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Autonomic dysfunction and Chagas Disease: what we know and what we need to integrate into clinical practice

Disfunção autonômica e Doença de Chagas: o que sabemos e o que precisamos saber para integrar a prática clínica

Disfunción autonómica y Enfermedad de Chagas: Lo que sabemos y lo que necesitamos integrar en la práctica clínica

Mônica Regina Hosannah da Silva e Silva[1], Débora Raysa Teixeira de Sousa[1], Jessica Vanina Ortiz[1], Elsa Isela Guevara-Moctezuma[1], Márcia Regina Silva e Silva[1], Kátia do Nascimento Couceiro[2], Guilherme Peixoto Tinoco Areas[3], Jorge Augusto de Oliveira Guerra[1,2,4], Maria das Graças Vale Barbosa Guerra[1,2], João Marcos Bemfica Barbosa Ferreira[1,2].

ABSTRACT

Objective: To provide a general, comprehensive and up-to-date overview of the action of the autonomic nervous system in Chagas' disease and the validation of Heart Rate Variability (HRV) as a tool for assessing the autonomic nervous system in Chagas' disease. **Methods:** This review was based on a search of the databases of the Scientific Electronic Library Online (SCIELO) and PUBMED between May and December 2023, using the terms Chagas disease and heart rate variability between 2011 and 2023. **Results:** The Autonomic Nervous System (ANS) has been extensively analyzed in relation to Chagas Disease. These findings characterize a parasympathetic-deprived cardiopathy with sympathetic predominance. Heart rate variability (HRV) investigates the oscillations in the intervals between consecutive heartbeats (RR intervals) that are confidently related to the influence of the ANS on the sinus node over a certain period of time. **Final Considerations:** Autonomic nervous system dysfunction is one of the main mechanisms of injury in Chagas disease, and heart rate variability is one of the ways to detect this condition. However, the use of heart rate variability should be incorporated into clinical practice for the assessment of patients diagnosed with Chagas' disease.

Keywords: Chagas Disease, Autonomic nervous system, Heart rate variability.

RESUMO

Objetivo: Fornecer uma visão geral, abrangente e atualizada da ação do sistema nervoso autônomo na doença de Chagas e a validação da Variabilidade da Frequência Cardíaca (VFC) como uma ferramenta para avaliar o sistema nervoso autônomo na doença de Chagas. **Métodos:** Esta revisão foi baseada em uma pesquisa nas bases de dados da Scientific Electronic Library Online (SCIELO) e PUBMED entre maio e dezembro de 2023, usando os termos doença de Chagas e variabilidade da frequência cardíaca entre 2011 e 2023. **Resultados:** O Sistema Nervoso Autônomo (SNA) tem sido amplamente analisado em relação à doença de Chagas. Esses achados caracterizam uma cardiopatia com privação parassimpática e predominância simpática. A variabilidade da frequência cardíaca (VFC) investiga as oscilações nos intervalos

[1] Programa de Pós-Graduação em Medicina Tropical, Universidade do Estado do Amazonas/Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus - AM.
[2] Universidade do Estado do Amazonas, Manaus - AM.
[3] Universidade Federal do Amazonas, Departamento de Fisiologia, ICB, Manaus - AM.
[4] CEUNI FAMETRO, Medicina, Manaus - AM.

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entre batimentos cardíacos consecutivos (intervalos RR), que estão seguramente relacionadas à influência do SNA no nó sinusal em um determinado período de tempo. **Considerações finais:** A disfunção do sistema nervoso autônomo é um dos principais mecanismos de lesão na doença de Chagas, e a variabilidade da frequência cardíaca é uma das formas de detectar essa condição. Entretanto, o uso da variabilidade da frequência cardíaca deve ser incorporado à prática clínica para a avaliação de pacientes diagnosticados com doença de Chagas.

Palavras-chave: Doença de Chagas, Sistema nervoso autônomo, Variabilidade da frequência cardíaca.

