ORIGINAL ARTICLE

Evaluation of the Autonomic Nervous System in Chronic Chagasic Cardiopathy: A Systematic Review of the Literature

Lorena dos Santos Marreto Rimolo,[1] Roberto Magalhães Saraiva,[2] Ademir Batista da Cunha[1]

Hospital Universitário Antonio Pedro,[1] Niterói, RJ – Brazil.
Fundação Oswaldo Cruz, Rio de Janeiro,[2] RJ – Brazil.

Abstract

Background: The importance of regional sympathetic denervation in the pathophysiology and prognosis of Chagas disease has been recognized.

Objective: To conduct a review of studies that have assessed dysautonomia in chronic Chagas heart disease.

Methods: The search was performed on the Medline, Pubmed, Lilacs and SciELO databases. The inclusion criteria were: original articles published in full; studies on individuals with Chagas disease, that used diagnostic methods for chagasic cardiomyopathy, and had clear inclusion and exclusion criteria. Duplicate studies, studies including children (0 to 10 years old), studies involving animals, *in vitro* experiments, case reports, editorials, theses, and dissertations were excluded.

Results: A total of 281 articles were retrieved, and 10 met the inclusion criteria and were analyzed. There was great heterogeneity as to the technique for assessing dysautonomia, groups of patients studied and classification of Chagas disease. The methods used for studying the autonomic system was immunohistochemistry (n=1), Valsalva and tilt-test (n=1), scintigraphy (n=6) and Holter monitoring (n=2). The results indicated dysautonomia in the indeterminate, digestive and cardiac forms of Chagas disease, and sympathetic denervation in the indeterminate and cardiac forms of the disease. There was agreement between areas of denervation, hypoperfusion and fibrosis, but areas of denervation were larger than those of hypoperfusion. The frequency of denervation and its extension increased from the indeterminate to the cardiac form. There was an association between extension of denervation and previous history of malignant ventricular arrhythmia.

Conclusions: The evidence presented in this review supports that an early diagnosis of autonomic denervation in chronic Chagas' disease allows the identification of patients with an increased risk of sudden death. (Int J Cardiovasc Sci. 2020; 33(6):648-655)

Keywords: Chagas Disease; Chagas Cardiomyopathy; Arrhythmias, Cardiac; Primary Dysautonomias; Autonomic Nervous System.

Introduction

Several authors state that there are still important gaps in knowledge about Chagas disease that must be overcome to effectively deal with this widely neglected disease.[1]

Chagas disease is a significant public health problem in most countries in Latin America. Although occurring mainly in rural areas, in the last decades, the disease has spread to non-endemic cities and countries, mainly as a result of migration of infected people.[1]

An increasing number of cases has been identified in the United States, Spain and other countries, making the diagnosis and management of Chagas disease of growing interest worldwide.[1] During an antimalarial campaign in Lassance (Minas Gerais, Brazil) in 1909, Carlos Chagas identified the parasite Trypanosoma cruzi,

Mailing Address: Lorena dos Santos Marreto Rimolo
Rua Oliveira Botelho, nº 37. Postal Code: 24033-900, Niterói, RJ – Brazil.
E-mail: rimololorena@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190122

Manuscript received June 05, 2019; revised manuscript December 25, 2019; accepted July 05, 2020.

its transmission vector – triatomines (named differently in each country: kissing bugs, "barbers", *vinchuca*, bed bugs, etc.) – and described the initial cases of the disease.[2] Although defined as a new morbid entity, Chagas disease was not uncommon, afflicting millions of patients. In Brazil, the main probable forms of transmission are oral transmission (72%), vector transmission (9%) and unknown mode of transmission (18%).[3]

In the acute phase of the disease, a large number of parasites is found in the blood, and in the chronic phase, parasitemia decreases while serology becomes positive. Cardiac involvement is considered the most severe manifestation and can affect up to 30% of chronically infected patients.[4] In a study published by Marin-Neto et al.,[5] heart rate responses to tilt test were used to evaluate parasympathetic and sympathetic chronotropic control of the heart during the initial 10-second and late 5-minute phases, respectively. Other works have shown that changes in the sympathetic system precede changes in perfusion and contractility.[5] Cardiac autonomic impairment and right heart failure are prominent features of Chagas disease; however, no causal relationship between these phenomena has been defined so far, and the pathophysiology of such manifestations is unclear.[6]

