

Novel Physiotherapies in the Setting of Chagas Heart Disease: A Summarized Review of Functional Evaluation

Henrique Silveira Costa^{1*}, Marcia Maria Oliveira Lima², Pedro Henrique Scheidt Figueiredo² and Manoel Otavio da Costa Rocha¹

¹Postgraduate Course of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Medical School and Hospital das Clínicas of the Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil

²Physical Therapy School, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina, Brazil

*Corresponding author: Henrique Silveira Costa, PhD, Rua Timbiras, 2505/903, Santo Agostinho, 30.140-063, Belo Horizonte, Minas Gerais, Brazil, Tel +55 31 32754205; E-mail: henriquesilveira@yahoo.com.br

Received date: January 16, 2018; Accepted date: January 29, 2018; Published date: February 2, 2018

Copyright: © 2018 Costa HS, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Introduction: Chagas disease remains a public health problem in Latin America and currently in non-endemic countries. The cardiac form is the most severe and exercise training has been shown to be effective in the treatment of these patients. However, a review of the clinical findings of pre-training assessment is necessary to guide the exercise prescription. Objective: to describe the cycle of the disease and the physiotherapeutic evaluation and of patients with Chagas disease, focusing on the patient with cardiopathy.

Methods: a literature search in MEDLINE/Pubmed, Scientific Electronic Library Online, Cumulative Index of Nursing and Allied Health Literature, Latin American and Caribbean Health Sciences Literature and Web of Science databases performed between November 2017 and January 2018.

Results: In the anamnesis, drug therapy and functional class of the New York Heart Association should be investigated. In the maximum exercise testing, the presence of ventricular arrhythmias, the peak of oxygen uptake and the slope of increase of ventilation relative to carbon dioxide production may assist in the functional evaluation, risk stratification and prognosis establishment. Field tests, such as the Six-Minute Walk Test and Incremental Shuttle Walk Test, are inexpensive and effective in functional assessment. Respiratory evaluation has received special attention in recent years by the prevalence of inspiratory muscle weakness. Finally, quality of life is a crucial point in the evaluation of the chagasic patient, mainly due to the stigmatizing nature of the disease.

Conclusion: The peculiarities of Chagas heart disease should be taken into account in the functional evaluation of the patient and plays a key role in the exercise prescription before physical training.

Keywords: Chagas disease; Chagas heart disease; Functional capacity; Functional evaluation

Introduction

Chagas disease, more than a century after its discovery [1], remains a serious public health problem in Latin America [2]. The disease affects approximately 6 million to 7 million people worldwide [3], with great impact on the health and quality of life of the infected people. Surprisingly, about 80% of the patients did not have access to diagnosis or appropriate treatment [4], emphasizing the neglected aspect of the disease. The chronic cardiac form is the most important manifestation of the disease because is the most frequent (30 to 40% of the cases) and severe clinical form, causing heart failure, arrhythmias, heart block, thromboembolism, stroke and sudden death [5].

In addition, the disease emerges in non-endemic regions, mainly in the countries of North America [6] and Europe [7,8], where knowledge of the condition and experience with its clinical management are limited [9]. The dramatic increase in the prevalence of the disease in non-endemic countries may be the result of globalization and immigration [10]. In the USA, a review reported that the prevalence of Chagas disease is from 300,000 to over 1 million cases [6]. Moreover,

an estimated 94 to 96% of migrants living with Chagas disease in non-endemic areas are unaware of their disease [7].

Recently, the clinical trial BENEFIT [11] demonstrated that parasitocidal treatment does not aid in the regression of cardiac damage. However, many studies have reported that exercise training is effective in improving functional capacity [12-14], cardiac function [14], and quality of life [12] of infected patients. For these patients, physiotherapy based on exercise prescription emerges as a potentially useful method to reduce morbidity and mortality. For effective exercise training, a detailed functional assessment of the patient is required. However, the information found in the literature regarding the functional evaluation of the patients with Chagas disease, especially in the cardiac form, has not yet been reviewed. So, the present study was addressed to describe the cycle of the disease and the physiotherapeutic evaluation and of patients with Chagas disease, focusing on the patient with cardiopathy.