RESUMEN

Objetivo: Proporcionar una visión general, completa y actualizada de la función del sistema nervioso autónomo en la enfermedad de Chagas y validar la variabilidad de la frecuencia cardíaca (VFC) como herramienta de evaluación del sistema nervioso autónomo en la enfermedad de Chagas. **Métodos:** esta revisión se basó en una búsqueda en las bases de datos de la Scientific Electronic Library Online (SCIELO) y PUBMED entre mayo y diciembre de 2023, utilizando los términos «enfermedad de Chagas» y «frecuencia cardíaca variable» entre 2011 y 2023. **Resultados:** se ha analizado ampliamente el Sistema Nervioso Autónomo (SNA) en relación con la enfermedad de Chagas. Estos hallazgos caracterizan una cardiopatía parasimpática deprimida con predominio simpático. La variabilidad de la frecuencia cardiaca (VFC) investiga las oscilaciones en los intervalos entre latidos consecutivos (intervalos RR) que se relacionan con certeza con la influencia del sistema nervioso autónomo en el nódulo sinusal durante un cierto período de tiempo. **Consideraciones finales:** La disfunción del sistema nervioso autónomo es uno de los principales mecanismos de lesión en la enfermedad de Chagas y la variabilidad de la frecuencia cardiaca es una de las formas de detectar esta condición. Sin embargo, el uso de la variabilidad de la frecuencia cardiaca debería incorporarse a la práctica clínica para la evaluación de los pacientes diagnosticados de enfermedad de Chagas.

Palabras clave: Enfermedad de Chagas, Sistema nervioso autónomo, Variabilidad de la frecuencia cardíaca.

INTRODUCTION

Chagas disease (CD) is a potentially fatal anthropozoonosis caused by the parasite *Trypanosoma cruzi*. CD is widely distributed throughout the Americas and was discovered by Carlos Ribeiro Justiniano Chagas in 1909. The World Health Organization (WHO) unequivocally classifies CD as one of the neglected tropical diseases. Approximately 6 to 7 million people are currently infected with T. cruzi, with an additional 70 million at risk of exposure (MARIN-NETO JA, et al., 2023; BESTETTI RB, et al., 2016).

Chagas disease can be transmitted through various means, including vectors, oral ingestion, transplacental transmission, blood transfusions, organ transplants and sharing of contaminated needles among illicit drug users. The disease has two distinct phases in its natural history: acute and chronic (MARIN – NETO JA, et al., 2023; BESTETTI RB, et al., 2016; FERREIRA JMBB, et al., 2009).

The Autonomic Nervous System (ANS) has been extensively analyzed in relation to Chagas Disease. Numerous authors have reported the presence of a mononuclear infiltrate in ganglion nerves near the inflammatory focus, global neuronal reduction, and numerical decrease of parasympathetic nerve cells. These findings characterize a parasympathetic-deprived cardiopathy with sympathetic predominance (RIBEIRO ALP, et al., 2020; VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2009).

A variety of tests are used to evaluate the autonomic nervous system (ANS), including 24-hour Holter or short-term heart rate variability (HRV) analysis. These tests provide a comprehensive assessment of ANS function and allow for accurate diagnosis and treatment. Patients with chronic Chagas disease, with or without cardiac involvement, have demonstrated autonomic nervous system (ANS) dysfunction in several studies (MAREK M, et al., 1996).

Heart Rate Variability (HRV) is a highly effective and non-invasive measure that can accurately identify phenomena related to the autonomic nervous system in healthy or unhealthy individuals. This analysis confidently examines the oscillations in the intervals between consecutive heartbeats (RR intervals) that are confidently related to the influence of the ANS on the sinus node over a period of time, two, five or fifteen minutes (NIELSEN JC, et al., 2020).

Linear methods are analyzed in the time and frequency domains, using statistical indices, mathematical equations transcribed into geometric methods, and spectral analysis. Non-linear methods consist of analyzing fluctuations purged of trends, correlation function, Hurst exponent, fractal dimension, and Lyapunov exponent. Both linear and non-linear methods can be used to analyze HRV, providing accurate and precise measurements of the RR interval. The methods are described below (NIELSEN JC, et al., 2020; HAYANO J, et al., 2019; CATAI AM, et al., 2020). The involvement of the Autonomic Nervous System (ANS) has been a subject of investigation since the initial description of Chagas disease.