Cases of sudden death in asymptomatic patients with fibrosis and denervation have been confirmed by anatomopathological studies.[7] Regional sympathetic denervation was observed in areas without contractile abnormalities in a high percentage of patients and was the first evidence of ventricular sympathetic system disorder in chronic chagasic heart disease.[8]

The aim of this article is to review available data on dysautonomia (sympathetic and parasympathetic branches) in chronic chagasic heart disease.

Methods

A systematic review of the literature was performed to assess articles investigating dysautonomia in Chagas heart disease. This type of review is an authorial contribution that presents the status of the literature about a subject.[9-10] The systematic review was carried out in five stages: definition of search strategy, selection of descriptors, definition of inclusion and exclusion criteria, identification of pre-selected and selected studies.

The following keywords were used in the search: 'Chagas' cardiomyopathy', 'arrhythmia' and 'dysautonomia'. These keywords were used in English, Portuguese and Spanish. The search was automated and carried out in the bibliographic bases: *Medical Literature Analysis and Retrieval System Online* (Medline) via Pubmed, Latin America and Caribbean Health Sciences Literature (Lilacs) and *Scientific Eletronic Library Online* (SciELO). The studies included in the review were freely available online in the databases used.

The inclusion criteria for the studies were: full-text original articles, the study population included patients with Chagas disease, the study assessed dysautonomia using diagnostic methods of chagasic cardiomyopathy, had clear criteria for patient inclusion, exclusion and discontinuation (if appropriate).

Duplicate articles, studies on patients aged from 0 to 10 years, animals, in vitro experiments, case reports, editorials, theses, dissertations, and other types of articles that did not meet the objective of the research were excluded. First eligible studies were retrieved from the databases. Subsequently, the studies were selected by reading the title and abstract. If necessary, the full text was read to confirm whether the study met the inclusion criteria of the review. According to Proença and Silva,[9] this type of survey is considered systematic by using heuristics to eliminate biases resulting from the consultation and use of sources.

Statistical Analysis

The high heterogeneity among the reviewed studies regarding the methods used to assess dysautonomia, the groups of patients studied, and classification of patients with Chagas disease prevented us from performing a meta-analysis. Thus, the description of the findings in the articles was made qualitatively.

Results

Of the 281 articles retrieved from the three databases, 20 articles published between 1990 and 2018 were selected for this review. Nine of the 20 were available in the PubMed database, which indexes the largest number of publications, especially when using cross-descriptors. After analysis for inclusion and exclusion criteria, 10 articles were excluded, and 10 articles composed the study sample. Figure 1 illustrates the search process, and Table 1 describes the main characteristics of the articles included in the systematic review.

Regarding the temporal distribution of the articles, half of the articles were published in the penultimate and the other half in the last ten years (2008-2018).