Methods

This review is a summary of the evidence on the physiotherapy in Chagas disease patients. It was conducted the literature search in MEDLINE/Pubmed, Scientific Electronic Library Online (SciELO), Cumulative Index of Nursing and Allied Health Literature (CINAHL),

Latin American and Caribbean Health Sciences Literature (LILACS) and Web of Science databases.

The keywords used in the search strategy included Chagas, Chagas disease, Chagas heart disease, Chagas cardiomyopathy, physiotherapy, exercise, exercise testing, functional capacity and health-related quality of life. The literature search was performed between November 2017 and January 2018.

The Clinical Course of Chagas Disease

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* through blood transfusion or transplantation, contaminated

food, maternal transmission, laboratory accidents and, mainly, from the infected feces of blood sucking insects through the skin at bite sites or the mucosa [4,5,15,16].

Chagas disease presents two phases: acute and chronic. The clinical progression of Chagas disease is shown in Figure 1.

The acute phase, presented immediately after the initial contact with the protozoan, is characterized by few specific signs and symptoms, which include fever, malaise and disproportionate tachycardia [16]. The acute phase lasts approximately 4 to 8 weeks [16]. Being a period of intense infectious activity, exercise is not indicated at this stage.

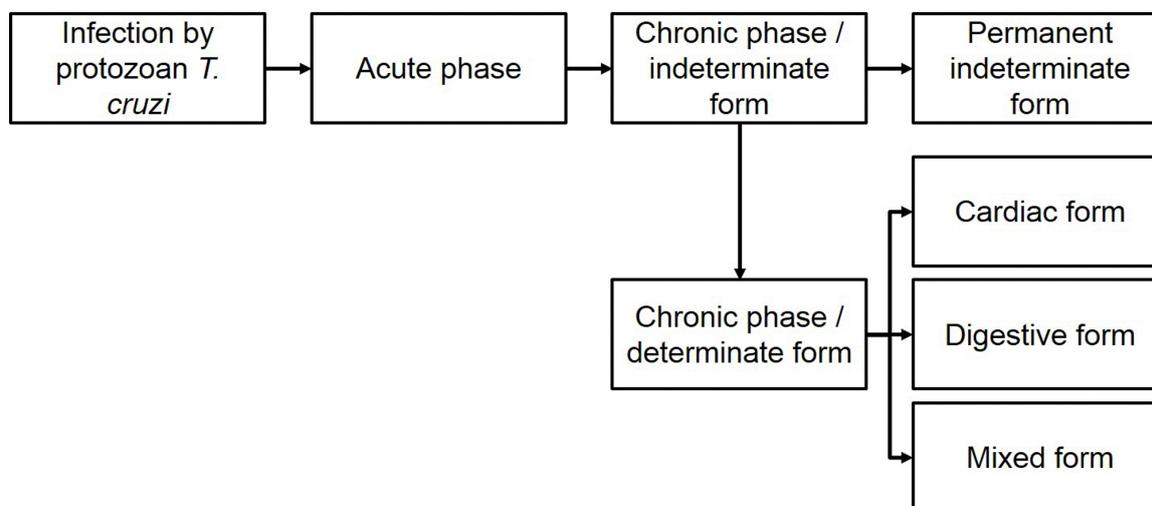


Figure 1: Clinical progression of chagas disease.

The chronic phase, subsequent to the acute phase, is characterized by indeterminate, digestive, cardiac and mixed clinical forms. In the indeterminate phase, the patient is asymptomatic and presents mild electrocardiographic and echocardiographic changes [5,16]. Despite this, a previous study [17] has shown that ventricular arrhythmias during exercise are more prevalent than in the healthy population. However, patients in this stage have good exercise tolerance [18,19] and the survival is comparable to that of healthy individuals [20]. The patient may remain indefinitely at this stage or evolve, 10 to 20 years later, into the digestive, cardiac or mixed forms [5].

