the head kept in a neutral position and hips flexed at 90˚, with a minimum of 5-10 min of rest before the exam. Three to eight maneuvers were performed, so that in the end, three blows were obtained that passed the criteria, with at least 6 sec of exhalation, and the last blow could not be the best. The patients received visual and auditory feedback, and all the disposable nozzles were changed and used individually for each patient.

The values that were obtained from the patients were compared to predicted values adequate for the population evaluated, and the percentages were adjusted for sex, height, weight and age (14). Obstructive or restrictive diseases were identified, evaluating the following variables: Forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR) and FEV_1/FVC (Tiffeneau index) (12).

Statistical analysis. All data were tabulated and organized into worksheets using Microsoft Excel (version 16.0.9226.2156; Microsoft Corporation) and IBM SPSS Statistics (version 20; IBM Corp.) software. The normality of the data obtained was verified using the Kolmogorov-Smirnoff and Shapiro-Wilk tests.

The comparison of the test values obtained between the groups of patients stratified according to their clinical form and risk of death and stroke was performed using the t-test for independent samples when there was a normal distribution, and the Mann-Whitney when there was a non-normal distribution. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Comparison of the spirometric values in patients with a low and intermediate/high risk of death.

	Rassi's risk of death score		
Parameter	Low risk-group (n=24)	Intermediate/high-group (n=18)	P-value
Spirometry			
FVC	3.04±0.84	3.47±1.05	0.148[a]
FVC percentage	85.70±12.48	87.33±12.48	0.733[a]
FEV_1	2.63±0.69	2.84±0.89	0.390[a]
FEV_1 percentage	90.75±11.55	87.83±18.65	0.536[a]
Tiffeneau index	88.79±7.44	82.27±7.41	0.008[a,b]

Data are presented as the mean ± standard deviation. [a]P-value calculated by Student's t-test. [b]P<0.05.

Table II. Comparison of the spirometric values in patients with a low and intermediate/high risk of stroke.

	Stroke risk score		
Parameter	Low-risk group ((n=50)	Intermediate/high-risk group (n=12)	P-value
Spirometry			
FVC	3.38±0.95	3.19±0.82	0.533[a]
FVC percentage	91.64±13.43	81.16±17.56	0.026[a,b]
FEV_1	2.87±0.78	2.65±0.66	0.372[a]
FEV_1 percentage	94.98±12.12	82.66±18.78	0.007[a,b]
Tiffeneau index	86.26±7.77	83.66±9.10	0.320[a]

Data are presented as the mean ± standard deviation. [a]P-value calculated by Student's t-test. [b]P<0.05.

Results

The percentages recorded are values obtained relative to predicted values for the population evaluated, adjusted for sex, height, weight and age (14). It was not specifically observed whether there were respiratory disorders, i.e. values below the limits of normality, but rather if the worsening of the respiratory flow and volume values accompanied the risks of clinical aggravation and complications in the chagasic patients.

Blood was initially collected from 82 patients who went to the FACS-UERN Chagas Disease Ambulatory Service to undergo laboratory and clinical examinations and periodic medical consultations. After applying the inclusion and exclusion criteria, 10 subjects were eliminated from the study and 72 patients (33 women and 39 men) remained; however, not all patients had a full set of clinical characteristics available, so when divided into the groups, there were 42 patients in the death risk group, 62 in the stroke risk group and 67 patients classified into different clinical forms. All patients were from the West Potiguar mesoregion of Rio Grande do Norte in Brazil, mainly from the city of Mossoró (25 patients). The majority (55.6%) of the patients lived in the urban area of these municipalities. The patient ages ranged from 26 to 69 years, with a mean [± standard deviation (SD)] of 48.3±10.9 years. The mean (± SD) weight was 70.1±13.7 kg, the mean (± SD) height was 1.60±0.09 m and the mean (± SD) BMI was 27.0±4.4.

It was observed that 4.2% of patients were reported with diabetes, 33.3% with hypertension, 5.6% with dyslipidemia and 34.3% with musculoskeletal disorders. It was also observed that 56.9% of the cohort used some form of medication, mainly antihypertensive drugs (30.6% of the total patients). With regard to lifestyle, only 18 (25%) patients performed regular physical activities and 21 (29.2%) were smokers or former smokers (data not shown).

The distribution of patients according to Rassi's risk-of-death score (11) revealed that 24 patients (33.3%) were at a low risk of death, 11 (15.3%) were at intermediate risk and 7 (9.7%) were at high risk. A total of 11 patients (15.3%) had not yet been classified and 19 (25.4%) did not meet the criteria for determining the risk of death. For comparison purposes, the patients were divided into two groups according to the scores, namely the group with a low risk of death and the group with an intermediate/high risk of death, as shown in Table I.