Several authors have reported the presence of mononuclear infiltrates in ganglionic nerves near the inflammatory focus, global neuronal reduction, and a numerical decrease in parasympathetic nerve cells, characterizing a parasympathetic-deprived cardiomyopathy with sympathetic predominance (MARIN-NETO JA, et al., 2023; VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2009). To assess ANS function, several tests are employed, including atropine, methacholine, and phenylephrine injections; isovolumetric exercises; postural tilt tests; facial immersion; the Valsalva maneuver; respiratory sinus arrhythmia; treadmill exercise testing; myocardial scintigraphy with I-123 MIBG; and heart rate variability (HRV) analysis using a 24-hour Holter monitor or short-term recordings.

Multiple studies have demonstrated ANS dysfunction in patients with the chronic form of Chagas disease, with or without cardiac involvement. HRV is one of the most widely used measures. It is a non-invasive measure with practical applicability and the ability to detect phenomena related to ANS function in healthy individuals, athletes and patients. This analysis examines fluctuations in the intervals between consecutive heartbeats (RR intervals), which reflect the influence of the ANS on the sinus node over a given period of time (2, 5 or 15 minutes) (MAREK M, et al, 1996; NIELSEN JC, et al., 2020). HRV can be analyzed using linear and non-linear methods.

Linear methods are conducted in the time and frequency domains and are assessed through statistical indices and mathematical equations, which translate into geometric methods and spectral analysis. Non-linear methods include detrended fluctuation analysis, correlation function, Hurst exponent, fractal dimension, and Lyapunov exponent (MAREK M, et al., 1996; NIELSEN JC, et al., 2020; HAYANO J, et al., 2019; CATAI AM, et al., 2020). Statistical indices in the time domain are obtained by analyzing RR intervals over a given period. These indices are derived using statistical or geometric methods, such as mean values, standard deviation, histogram-derived indices, and Cartesian coordinate mapping of RR intervals. These indices include:

NN: Mean value of all normal cardiac cycles recorded during the assessment, expressed in milliseconds (ms); **NNs:** Total number of measured cycles; **NNNs:** Total number of consecutive normal cycles; **SDNN:** Standard deviation of all normal RR intervals recorded over a period of time, expressed in ms; **SDANN:** Standard deviation of the means of normal RR intervals in successive 5-minute periods, expressed in ms; **SDNNi:** Mean of the standard deviations of adjacent normal RR intervals over a period of time, expressed in ms; **rMSSD:** Square root of the mean squared differences between adjacent normal RR intervals, expressed in ms; **pNN50:** Percentage of adjacent RR intervals with a difference greater than 50 ms.

SDNN, SDANN, and SDNNi represent both sympathetic and parasympathetic activity, but they do not allow differentiation between increased sympathetic tone and vagal withdrawal. In contrast, rMSSD and pNN50 are specific markers of parasympathetic activity (MAREK M, et al., 1996; NIELSEN JC, et al., 2020; HAYANO J, et al., 2019; RIBEIRO ALP, et al., 2009; CATAI AM, et al., 2020). Another linear method for HRV assessment is spectral power density analysis in the frequency domain. This analysis decomposes HRV into fundamental oscillatory components:

High-Frequency (HF, 0.15–0.4 Hz): Corresponds to respiratory modulation and vagal influence on the heart; **Low-Frequency (LF, 0.04–0.15 Hz):** Reflects the combined action of vagal and sympathetic components on the heart, with sympathetic predominance; **Very Low Frequency (VLF) and Ultra Low Frequency (ULF):** Less commonly used indices with unclear physiological significance, possibly related to the renin-angiotensin-aldosterone system, thermoregulation, and peripheral vasomotor tone; **LF/HF Ratio:** Reflects the absolute and relative changes between the sympathetic and parasympathetic components,

characterizing the sympathetic-vagal balance of the heart (MAREK M, et al, 1996; NIELSEN JC, et al., 2020). To obtain spectral indices, frequency tachograms undergo mathematical processing, generating a graph that expresses RR interval variation over time.