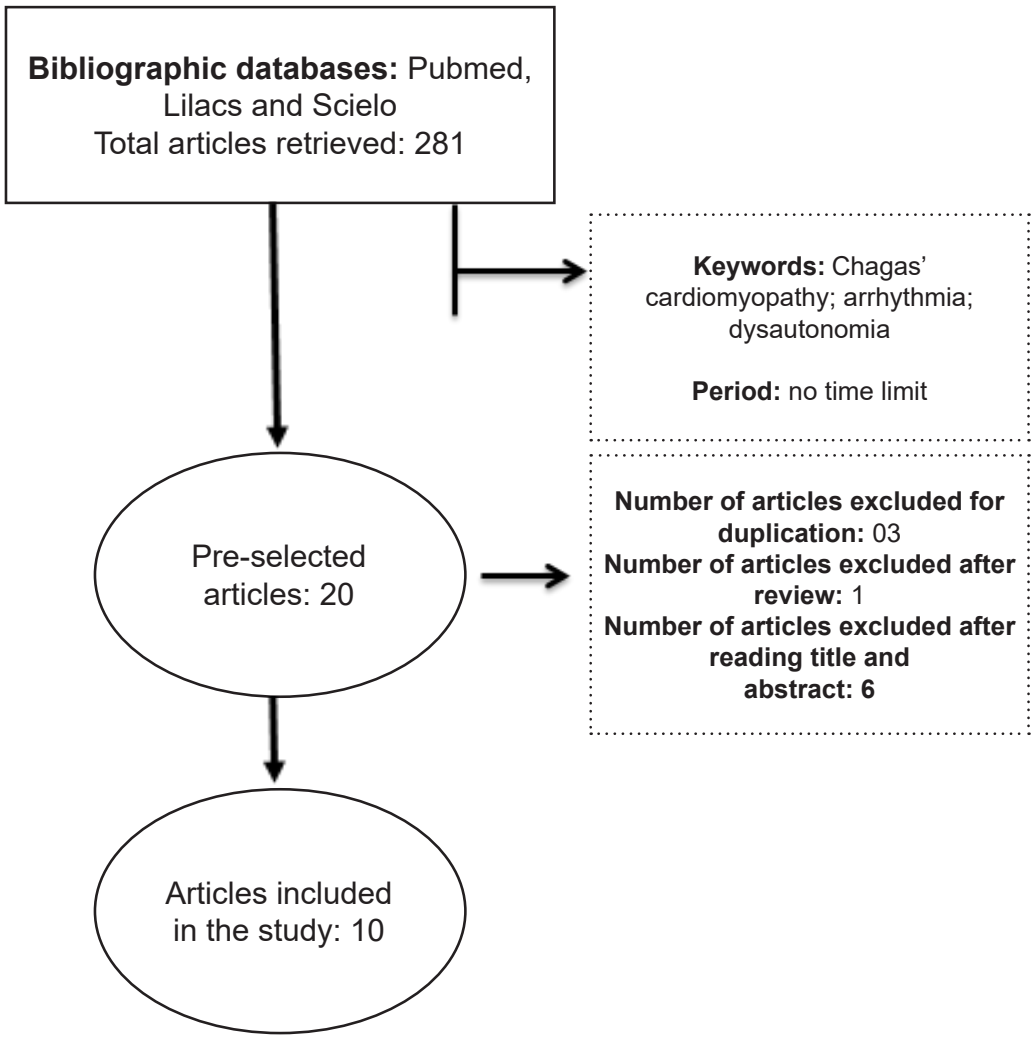

Figure 1 – Selection process of the studies in the systematic mapping of the literature.

Of the 16 articles included in the study, seven (46.6%) were in English, nine in Portuguese, and none in Spanish. This was probably due to the journals selected by the authors to submit their articles. Of the 16 selected publications, four had a qualitative approach.

The diagnosis of chronic Chagas' disease in the studies was established by positivity in two different serological methods. The patients were aged between 18 and 80 years. In most studies, there was no record of the time of disease progression. Most participants of the studies were recruited from a cardiology, cardiac arrhythmia, chagasic heart disease or heart failure outpatient clinics. In the studies by Marin-Neto et al.,[4] and Simões et al.,[5] patients were selected after testing positive for Chagas disease in a screening among blood donors.

Regarding the study design, there was only one longitudinal prospective study comparing heart rate variability (HRV) assessed by Holter monitoring before and after a cardiac rehabilitation program in patients with Chagas' disease and heart failure.[11] The other studies had a cross-sectional design.

The search for patients in almost all articles was not limited by period in most studies, except in three studies: the study by Landessman et al.,[12] in which patients were studied from October 2003 to November 2006; in the study by Souza et al.,[11] in which patients were studied between April 2009 and November 2010, and the study by Marino et al.[13], where patients were selected from March 2014 to February 2016. All selected articles included both men and women, with no restrictions on gender.