Regarding stroke risk scores (9), 49 patients (68.1%) had a low risk of developing a stroke, 6 (8.3%) had a moderate risk, 7 (9.7%) had a high risk and 10 (13.9%) had not yet been classified. For comparison purposes, the patients were divided into two groups, according to the scores, namely the group with a low risk of stroke and the group with an intermediate/high risk of stroke, as shown in Table II.

In the clinical forms classification, 30 patients (41.7%) had an undetermined clinical form, while 18 (25.0%) had a cardiac form, 8 (11.1%) had a digestive form and 11 (15.3%)

Table III. Comparison of the spirometric values in patients with the cardiac form and the non-cardiac form.

Parameter	Clinical forms		P-value
	Cardiac group (n=29)	Non-cardiac group (n=38)	
Spirometry			
FVC	3.25±0.87	3.47±0.98	0.594[a]
FVC percentage	82.89±13.83	94.16±14.79	0.005[a,b]
FEV_1	2.75±0.73	2.92±0.80	0.380[a]
FEV_1 percentage	86.26±15.76	96.27±13.01	0.001[a,b]
Tiffeneau index	86.0 (27)	87.0 (41)	0.217[c]

Values are presented as the median (IQR; Q3-Q1) or presented as the mean ± standard deviation. [a]P-value calculated by Student's t-test. [b]P<0.05. [c]P-value calculated by the Mann-Whitney U test.

had a cardiodigestive form. In addition, 5 (6.9%) still needed to undergo complementary tests to determine their clinical form. For comparison purposes, the patients were divided into two groups, namely the cardiac group, with cardiac or cardiodigestive clinical forms, and the non-cardiac group, with undetermined and digestive clinical forms, as shown in Table III.

The comparison of the respiratory and functional parameters of the patients, taking into account the risk of death scores, showed that the group with low risk (scores 0 to 2) had significantly higher values for the Tiffeneau index (Table I). The evaluation of cardiorespiratory capacity according to the risk of stroke, on the other hand, showed that patients with low risk had significantly higher percentage values for FVC and FEV_1 (Table II).

When comparing the respiratory and functional parameters among the patients with the undetermined or digestive clinical form (non-cardiac group) and those with the cardiac or cardiodigestive forms (cardiac group), the percentage values of FVC and FEV_1 were significantly higher in the non-cardiac group (Table III).

Discussion

In the present study, the Tiffeneau index was significantly different between the groups with a high and a low risk of death in the chagasic patients. The index represents the association between FEV_1 and FVC (FEV_1/FVC), and has normal values between 0.70 and 0.80 (15), or 0.70, so that lower values suggest a limitation of air flow. The present results suggest that patients at a high risk of death presented with more obstructive characteristics than those at a low risk. Although there have been no previous studies with chagasic patients, this association has been reported in patients with heart failure, among whom those with restrictive or obstructive ventilation had a higher mortality rate and the lower limit of the Tiffeneau Index was an independent variable for this outcome (16).

Physical activities and ADLs increase ventilatory demand, and airway obstruction in these efforts generates dynamic pulmonary hyperinflation. This imprisonment generates increasing difficulty for the aforementioned activities by the impairment of function and pulmonary mobility. Thus, a patient with poor pulmonary function tends to decrease the amount of activity undertaken, compromising their independence and functionality, and this set of factors is known to be associated with higher mortality (17,18).

In the present study, when the groups were divided according to the stroke risk score (9), the patients who had a lower risk had significantly higher mean percentage values for FVC and FEV_1. Despite the existence of other factors, such as hypercoagulability, in the majority of cases, stroke in the chagasic patient is associated with cardioembolism (9). In a cardioembolism, emboli are formed in the cardiac cavities that leave the heart through the left ventricle through the aortic artery and reach the cerebral irrigation arteries, obstructing the blood flow and causing consequent ischemia and neuronal tissue hypoxia (19). The cause of the formation of these emboli is mainly dysfunction of cardiac contractility, function and rhythm, in which inefficient pumping leads to stasis and blood coagulation, with subsequent embolization of the heart to the brain (20). Thus, it has been observed that the simple presence of systolic dysfunction in chagasic heart disease, regardless of the degree of myocardial involvement, is associated with the high incidence of ischemic stroke (9).