In the digestive form, the main clinical finding is the presence of megaesophagus and megacolon [5,15]. Finally, the cardiac form has a heterogeneous clinical presentation. ECG abnormalities (arrhythmias and conduction disorders) are present in the early stages and evolves to left ventricular dysfunction with signs and symptoms of heart failure [16], especially fatigue and dyspnea. In addition, heart failure secondary to Chagas disease has peculiarities compared to other etiologies [5], being the most fibrosing of the known heart diseases, with significant arrhythmogenic substrate and worse prognosis compared to other cardiomyopathies.

Several studies [21-28] have demonstrated relevant results in the physiotherapeutic evaluation of patients in the cardiac form, the most severe of all clinical forms. As a result, the functional assessment of patients with Chagas heart disease will be the focus of the present study.

The Physiotherapeutic Evaluation of Patients with Chagas Heart Disease

In the first evaluation of the patient with Chagas heart disease, 3 factors should be taken into consideration before exercise training [29]. Firstly, Chagas disease patients have significant arrhythmogenic substrate, even in the early stages of the disease [17]. Complementary exams, such as ECG at rest, 24h-Holter monitoring, or electrocardiography during exercise testing, should be carefully analyzed. In addition, Chagas heart disease patients generally evolve with autonomic dysfunction and chronotropic incompetence, which must be verified before exercise prescription. Finally, the disease can progress with thromboembolic events. Previous studies demonstrated the strong association between stroke and Chagas disease [30,31] and the prevalence of ischemic cerebrovascular events in patients with CHD was estimated in 20% [32]. Therefore, it is important to verify whether patients are under appropriate anticoagulant medication.

During the anamnesis, the functional class of the New York Heart Association (NYHA) [33] should be verified. Details of the functional class evaluation are shown in Table 1. In patients with Chagas heart disease, NYHA functional class is a well-established marker of survival [34,35]. Patients with symptoms of fatigue and dyspnea during ordinary effort or at rest, i.e., in NYHA functional class III/IV, have a worse prognosis [36]. These patients should be on optimized therapy and the benefits of rehabilitation should be reviewed.

Functional class	Characteristics of the patient
NYHA I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitations.
NYHA II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris.
NYHA III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
NYHA IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure present at rest.

Table 1: New York heart association (NYHA functional class).

During the maximal exercise testing, the presence of frequent ventricular arrhythmias and nonsustained ventricular tachycardia, both during exercise and during the recovery phase, are markers of worse prognosis [34,35]. These patients should be evaluated by the cardiologist about the need for pacemaker implantation. The peak oxygen uptake (VO₂peak) is also extremely valuable both in the first assessment and in evaluating the effectiveness of exercise training. Several studies [22,37,38] demonstrated lower values of VO₂peak in Chagas disease patients compared to health individuals. In the first evaluation, patients with VO₂peak below 20ml.kg.min have functional impairment [39] and should undergo cardiac rehabilitation with supervision. Values below 14 ml.kg.min, without beta-block therapy, may indicate the need for heart transplantation [16]. And, after the cardiac rehabilitation, increase of VO₂peak above 10% is considered clinically relevant [40]. Additionally, the slope of increase of ventilation relative to carbon dioxide production (VE/VCO₂ slope), evaluated only by the Cardiopulmonary Exercise Testing (CPET), represents the ability of the patient to eliminate carbon dioxide during exercise. A previous study [41] has shown that it is the functional parameter with the greatest prognostic value in patients with Chagas heart disease, and the survival cutoff point was estimated at 32.5.

Field tests are widely used in physiotherapy routine to evaluate functional capacity. The American Thoracic Society [42] standardized the Six-Minute Walk Test and Singh et al. [43] first described ISWT. In Chagas heart disease, the efficacy of two field tests was verified: the Six-Minute Walk Test (6MWT) and the Incremental Shuttle Walk Test (ISWT). The 6MWT is a time-limited submaximal test and, briefly, the patient should walk for six minutes at the highest possible speed in a 30-meter corridor [42]. Functional capacity is determined by the longest walking distance in two tests.