Table 1- Characteristics of the articles included in the systematic review study

References	Objectives	Design	Techniques	n	Main Results
MARINO et al., 2018[18]	To compare cardiac sympathetic dysfunction of patients with HF due to CHD or other etiologies	Cross-sectional	MIBG scintigraphy estimating HMR uptake and cardiac washout	25 CHD patients with HF 25 non-CD HF	The HMR of 123I-MIBG uptake and cardiac washout were similar in patients with HF with or without CD. Late HMR values showed a positive correlation with LVEF in patients with CHD and HF
BARIZON et al., 2018[19]	To test the correlation between areas of hypoperfusion, autonomic denervation and fibrosis in patients with CD	Cross-sectional	MIBG SPECT, rest/stress MIBI and MRI	13 CHD	Denervation areas were larger than the areas of rest- or stress-induced hypoperfusion and areas with myocardial fibrosis. In individual patients, there was a strong anatomic correlation between areas of hypoperfusion, denervation, and fibrosis
GADIOLI et al., 2016[17]	To investigate the correlation between the extent of myocardial sympathetic denervation and fibrosis and the severity of ventricular arrhythmias in CHD	Cross-sectional	MIBG SPECT, rest/stress MIBI	15 CHD with SVT 11 CHD with NSVT 17 CHD no arrhythmia	The extent of denervated but viable myocardium was higher in SVT group than in the control group and the NSVT group. The occurrence of ventricular arrhythmias correlates with the extent of cardiac sympathetic denervation, but not with the extent of fibrosis, suggesting that myocardial sympathetic denervation plays a major role in triggering ventricular arrhythmia in CHD
SOUZA et al., 2013[11]	To evaluate if cardiac rehabilitation improves autonomic function of patients with CHD and dysautonomia on Holter monitoring	Prospective	Heart rate variability on Holter monitoring	18 CHD patients with HF	Heart rate variability parameters in patients with CHD with HF did not show statistically significant changes after a six-month cardiac rehabilitation program
MIRANDA et al., 2011[16]	To compare the extent of sympathetically denervated viable myocardium between patients with CHD with or without SVT	Cross sectional	MIBG SPECT, rest/stress MIBI	15 CHD with SVT 11 CHD without SVT	The amount of sympathetically denervated viable myocardium is associated with the occurrence of SVT. The presence of more than 3 mismatch defects was strongly associated with SVT. Myocardial sympathetic denervation may participate in triggering malignant ventricular arrhythmia in CHD
LANDESMANN et al., 2007[15]	To evaluate if patients with CD IND form present early changes in sympathetic autonomic cardiac innervation	Cross sectional	MIBG SPECT	26 IND 8 controls	The HMR in patients with CD was lower than controls. Patients with CD IND form may have changes in sympathetic cardiac innervation

RIBEIRO et al., 2002[14]	To describe heart rate variability patterns in different groups of CD	Cross sectional	Holter monitoring	85 CD with normal echo 49 CHD with wall motion abnormality 26 CHD with LV systolic dysfunction 26 controls	Compared to controls, patients with CD have reduced vagal indexes and abnormal fractal patterns of heart rate variability that are independent of the presence of regional or global LV systolic dysfunction
MACHADO et al., 2000[8]	To assess the densities of sympathetic and parasympathetic nerve terminals in hearts of patients with HF with or without CD	Cross sectional	Histopathology	11 CHD with HF 8 non CD HF	Parasympathetic denervation was more severe in CHD while the degree of sympathetic denervation was similar in both groups
SIMÕES et al., 2000[5]	To detect the regional ventricular sympathetic innervation disturbances and myocardial perfusion abnormalities in various CD forms	Cross sectional	MIBG SPECT, rest/stress MIBI	12 IND 13 CHD with normal LV EF 12 CHD with LV systolic dysfunction 18 controls	Extensive impairment of cardiac sympathetic function at the ventricular level occurred early in CHD and was related to regional myocardial perfusion disturbances, before wall motion abnormalities
MARIN-NETO et al., 1998[6]	To assess cardiac autonomic control and biventricular function in CD patients with no evidence of heart disease	Cross sectional	Radionuclide angiography, Valsalva maneuver, head-up tilt and baroreflex sensitivity	16 IND 15 DIG 14 controls	No significant differences in autonomic functions were found between controls and IND group. CD patients with the DIG form showed abnormally lower Valsalva ratio, baroreflex sensitivity and parasympathetically-dependent heart rate response to tilt and higher Valsalva delay values compared with the controls