The main mathematical algorithms used are Fast Fourier Transform (FTT) and Autoregressive Models (AR). Frequency-domain indices can be expressed in absolute values (ms²) or normalized units (un), representing each component's value relative to total power. Data normalization in spectral analysis is often used to minimize the effect of VLF (VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2009; MAREK M, et al., 2020; NIELSEN JC, et al., 2020). HRV can also be analyzed using geometric methods, such as the triangular index, Lorenz (Poincaré) plot, SD1, and SD2.

Triangular Index: Calculated from the density histogram of normal RR intervals. It is obtained by dividing the total area of the RR intervals by the height corresponding to the number of intervals at the modal frequency; **Poincaré or Lorenz Plot:** A geometric method for dynamic HRV analysis that represents a time series within a Cartesian plane, in which each RR interval is correlated with the previous interval and defines a point on the plot; **SD1:** Represents the dispersion of perpendicular points to the line of identity and is an index of instantaneous recording of beat-to-beat variability. It is indicating short-term HRV and parasympathetic influence; **SD2:** Represents the dispersion of points along the line of identity, associated with sympathetic influence and vagal inhibition; **SD1/SD2 Ratio:** Indicates the balance between short and long-term RR interval variations (VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2009; MAREK M, et al., 2020; NIELSEN JC, et al., 2020).

Non-linear HRV analysis methods include:

Acceleration Capacity (ACC) and Deceleration (DEC) Capacity

Represented by accelerations and deceleration of RR intervals (ms). The ability to accelerate and decelerate the heart rate, determining greater frequency variability, demonstrates normality of autonomic nervous system.

Porta, Guzik, and Ehlers Asymmetry indices

Assess whether positive changes in RR interval are similar to negative changes. Porta and Guzik indices are expressed as percentages, while the Ehlers index is dimensionless, values equal to zero indicate time-reversible series.

Detrended Fluctuation Analysis (DFA)

Quantifies the presence or absence of fractal correlation properties in RR interval time series. DFA1 and DFA2 indices describe these properties, where a mean value of 0.5 indicates randomness, a value of 1 suggests chaotic behavior, and a value of 1.5 corresponds to regularity.

Correlation dimension

Estimates the dynamics of a system based on the size of its attractor, defined as the slope of the regression line in a logarithmic representation. Higher values indicate greater system complexity.

Entropy

Quantifies the irregularity or unpredictability of RR interval fluctuations in a time series repeated over time. It requires noise-free data and can use short or long recordings. Higher entropy indicates greater irregularity and complexity, while lower entropy reflects more regular and less complex intervals evaluated (VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2009; MAREK M, et al., 2020; NIELSEN JC, et al., 2020).

The aim of this review is to systematically analyze the role of the autonomic nervous system in Chagas' disease and to evaluate the validity of Heart Rate Variability (HRV) as a diagnostic and prognostic tool for autonomic assessment in this context. As a literature review, this study did not require approval from a research ethics committee; however, ethical standards were followed with regard to the proper attribution and use of copyrighted sources.

METHODS

This study is structured as an integrative review, aiming to synthesize and critically evaluate the available scientific evidence on the role of the autonomic nervous system in Chagas' disease. To ensure a systematic and objective approach, the guiding research question was formulated based on the PICO strategy (Population, Intervention, Comparison, Outcome): In individuals with Chagas' disease (P), how effective is Heart Rate Variability (HRV) analysis (I) compared to other autonomic assessment methods (C) in evaluating autonomic nervous system function (O)? This question was designed to address a significant gap in the literature regarding the reliability and clinical applicability of HRV as a tool in this specific population. The integrative review method was chosen to provide a comprehensive understanding of the topic by incorporating findings from diverse study designs, ultimately contributing to evidence-based knowledge and guiding future research and clinical practice.