In Chagas heart disease, the distance walked during the test showed good correlation with VO₂peak [25], left ventricular ejection fraction [28,44], biochemical markers [28], and was effective in verifying the efficacy of exercise training [12,45]. Recently, Costa et al. [24] proposed a model of VO₂peak prediction using the distance walked during the 6MWT and other variables of easy measurement. The model, represented by the equation $VO_{2peak} = 53.43 + (1.35 \times \text{gender}; \text{code } 0 \text{ for females and } 1 \text{ for males}) - (5.59 \times \text{NYHA}) + (0.01 \times \text{6MWT distance}) - (0.29 \times \text{age}) - (0.035 \times \text{body mass index})$, showed a good performance to predict VO₂peak ($r^2=0.61$) and has potential value in the assessment of functional capacity in resource-limited areas. In addition, the walking distance of 522 meters is the cutoff point with the best sensitivity and specificity in identifying patients with Chagas' heart disease with functional impairment (VO₂peak values below 20 mL.kg.min) [25].

Another field test already used in Chagas heart disease is the Incremental Shuttle Walk Test (ISWT). Unlike the 6MWT, the ISWT is symptom-limited and the patient is instructed to walk or run a 10-meter corridor at the highest possible speed [43]. The test has 12 stages and, being incremental, each stage must be traveled at a higher speed than the previous one, determined by an audio signal [43]. In the setting of Chagas heart disease, the ISWT showed good correlation with VO₂peak [21,23] and quality of life [23]. The distance of 407 meters was predictive of functional impairment [23] and many equations were proposed to predict VO₂peak, based on distance traveled, sex and NYHA functional class [21]. However, it should be highlighted that the prognostic role of field tests in Chagas heart disease patients remains unknown.

Another important clinical parameter in Chagas heart disease has received special attention in recent years: the evaluation of respiratory muscle strength. To evaluate the respiratory muscle strength, patients should be instructed to breathe through a mouthpiece connected to a vacuum manometer from functional residual capacity (inspiratory muscle strength) or total lung capacity (expiratory muscle strength). The respiratory muscles weakness, especially the diaphragm, can reflect the generalized muscular atrophy present during the progression of the disease and may increase the sensation of dyspnea and reduce the functional capacity. Previous studies have shown that inspiratory muscle strength is lower in patients with Chagas heart disease when compared to healthy patients [22,46], and that the prevalence of inspiratory muscle weakness in the sample evaluated was 35% [27]. Despite the presence of inspiratory muscle weakness, no studies were found that performed inspiratory muscle training in the chagasic population.

Finally, the evaluation of quality of life in patients with Chagas heart disease is a crucial point in the physiotherapeutic evaluation, since it reflects the patient's perception of the symptoms presented and also the stigma related to the disease. It has previously been shown that patients with Chagas disease have worse quality of life compared to healthy individuals [47] and cardiac involvement is associated with a worse quality of life [9].

There is no specific questionnaire used in patients with Chagas disease and many questionnaires were used. In the absence of heart failure, many authors used the Short-form of Health Survey (SF-36) [23,47,48] and World Health Organization Quality of Life (WHOQoL) [49,50]. In patients with heart failure secondary to Chagas heart disease, the Minnesota Living with Heart Failure Questionnaire (MLwHF) is the most used because [23,41,51] it is specific for the limitations presented by the disease. In patients with pacemakers, the questionnaire Assessment of QUality of Life And RElated Events (AQUAREL) can also be an option to evaluate the quality of life [52].