Georgiopoulou *et al* (21) found a correlation between the FVC and FEV_1 percentages and the risk of developing HF in the elderly, concluding that abnormal findings in the spirometry were associated with an increased risk of this dysfunction. Barr *et al* (22) found that the percentage values for emphysema and the FEV_1/FVC ratio were associated with left ventricular filling, which reinforces the correlation between lung volumes and flows and cardiac function. Considering that the stroke has a direct causal relationship with HF in the chagasic patient, reduced percentages of FVC and FEV_1 have a positive association with the risk of developing this clinical complication, as shown in the present study. This relationship can be explained by the high oxidative stress characteristic of impaired gas exchange in abnormal pulmonary function, which directly affects myocardial function (23), and by changes in respiratory mechanics and intrathoracic pressure, which may reduce cardiac output by interference with the preload, as there is a mechanical relationship between the respiratory and cardiovascular systems, since the two are closely accommodated in the thoracic region (24).

A significant difference was also observed in the mean percentages of FVC and FEV_1 among cardiac and non-cardiac patients. The same results cited previously in the studies by Georgiopoulou *et al* (21) and Barr *et al* (22) explain this difference, since these studies correlated the abnormal values in spirometry with cardiac dysfunction.

A previous review has shown significant differences in functional capacity (maximum oxygen consumption values) among cardiac and non-cardiac chagasic patients (24), but no studies have shown specific differences in pulmonary function in these patients. By contrast, Baião *et al* (25) found that cardiac chagasic patients have lower FVC values than cardiopaths of other etiologies. However, other studies have found no significant differences in pulmonary flow and volumes when cardiac chagasic patients were compared with healthy individuals, as well as in the comparison of those indeterminate patients, who are asymptomatic, and their pairs with pulmonary hypertension (26,27).

In addition to the chronic oxidative stress caused by the pulmonary volume deficit previously mentioned (23), restrictive physiological findings have been reported in patients with heart disease and are mainly attributed to subclinical interstitial and alveolar pulmonary edema, in addition to cardiomegaly, increased central blood volume and fibrotic stiffening of the lung parenchyma. All this leads to a reduction in pulmonary complacency and an increased difficulty to breathe in these patients, which explains the significant difference found in the present study (28,29). However, despite the differences between the groups, the mean values of the cardiac patients were within the limits of normality, >80% of that expected, so preventative maintenance of values using physical exercises is recommended to avoid a decline in these values. In addition to the interference of cardiac dysfunction in the functioning of the respiratory system, there is also the hypothesis of an inverse interaction in which the inefficient respiratory system can interfere chronically in the cardiovascular system. These dysfunctions may be added continuously and cause deterioration of physical and functional cardiopulmonary system capacity (30,31). The dysfunction of one of these systems requires early follow-up so that the injury does not develop in the other.

The decrease in pulmonary volumes and capacities accompanied a higher risk of death and stroke related to the cardiac form of Chagas disease in the present study, which confirms previous discussions in the literature that associate the higher risk of clinical worsening with worse respiratory function (32).

Spirometry proved to be a good analytical tool in the present study and showed a good association with clinical forms and risk of death and stroke scores in patients with Chagas disease. Therefore, it is suggested that the spirometric parameters of Tiffeneau index, FVC value and FEV_1 value may give indications that the patient is suffering from a clinical worsening of their condition.

To the best of our knowledge, this is the first study to find significant differences in the stratifications cited in chagasic patients, as some of these associations were only studied in other categories of patients.

Chagas disease is a pathology that can have a heterogeneous course. The condition is widely studied and the different clinical forms and prognostic instruments for the risk of stroke and death are already known. Thus, data that correlate with these disease progression variables are important to guide therapeutic approaches and predict injuries. The present study concluded that spirometry is a relatively simple yet important clinical tool that correlates with the risk of death and stroke, and the development of the most severe form of the disease. In view of the data, these patients should also be challenged to avoid a sedentary lifestyle and be physically active, as these are attitudes that directly influence lung function assessed by spirometry.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NMM and TAAMF were responsible for the conception and design of the study. NMM, VDA and LCCML collected the data, and NMM, MFA, CMA, CMB, EGCN, JVF and TAAMF performed the data analysis and interpretation. MFA and VDA contributed to the statistical analysis. NMM was primarily responsible for writing the manuscript, with contributions from LCCML, TAAMF, CMA, CMB, EGCN and JVF. CMA, CMB, EGCN and JVF also made a critical review and approved the final version for publication. NMM and TAAMF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The research followed the criteria of the Declaration of Helsinki (1997) and respected the ethical principles of Resolution 466/2012 of the National Health Council from Brazil. The ethical aspects were approved by the Research Ethics Committee of the University of Rio Grande do Norte State (grant nos. 1.510.620 and CAAE 53362316.8.0000.5294). Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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