REVIEW CRITERIA

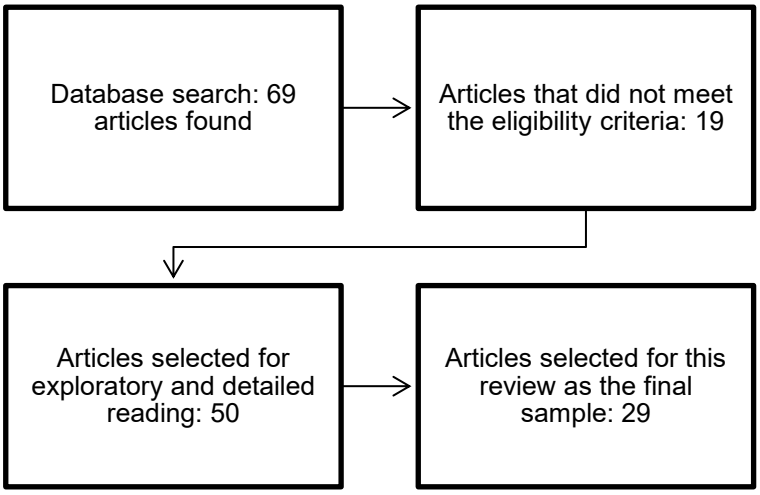
Publications were searched in the Scientific Electronic Library Online (SCIELO) and PUBMED databases between May and December 2023, using the terms Chagas disease and heart rate variability. The following eligibility criteria were applied: articles available in electronic media, full texts on the subject found in international databases, in English and Portuguese, bibliographic reviews, clinical trials, and published between 2011 and 2023.

Exclusion criteria were: abstracts of scientific proceedings, books and articles not in their entirety or in other languages, outside the research period, duplicate studies in the databases and that did not address the proposed topic. As a literature review, this study did not require the approval of a research ethics committee; however, ethical considerations were considered regarding the copyright of the selected articles.

RESULTS

A total of 69 articles were identified as a result of the search methodology. Of these, 19 articles did not meet the eligibility criteria were removed. After careful reading, 29 articles were selected as the final sample. The details of the search are shown in the flowchart in (**Figure 1**).

Figure 1 - Flowchart of the article search.



Source: Silva MRH, et al., 2025.

The summary of the 29 selected articles is shown in **Table 1**, which includes the title of the article, the authors, the year of publication of the journal, and the main findings of each article. They were selected based on their relevance to the proposed topic, the impact factor of the journal published and their citations.

Table 1 - The main findings according to the criteria that were established for this review.