CD: Chagas disease; CHD: Chagas' heart disease; DIG: CD digestive form; HF: heart failure; HMR: heart-to-mediastinum ratio; IND: CD indeterminate form; LV EF: left ventricular ejection fraction; MIBG: iodine-123 (I-123) meta-iodobenzylguanidine; MIBI: 99mTc-Sestamibi; MRI: magnetic resonance; NSVT: non-sustained ventricular tachycardia; SPECT: single photon emission computed tomography; SVT: sustained ventricular tachycardia;
All of the aforementioned studies used a statistical significance level of 5%

Among the methods used for assessment of autonomic denervation of patients with Chagas disease, Marin-Neto et al.,[6] submitted the participants to the Valsalva maneuver, tilt test with head elevation and assessment of baroreflex sensitivity through intravenous injection of phenylephrine. Landessman et al.,[12] and Marino et al.,[13] used myocardial scintigraphy with metaiodobenzylguanidine (MIBG) to verify denervation of autonomic nervous system. Simões et al.,[5] Miranda et al.,[14] Barizon et al.,[15] and Gadioli et al.,[16] compared myocardial scintigraphy with MIBG to assess denervation, and myocardial perfusion scintigraphy using the sestamibi technetium (Tc-MIBI). In order to correlate the areas of myocardial fibrosis with the anomalous extension of the myocardial denervation (MIBG) and its hypoperfusion, Barizon et al.,[15] included magnetic resonance imaging (MRI) in their study. Souza et al.,[11] and Ribeiro et al.,[17] analyzed HRV and cardiac autonomic function by 24-hour Holter monitoring. Machado et al.,[8] evaluated sympathetic denervation by immunohistochemical study in human myocardium of patients who underwent heart transplantation or ventriculectomy.

None of the selected articles included analysis of biochemical or inflammatory markers in their methodology.

Regarding the results, one histopathology study compared patients with heart failure caused by Chagas

disease or not. Both groups showed sympathetic and parasympathetic denervation. Parasympathetic denervation was more evident in the group with Chagas disease than in those without Chagas disease, while the degree of sympathetic denervation was similar in both groups.[7] The two studies that used Holter monitoring involved different populations: one included only patients with heart failure[11] and the other included patients with different stages of Chagas disease and left ventricular (LV) systolic dysfunction and one control group.[17] The first study performed a longitudinal analysis of patients and found no changes in dysautonomia after a cardiac rehabilitation program.[11] The second study found that, after adjusting for covariates, the values of the short-term 24-hour HRV index were consistently lower in groups with Chagas disease. The values of the beta slope index (derived from the analysis of the HRV power law) were also lower in the groups with Chagas disease (group 1: normal echocardiograms, group 2: segmental alteration on the echocardiogram without LV systolic dysfunction, group 3: dysfunction LV systolic) than controls. This decomposition of the long-range fractal correlation of the RR interval dynamics, a strong predictor of mortality in other cardiomyopathies, may reflect cardiac dysautonomia that may have been detected in the long-term analysis in the time domain.

The study that used Valsalva's maneuver and tilt test showed that there were no significant differences between controls and patients with indeterminate form of Chagas disease, while patients with the digestive form had dysautonomia. This study did not include patients with cardiac form.[6]

The studies that used MIBG myocardial scintigraphy had a heterogeneous study population, since one included patients with indeterminate Chagas disease [12] and the other patients with heart failure.[13] The first study suggested the presence of sympathetic denervation in patients with the indeterminate form[12] and the second failed to demonstrate a higher degree of sympathetic denervation in patients with Chagas' disease and heart failure than in patients with heart failure of other etiologies.[13]