Conclusion

The peculiarities of patients with Chagas heart disease should be considered in functional evaluation before exercise training. In the anamnesis, drug therapy, especially the use of antiarrhythmics and anticoagulants, and NYHA functional class should be investigated. In the maximal exercise testing, it is important to investigate the presence of ventricular arrhythmias during exercise and in the recovery phase, as well as the VO₂peak and VE/VCO₂ slope values, important markers of worse prognosis. During the field tests, instruments widely used in the physiotherapeutic routine, the distance walked in the Six-minute Walk Test (6MWT) is effective in the functional evaluation of the

patient with Chagas heart disease. Distances less than 522 meters may reflect the functional impairment. During the Incremental Shuttle Walk Test (ISWT), distances below 407 meters also reflect functional impairment. Both tests had good correlation with VO₂peak in patients with Chagas heart disease. Respiratory muscle strength also should be assessed, being the inspiratory weakness a common clinical finding in patients with cardiopathy. Finally, the quality of life, worse in patients with Chagas disease compared to healthy individuals, is an important method in the assessment of the patient's perception of the effects of the disease. It can be evaluated by generic (Short-form of Health Survey - SF-36 and World Organization Quality of Life - WHOQOL) or specific questionnaires (Minnesota Living with Heart Failure - MLWHF), in the presence of heart failure. So, the present study reports the importance of a detailed functional evaluation in patients with Chagas heart disease based on the main findings in the literature search.