Nº	Author/Publication Date	Main findings
1	Sassi R, et al., (2015)	The novel approaches to HRV analysis summarized in this text contributed in the technical understanding of the signal character of NN sequences. On the other hand, their success in developing new clinical tools, such as those for the identification of high-risk patients, has been so far rather limited.
2	Llaguno M, et al., (2011)	Chagas disease patients with the indeterminate form and with the symptomatic/determinate clinical forms both presented a lower vagal response at baseline. The ApEn in Chagas disease patients with the symptomatic form was diminished and this index in other heart diseases has been associated with increased cardiovascular risk for ventricular fibrillation and sudden death.
3	Ferreira JMBB, (2022)	This study demonstrated the cardiac involvement in the acute phase of this disease in order to elucidate the pathophysiological mechanisms that influence the evolution of the disease.
4	Ferreira JMBB, et al., (2015)	This study investigates the influence of cardiac autonomic function, estimated by HRV and serum adipocytokines in Chagas disease patients. In Chagas disease,
5	Junqueira-Junior LF, (2012)	Indirect evidence suggests that cardiac autonomic dysfunction probably plays an important role as a primary trigger or mediator favoring the development of various cardiovascular dysfunctions.
6	Barizon GC, et al., (2020)	Autonomic myocardial denervation may be a more sensitive marker of cardiac involvement in Chagas Disease than finding by other imaging modalities.
7	Chadalawada S, et al., (2020)	A systematic review was conducted to evaluate data on factors associated with progression from the acute phase or indeterminate chronic form of Chagas disease to the chronic cardiac form of the disease.
8	Pedrosa RC, (2020)	This study investigates the role of cardiac autonomic modulation in Chagasic patients and demonstrates the need to understand the role of autonomic modulation in the clinical severity of ventricular arrhythmias in CCC.
9	Guedes PM, et al., (2012)	The study investigates the role of cytokines in guiding the evolution of chronic chagasic cardiomyopathy.
10	Pérez AR, et al., (2011)	The study demonstrated the correlation between neuroendocrine dysfunction and the systemic inflammatory profile in Chagas disease.
11	Ouarhache M, et al., (2021)	Mitochondrial dysfunction and inflammation may be genetically determined in CCC, driven by rare genetic variants for increased mitochondrial susceptibility to IFN-γ-induced damage in the myocardium, leading to the cardiomyopathy phenotype in Chagas disease.
12	Thiers CA, et al., 2012	Lower vagal reserve with preserved function and functionally active anti-m2 or anti-β1 antibodies were associated in this study.
13	Beltrame SP, et al., (2020)	This study proposes an Interact between anti-M2R Ab and M2R, promoting a conformational change in the receptor molecule, resulting in an impaired activation state upon agonist binding. Chronic exposure of the cardiac M2R to CD antibodies could result in inhibition of AC-mediated responses, which may contribute to the inhibition of cardiac parasympathetic modulation.
14	Daliry A, et al., (2014)	The study demonstrated that chronically infected mice showed a significant increase in antibodies anti-M2-CR, Anti-B1-AR and Anti-B2-AR, suggesting that T. cruzi infection leads to cardiac electrical changes due to damage in receptors.
15	Alencar MC, et al., (2014)	They observed attenuated HRR after exercise in asymptomatic Chagas patients with RBBB compared being with patients in indeterminate form and controls.
16	Rodriguez HO (2020)	This study suggests a complex association among parasite persistence, sinus disease, micro-ischemia foci, and neural inflammation in the genesis of malignant arrhythmias of Chagas disease despite the absence of structural disease or massive necrosis

17	Chevillard C, et al., (2018)	This study observed that the complex pathophysiology of Chagas Disease is associated with the genesis of complex ventricular arrhythmias despite the existence of structural lesions.
18	Vasconcelos DF e Junqueira-Junior LF, (2012)	The authors found sympathetic and parasympathetic dysfunctions with preserved balance in chagasic patients with no association with ventricular dysfunction. Therefore, cardiac autonomic dysfunction may precede and not be associated with the presence or severity of ventricular dysfunction.
19	Silva LEV, et al., (2022)	The study showed a decrease in the slow HRV components, worst prognosis with increased heart rate fragmentation in mixed form of Chagas' disease.
20	Nascimento BR, et al., (2014)	HRV indexes' variations were similar between the active and inactive groups.
21	Sarmento AO, et al., (2021)	The variation of HRV indexes was similar between the active and inactive groups. Clinical improvement with physical activity seems to be independent from autonomic dysfunction markers in CHD.
22	Peña MM, et al., (2018)	The loss of parasympathetic modulation was present in all Rassi risk groups. It indicates morphological and neurofunctional changes.
23	Alberto AC, et al., (2020)	The modification in degree of HRV and its circadian changes are associated with sudden death and arrhythmias.
24	Nassario-Junior O, et al., (2015)	In Chagas' disease, HRV does not increase in proportion with the RR-interval as it happens in healthy subjects. This indicates cardiac vagal incompetence.
25	Oliveira MAR, et al., (2022)	There was no association between the degree of dysautonomia, evaluated by Holter monitoring.
26	Dabarian AL, et al., (2019)	This study evaluated metabolism and inflammatory activity in patients with idiopathic dilated cardiomyopathy (IDC) and Chagas cardiomyopathy (CHG) and their correlation with the ANS.
27	Beleigoli AM, et al., (2012)	Vagal HRV indexes were not associated with BMI or WC among the elderly individuals in the Bambuí cohort.
28	Truccolo AB, et al., (2013)	Relationship Between Autonomic Modulation Alterations and Endothelial Function in Patients with Indeterminate Chagas' Disease
29	Rabelo DR, et al., (2014)	In this study, impaired coronary flow reserve was observed in patients with undetermined chagas disease. Age and positive serology were independent factors for this loss of flow reserve.