Four studies used myocardial scintigraphy with MIBG to assess denervation, and MIBI to assess myocardial perfusion. The first also included MRI to assess patients with cardiac form of Chagas disease.[15] This study demonstrated a strong correlation between areas of denervation, hypoperfusion and fibrosis, but the areas of denervation were larger than areas of hypoperfusion or fibrosis.[15] Another study included patients with indeterminate form and cardiac form with or without systolic dysfunction and demonstrated that changes in sympathetic denervation occurred early in Chagas' disease and that they correlated with perfusion disorders and could occur before contractile changes were evident.[5] Finally, two of these studies compared the results of myocardial scintigraphy between patients with and without sustained ventricular tachycardia. One study showed that the denervated but viable myocardial area was associated with previous history of sustained ventricular tachycardia. The presence of three or more segments with "mismatch" between perfusion and sympathetic innervation was strongly associated with a history of sustained ventricular tachycardia.[14] The other study confirmed that the size of the "mismatch" area between perfusion and sympathetic innervation was greater in patients with a previous history of sustained ventricular tachycardia than in those with non-sustained ventricular tachycardia and controls.[16]

Discussion

Dysautonomia in Chagas disease has been recognized for a long time, since the description of a decreased response to atropine in patients with Chagas disease.[18] In 1949, the first report of cardiac neuronal damage was published[19] and in 1959, neuronal stress depopulation was described in patients with Chagas disease.[20] However, the autoimmune theory prevailed for decades over the pathophysiology of Chagas disease and studies on dysautonomia became of secondary importance. However, the importance of dysautonomia in the pathophysiology and prognosis of Chagas disease has been revisited, especially after the possibility of assessing sympathetic denervation in vivo through the use of scintigraphy and the finding of the correlation between sympathetic denervation and the occurrence of malignant ventricular arrhythmias. Despite this, in this review, the number of selected publications was small, which indicates a clear need for further technical-scientific research in Chagas disease.[21] In fact, authors have pointed out that there are few studies on sympathetic denervation, with small samples or experimental animal models.[22] However, the cardiac dysautonomia found in Chagas disease may explain the increased risk of sudden arrhythmic death found in these patients, even in the absence of LV dysfunction.[17]

The English language was the most used in publications and possibly reflects the international interest in the

nuances of Chagas disease and, consequently, in the autonomic nervous system in Chagas cardiomyopathy. Regarding the identification of types of research, cross-sectional studies were the most used. The choice of the research method was related to the objectives of the studies, since the research aims were to assess dysautonomia and to compare the findings across different groups of patients. Regarding clinical outcomes, only two studies correlated dysautonomia with the arrhythmic event, but not prospectively. There is a clear need for prospective studies that can elucidate the real prognostic value of identifying dysautonomia or sympathetic denervation in patients with Chagas disease. In addition, studies are needed on how to intervene in this process in a patient-friendly manner. It is known that the pathophysiology of sympathetic dysautonomia includes cardiac neuronal and nerve fiber destruction by inflammatory processes and parasitism and anti-β1 receptor autoantibodies,[23] leading to down-regulation of adrenergic receptors. Therefore, studies evaluating therapies in Chagas disease could also assess their effects on dysautonomia. In this review, we found only one study that evaluated the effect of an intervention, in this case, cardiac rehabilitation, on dysautonomia.[11] The study of the effect of other interventions, such as trypanocidal medications or inflammatory modulators, on dysautonomia or sympathetic denervation is clearly needed.

The articles analyzed in this review were highly heterogeneous, whether by the method used to assess dysautonomia, the group of patients studied, and the classification system used to characterize the patients. This prevented data from different studies from being combined for reanalysis. However, the data presented pointed to the presence of dysautonomia in the indeterminate form to cardiac forms with or without LV systolic dysfunction and also in the digestive form of Chagas disease,[4] which clearly showed that cardiac parasympathetic impairment can occur in the absence of any detectable LV function disorder. Sympathetic denervation has also been demonstrated in patients with the indetermate[5,12] and cardiac[5,14,16] forms of Chagas disease. There was a concordance between areas of denervation, hypoperfusion and fibrosis, however with areas of denervation larger than those of hypoperfusion, which characterized the "mismatch" [5,15]. The frequency of patients with sympathetic denervation and its extension gradually increased from the indeterminate form, to the cardiac form without LV dysfunction and with LV[5] systolic dysfunction. There was also a correlation between sympathetic denervation and degree of ventricular dysfunction[13] and an association between the degree of sympathetic denervation extension and the previous history of malignant ventricular arrhythmia.[14,16] In patients with chagasic heart disease, a history of sustained ventricular tachycardia correlated with the extent of sympathetic cardiac denervation, but not with the extent of fibrosis, indicating an important role of sympathetic cardiac denervation to trigger ventricular arrhythmia.[16]