References

1. Chagas C (1909) Nova tripanozomíase humana: estudos sobre a morfologia e o ciclo evolutivo do *Schizotrypanum cruzi* n. gen., n. sp., agente etiológico de nova entidade morbida do homem. *Memórias do Instituto Oswaldo Cruz* 1: 159-218.
2. Rassi Jr A, Rassi A, Marin-Neto JA (2009) Chagas heart disease: pathophysiologic mechanisms, prognostic factors and risk stratification. *Memórias do Instituto Oswaldo Cruz* 104: 152-158.
3. WHO. Fact sheet: Chagas disease (American trypanosomiasis).
4. Dias JCP, Ramos Jr. AN, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, et al. (2016) II Consenso Brasileiro em Doença de Chagas, 2015. *Epidemiologia e Serviços de Saúde* 25: 7-86.
5. Rocha MO, Teixeira MM, Ribeiro AL (2007) An update on the management of Chagas cardiomyopathy. *Expert Review of Anti-infective Therapy* 5: 727-743.
6. Hotez PJ, Dumonteil E, Betancourt Cravioto M, Bottazzi ME, et al. (2013) An unfolding tragedy of Chagas disease in North America. *PLoS Neglected Tropical Diseases* 7: e2300.
7. Basile L, Jansa JM, Carlier Y, Salamanca DD, Angheben A, et al. (2011) Chagas disease in European countries: the challenge of a surveillance system. *Euro surveillance*.
8. Requena-Mendez A, Aldasoro E, de Lazzari E, Sicuri E, Brown M, et al. (2015) Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 9: e0003540.
9. Sousa GR, Costa HS, Souza AC, Nunes MC, Lima MM, et al. (2015) Health-related quality of life in patients with Chagas disease: a review of the evidence. *Rev Soc Bras Med Trop* 48: 121-128.
10. Schmunis GA (2007) Epidemiology of Chagas disease in non endemic countries: the role of international migration. *Mem Inst Oswaldo Cruz* 102: 75-86.
11. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A, Jr., et al. (2015) Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. *N Engl J Med* 373: 1295-1306.
12. Lima MM, Rocha MO, Nunes MC, Sousa L, Costa HS, et al. (2010) A randomized trial of the effects of exercise training in Chagas cardiomyopathy. *Eur J Heart Fail* 12: 866-873.
13. Fialho PH, Tura BR, Sousa AS, Oliveira CR, Soares CC, et al. (2012) Effects of an exercise program on the functional capacity of patients with chronic Chagas' heart disease, evaluated by cardiopulmonary testing. *Rev Soc Bras Med Trop* 45: 220-224.
14. Mediano MF, Mendes Fde S, Pinto VL, Silva GM, Silva PS, et al. (2016) Cardiac rehabilitation program in patients with Chagas heart failure: a single-arm pilot study. *Rev Soc Bras Med Trop* 49: 319-328.
15. Botoni FA, Ribeiro AL, Marinho CC, Lima MM, Nunes Mdo C, et al. (2013) Treatment of Chagas cardiomyopathy. *BioMed Research International* 2013: 849504.
16. Andrade JPD, Marin Neto JA, Paola AAVd, Vilas-Boas F, Oliveira GMM, et al. (2011) I Diretriz Latino-Americana para o diagnóstico e tratamento da cardiopatia chagásica: resumo executivo. *Arquivos Brasileiros de Cardiologia* 96: 434-442.
17. Costa HS, Nunes MC, Souza AC, Lima MM, Carneiro RB, et al. (2015) Exercise-induced ventricular arrhythmias and vagal dysfunction in Chagas disease patients with no apparent cardiac involvement. *Rev Soc Bras Med Trop* 48: 175-180.
18. Rabelo DR, Rocha MO, de Barros MV, Silva JL, Tan TC, et al. (2014) Impaired coronary flow reserve in patients with indeterminate form of Chagas' disease. *Echocardiography* 31: 67-73.
19. de Alencar MC, Rocha MO, Lima MM, Costa HS, Sousa GR, et al. (2014) Heart rate recovery in asymptomatic patients with Chagas disease. *PLoS One* 9: e100753.
20. Ribeiro ALP, Rocha MOdC (1998) Forma indeterminada da doença de Chagas: considerações acerca do diagnóstico e do prognóstico. *Rev Soc Bras Med Trop* 31: 301-314.
21. Alves R, Lima MM, Fonseca C, Dos Reis R, Figueiredo PH, et al. (2016) Peak oxygen uptake during the incremental shuttle walk test in a predominantly female population with Chagas heart disease. *Eur J Phys Rehabil Med* 52: 20-27.
22. Baiao EA, Costa Rocha MO, Lima MM, Beloti FR, Pereira DA, et al. (2013) Respiratory function and functional capacity in Chagas cardiomyopathy. *International Journal of Cardiology* 168: 5059-5061.
23. Costa HS, Alves RL, da Silva SA, Alencar MC, Nunes Mdo C, et al. (2014) Assessment of Functional Capacity in Chagas Heart Disease by Incremental Shuttle Walk Test and its Relation to Quality-of-Life. *Int J Prev Med* 5: 152-158.
24. Costa HS, Lima MM, Alencar MC, Sousa GR, Figueiredo PH, et al. (2017) Prediction of peak oxygen uptake in patients with Chagas heart disease: Value of the Six-minute Walk Test. *Int J Cardiol* 228: 385-387.
25. Costa HS, Lima MM, de Sousa GR, de Souza AC, Alencar MC, et al. (2014) Functional capacity and risk stratification by the Six-minute Walk Test in Chagas heart disease: comparison with Cardiopulmonary Exercise Testing. *Int J Cardiol* 177: 661-663.
26. Costa HS, Lima MM, Silva MG, Alencar MC, Nunes MC, et al. (2014) Effect of acute aerobic exercise on serum BDNF levels in patients with Chagas heart disease. *Int J Cardiol* 174: 828-830.
27. Costa HS, Lima MMO, Nunes MCP, Sousa GR, Almeida FRd, et al. (2017) Inspiratory muscle weakness in patients with Chagas heart disease: Echocardiographic and functional predictors. *IJC Metabolic & Endocrine* 14: 21-25.
28. Sousa L, Botoni FA, Britto RR, Rocha MO, Teixeira AL, et al. (2008) Six-minute walk test in Chagas cardiomyopathy. *Int J Cardiol* 25: 139-141.
29. Borghi-Silva A, Trimer R, Mendes RG, Arena RA, Schwartzmann PV (2015) Rehabilitation practice patterns for patients with heart failure: the South American perspective. *Heart Fail Clin* 11: 73-82.
30. Carod-Artal FJ (2010) Trypanosomiasis, cardiomyopathy and the risk of ischemic stroke. *Expert Rev Cardiovasc Ther* 8: 717-728.
31. Cardoso RN, Macedo FY, Garcia MN, Garcia DC, Benjo AM, et al. (2014) Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies. *J Card Fail* 20: 931-938.
32. Nunes MC, Kreuzer LJ, Ribeiro AL, Sousa GR, Costa HS, et al. (2015) Prevalence and risk factors of embolic cerebrovascular events associated with Chagas heart disease. *Glob Heart* 10: 151-157.
33. Bennett JA, Riegel B, Bittner V, Nichols J (2002) Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. *Heart Lung* 31: 262-270.
34. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO (2012) Diagnosis and management of Chagas disease and cardiomyopathy. *Nat Rev Cardiol* 9: 576-589.