Source: Silva MRH, et al., 2025.

DISCUSSION

In Chagas disease, ANS dysfunction can be detected before the development of ventricular dysfunction and heart failure and is also present in the indeterminate form of Chagas disease and in gastrointestinal involvement. ANS dysfunction may be involved in the genesis of arrhythmias and in the mechanism of sudden death in Chronic Chagas cardiomyopathy (CCDC). The autonomic nervous system consists of two antagonistic and complementary arms, the parasympathetic and sympathetic systems. The parasympathetic system is responsible for greater heart rate variability, or RR interval, while the sympathetic system produces less heart rate variability.

The predominance of parasympathetic action is protective. On the other hand, sympathetic activity makes the heart more susceptible to complex ventricular arrhythmias (SASSI R, et al., 2015; LLAGUNO M, et al., 2011; FERREIRA JMBB, et al., 2022). The possibility of a parasympathetic heart disease has been postulated, in which the catecholaminergic effects are not antagonized. The heart would lose its parasympathetic moderating effect and would be exposed to the stress of continued stimulation of the adrenergic system.

Sympathetic denervation seems to occur in parallel with myocardial inflammation or myocarditis during the acute phase, with gradual recovery as the inflammatory process diminishes. In an experimental study, an association was observed between myocarditis and sympathetic dysfunction through heart rate variability (SASSI R, et al., 2015; LLAGUNO M, et al., 2011; FERREIRA JMBB, et al., 2015; JUNQUEIRA-JUNIOR LF, 2012). Changes in the sympathetic nervous system have been demonstrated in vivo by myocardial

scintigraphy with metaiodobenzylguanidine-iodine-123 (MIBG-I123), and disturbances in cardiac sympathetic innervation have been observed anatomically, functionally, or both. The changes were found in the different forms of CD, but were more pronounced in CCDC.

The association between the degree of myocardial denervation and the risk of ventricular arrhythmias and sudden death has been demonstrated in several studies (JUNQUEIRA-JUNIOR LF, 2012; BARIZON GC, et al., 2020; CHADALAWADA S, et al., 2020). ANS dysfunction is important as a mechanism for sudden death because of the risk of progression to complex arrhythmias, as well as its involvement in inflammatory mechanisms, influence of neuroimmunomodulators, mitochondrial dysfunction, and genetic influence. The inflammatory environment, with high serum levels of IFN-γ and other pro-inflammatory cytokines, would lead to mitochondrial dysfunction, culminating in sudden death in individuals with susceptible genetic variants.

Organs with the highest metabolic demands, such as the heart and myoenteric ganglion cells, would be most affected. Llaguno et al. demonstrated the correlation between inflammatory cytokines, autonomic dysfunction and myocardial damage. It was observed that autonomic dysfunction in the different forms of myocardial damage increased with lower levels of IL-10 and higher levels of interferon-γ. The opposite behavior was observed in the indeterminate forms (SASSI R, et al., 2015; LLAGUNO M, et al., 2011; BARIZON GC, et al., 2020; CHADALAWADA S, et al., 2020; PEDROSA RC, 2020; GUEDES PM, et al., 2012; PEREZ AR, et al., 2011; OUARHACHE M, et al., 2021).

The mechanisms involved in acute neuronal loss are: direct parasitism of neurons, degeneration due to periganglionic inflammation and an antineuronal autoimmune response. In some studies, autoantibodies directed against muscarinic or beta-adrenergic receptors, which are involved in the destruction of autonomic neurotransmitter receptors, have been observed in patients with CCDC. The intramural neuronal suppression found is greater than that observed in other cardiovascular diseases.

Reduced ganglion density and neuronal depopulation are associated with ganglionitis, periganglionitis, neuritis, perineuritis, and Schwann cell and nerve fiber degeneration. When autonomic denervation involves the sinus node, patients are deprived of the tonic inhibitory action of the parasympathetic system and lack the vagal-mediated mechanism to respond to changes in heart rate, blood pressure, and venous return (THIERS CA, et al., 2012; BELTRAME SP, et al., 2020; DALIRY A, et al., 2014; ALENCAR MC, et al., 2014; RODRIGUEZ HO, 2020).