Marino et al.,[13] demonstrated scintigraphic evidence of sympathetic hyperactivity, based on the findings of low uptake of 123I-MIBG (early and late heart-mediastinal relationship) by presynaptic endings in patients with Chagas disease and heart failure. The low uptake of 123I-MIBG indicates dysfunction of the receptors and loss of integrity of the presynaptic sympathetic fibers, reinforcing the theory of sympathetic hyperactivity in the pathogenesis of HF.

Conclusion

The evidence presented in this review supports that an early diagnosis of autonomic denervation in chronic Chagas' disease, even in patients without changes in the electrocardiogram and echocardiogram, may allow the identification of patients with an increased risk of sudden death.

Therefore, this issue must be studied extensively so that existing knowledge gaps are addressed. This systematic review contributed to the analysis of publications on the assessment of dysautonomia in chronic Chagas heart disease. It should be noted that the systematic review aims to demonstrate the periodicity and numbers of publications on the subject investigated, which was achieved by this study.

Finally, the knowledge gap on dysautonomia of chagasic cardiomyopathy is highlighted, and it is suggested that more studies on the topic be developed to provide scientific basis for health policies and interventions. It is also recommended that further research on autonomic nervous system in Chagas cardiomyopathy be undertaken, so that the best treatment for this condition can be found.