35. Nunes MC, Carmo AA, Rocha MO, Ribeiro AL (2012) Mortality prediction in Chagas heart disease. *Expert Rev Cardiovasc Ther* 10: 1173-1184.
36. Rassi A Jr, Rassi A, Rassi SG (2007) Predictors of mortality in chronic Chagas disease: a systematic review of observational studies. *Circulation* 115: 1101-1108.
37. Mady C, Cardoso RH, Ianni BM, Arteaga E, Koide NS, et al. (1996) Normal maximal functional capacity in patients with congestive heart failure due to Chagas' cardiomyopathy. *Arq Bras Cardiol* 67: 1-4.
38. Oliveira FP, Pedrosa RC, Giannella-Neto A (2000) Gas exchange during exercise in different evolutionary stages of chronic Chagas' heart disease. *Arq Bras Cardiol* 75: 481-498.
39. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP (1982) Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 65: 1213-1223.
40. Smart N, Marwick TH (2004) Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 116: 693-706.
41. Ritt LE, Carvalho AC, Feitosa GS, Pinho-Filho JA, Andrade MV, et al. (2013) Cardiopulmonary exercise and 6-min walk tests as predictors of quality of life and long-term mortality among patients with heart failure due to Chagas disease. *Int J Cardiol* 168: 4584-4585.
42. ATS (2002) ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 166: 111-117.
43. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE (1992) Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 47: 1019-1024.
44. Chambela MC, Mediano MFF, Ferreira RR, Japiassu AM, Waghbi MC, et al. (2017) Correlation of 6-min walk test with left ventricular function and quality of life in heart failure due to Chagas disease. *Trop Med Int Health* 22: 1314-1321.
45. Lima MM, Nunes MC, Nascimento B, Costa HS, Sousa LA, et al. (2013) Improvement of the functional capacity is associated with BDNF and autonomic modulation in Chagas disease. *Int J Cardiol* 167: 2363-2366.
46. Vieira FC, de Melo Marinho PE, Brandao DC, Barbosa e Silva O (2014) Respiratory muscle strength, the six-minute walk test and quality of life in Chagas cardiomyopathy. *Physiother Res Int* 19: 8-15.
47. Oliveira BG, Abreu MN, Abreu CD, Rocha MO, Ribeiro AL (2011) Health-related quality of life in patients with Chagas disease. *Rev Soc Bras Med Trop* 44: 150-156.
48. Pelegrino VM, Dantas RA, Ciol MA, Clark AM, Rossi LA, et al. (2011) Health-related quality of life in Brazilian outpatients with Chagas and non-Chagas cardiomyopathy. *Heart Lung* 40: e25-31.
49. Ozaki Y, Guariento ME, de Almeida EA (2011) Quality of life and depressive symptoms in Chagas disease patients. *Qual Life Res* 20: 133-138.
50. Souza AC, Rocha MO, Teixeira AL, Dias Junior JO, Sousa LA, et al. (2013) Depressive symptoms and disability in chagasic stroke patients: impact on functionality and quality of life. *J Neurol Sci* 324: 34-37.
51. Dourado KC, Bestetti RB, Cordeiro JA, Theodoropoulos TA (2006) Assessment of quality of life in patients with chronic heart failure secondary to Chagas' cardiomyopathy. *Int J Cardiol* 108: 412-413.
52. Oliveira BG, Velasquez-Melendez G, Rincon LG, Ciconelli RM, Sousa LA, et al. (2008) Health-related quality of life in Brazilian pacemaker patients. *Pacing Clin Electrophysiol* 31: 1178-1183.