Author contributions

Conception and design of the research: Cunha AB. Acquisition of data: Rimolo LSM. Analysis and interpretation of the data: Souza AC, Saraiva RM. Statistical analysis: Cunha AB, Rimolo LSM. Writing of the manuscript: Cunha AB, Saraiva RM. Critical revision of the manuscript for intellectual content: Rimolo LSM, Saraiva RM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Dias JCP, Ramos Jr AN, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR ,et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol Serv Saude. 2016;25(21):1-10.
2. Lewinsohn R. Carlos Chagas and the Discovery of Chagas's Disease (American Trypanosomiasis). J Royal Soc Med. 1981;74(6):451-5
3. Brasil. Ministério da Saúde. Doença de Chagas: o que é, causas, sintomas, tratamento e prevenção. 2017. [Citado em 06 set 2018]. Disponível em: https://saude.gov.br/saude-de-a-z/doenca-de-chagas.
4. Marin-Neto JA, Bromberg-Marin G, Pazin-Filho A, Simões MV, Maciel BC. Specific diseases: cardiomyopathies and pericardial diseases. Other cardiomyopathiesIn: Yusuf S, Cairns J, Camm J, Fallen E, Gersh BJ, eds. GB: Evidence Based Cardiology, London, p.744-61, 1998.
5. Simões MV, Pintya AO, Bromberg-Marin G, Sarabanda AV, Antloga CM, Pazin-Filho A, et al. Relation of Regional Sympathetic Denervation and Myocardial Perfusion Disturbance to Wall Motion Impairment in Chagas' Cardiomyopathy. Am J Cardiol. 2000;86(9):975-81.
6. Marin-Neto JA, Bromberg-Marin G, Pazin-Filho A, Simões MV, Maciel BC. Cardiac autonomic impairment and early myocardial damage involving the right ventricle are independent phenomena in Chagas' disease. Int J cardiol.1998;65:261-9.
7. Lopes ER, Chapadeiro E, Almeida HO, Rocha A. Contribuição ao estudo da anatomia patológica dos corações de chagásicos falecidos subitamente. Rev Soc Bras Med. Trop. 1975;9(6):269-82 .
8. Machado CRS, Camargos ERS, Guerra LB, Moreira MCV. Cardiac Autonomic Denervation in Congestive Heart Failure: Comparison of Chagas' Heart Disease With Other Dilated Cardiomyopathy. Human Pathol.2016;28(2):233-40.
9. Proença D Jr, Silva ER. Contexto e processo do Mapeamento Sistemático da Literatura no trajeto da Pós-Graduação no Brasil. Transinformação. 2016;28(2):233-40.
10. Teza P, Miguez VB, Fernandes RF, Dandolini GA, Souza JA. Ideias para a inovação: um mapeamento sistemático da literatura. Gestão & Produção.2015; 23(1):60-83.
11. Souza MVAS, Soares CCS, Oliveira JR, Oliveira CR, Fialho PH, Cunha DM, et al. Variabilidade da frequência cardíaca: análise dos índices no domínio do tempo em portadores de cardiopatia chagásica crónica, antes e após um programa de exercícios. Rev Port Cardiol. 2013;32(3):219-27.
12. Landesmann, MCPP, Pedrosa RC, Albuquerque JC, Souza SAL, Fonseca LMB. Cintilografia Cardíaca com Metaiodobenzilguanidina Marcada com Iodo-123 em Pacientes no Estágio Inicial da Fase Crônica da Doença de Chagas. Rev SOCERJ. 207; 20(1):40-6.
13. Marino VSP, Dumont SM, Mota LG, Braga DS, Freitas SS, Moreira MCV. Sympathetic Dysautonomia in Heart Failure by 123I-MIBG: comparison between Chagasic, non-Chagasic and heart transplant patients. Arq Bras Cardiol. 2018;111(2):182-90.
14. Miranda CH, Figueiredo AB, Maciel BC, Marin-Neto JA, Simões MV. Sustained Ventricular Tachycardia Is Associated with Regional Myocardial Sympathetic Denervation Assessed with 123I-Metaiodobenzylguanidine in Chronic Chagas Cardiomyopathy. J Nucl Med. 2011;52(4):504-10.
15. Barizon GC, Simões MV, Schmidt A, Gadioli LP, Murta LO Jr. Relationship between microvascular changes, autonomic denervation, and myocardial fibrosis in Chagas cardiomyopathy: Evaluation by MRI and SPECT imaging. J Nucl Med. 2016;25(1):75-83.
16. Gadioli LP, Miranda CH, Pintya AO, Figueiredo AB, Schmidt A, Maciel BC, et al. The severity of ventricular arrhythmia correlates with the extent of myocardial sympathetic denervation, but not with myocardial fibrosis extent in chronic Chagas cardiomyopathy. J Nucl Med. 2016;25(1):75-83.
17. Ribeiro ALP, Lombardi F, Sousa MR, Barros MVL, Porta A, Barros VCV, et al. Power-Law Behavior of Heart Rate Variability in Chagas' Disease. Am J Cardiol, Belo Horizonte, v. 89, p.414-418, fev. 2002.
18. Chagas CRV, Villella E. Forma cardíaca da trypanosomiase americana. Mem Inst Oswaldo Cruz. 1922;14(1):1-61.
19. Ramos J, Oria J. Clínica e histopatologia do coração em portadores de megaesôfago e megacólon. Arquivos de Cirurgia Clínica e Experimental, 4. ed. São Paulo: Nacional, 1949. 442 p.
20. Koeberle F. Cardiopatia parassimpaticopriva. Munch Med Wschr.1959;101:1308-10.
21. Sabino EC, Ribeiro AL, Salemi VMC, Oliveira CL, Antunes AP, Menezes MM, et al. Ten-Year Incidence of Chagas Cardiomyopathy Among Asymptomatic Trypanosoma cruzi –Seropositive Former Blood Donors. . Circulation. 2013;127(10):1105-15.
22. Silva VJD, Machado MCP, Rocha AM, Padilha RM, Ramirez LE. Análise da função autonômica cardíaca em hamsters chagásicos. Ver Soc Bras Med Trop. 2003;36(2):11-2.
23. Talvani A, Rocha MOC, Ribeiro AL, Borda E, Sterin-Borda L, Teixeira MM. Levels of anti-m2 and anti-b1 autoantibodies do not correlate with the degree of heart dysfunction in chagas heart disease. Microbes and Infection.2006;8(9-10):2459-64.