The production of circulating autoantibodies against cholinergic receptors (ac-M) and adrenergic receptors (ac-β) is responsible for the destruction of neuroeffector junctions and cardiac acetylcholine levels during the acute phase. These autoantibodies act on the junctions due to antigenic mimicry between T. cruzi and human ribosomal proteins. During the chronic phase, functional recovery is disorganized, random, and incomplete as the inflammation progresses. The parasympathetic intramural ganglia and myenteric plexus are most affected (PEREZ AR, et al., 2011; OUARHACHE M, et al., 2021; THIERS CA, et al., 2012; BELTRAME SP, et al., 2020; DALIRY A, et al., 2014; ALENCAR MC, et al., 2014; RODRIGUEZ HO, 2020).

There is no robust evidence that catecholamine-mediated cardiac neuropathy is the primary cause of the cardiac form of CD. It has been observed that although vagal dysfunction is predominant, there is attenuation of adrenergic regulation of sinus node-mediated cardiac chronotropism (ALENCAR MC, et al., 2014; VASCONCELOS DF, et al., 2012; OLIVEIRA MAR, et al., 2022). Another theory postulated to explain the pathophysiology of dysautonomia is the cholinergic anti-inflammatory pathway, in which the inflammatory process installed in Chagas disease maintains the action of the ANS. The parasympathetic pathway acts on cells, such as macrophages, and organs of the immune system with an anti-inflammatory effect, with attenuation of the cytotoxicity of T lymphocytes through cholinergic-muscarinic stimulation, the so-called neuroimmune or inflammatory reflex.

In CD, there is evidence that depression of the cardiac parasympathetic system contributes to the exacerbation of inflammation during the chronic phase (FERREIRA JMBB, 2022; JUNQUEIRA-JUNIOR LF, 2012; CHADALAWADA S, et al., 2020). It has been proposed that autonomic denervation contributes to coronary microvascular spasm, triggering myocardial ischemia and possibly leading to myocardial necrosis.

This mechanism may be secondary to microvascular and coronary artery changes associated with inflammation stimulating increased vasoreactivity and spasm of small arterial branches, endothelial damage due to parasitic aggression, or dysfunction due to the action of inflammatory cytokines, culminating in ischemia, necrosis, and reparative myocardial fibrosis (JUNQUEIRA-JUNIOR LF, 2012; CHADALAWADA S, et al., 2020; VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2012).

Necroscopic studies show microvascular ischemia, myocytolysis and reparative fibrosis. Extreme vasodilation is observed with a decrease in distal perfusion pressure. Myocytolysis and ischemia are seen in the terminal arterial regions, which are more susceptible to ischemia. The common consequence of myocardial lesions is biventricular dysfunction, with generalized dilation and hypokinesia due to a combination of myocardial hypertrophy and fibrosis to varying degrees. Ventricular dyssynergy or aneurysms, global dilatation, venous stasis, and atrial fibrillation predispose to thromboembolic complications with an increased risk of systemic embolization to the central nervous system and lungs (ALENCAR MC, et al., 2014; OUARHACHE M, et al., 2021).

Heart rate variability analysis

Heart rate variability (HRV) analysis, both short and long term, has been used to assess ANS function, both to detect autonomic dysfunction and to evaluate sympathovagal modulation. In individuals with heart failure, cardiac rehabilitation with regular exercise has shown benefits in reducing catecholamine levels, mortality, and rehospitalization, as well as improving exercise capacity, quality of life, and autonomic function, with HRV analysis being the method of choice for evaluation (SILVA LEV, et al., 2012; NASCIMENTO BR, et al., 2014; SARMENTO A, et al., 2021).

It was observed that parasympathetic activity is impaired at any stage of Chagas' disease and is not associated with worsening ventricular ejection fraction, demonstrating that autonomic dysfunction precedes ventricular dysfunction. Long-term analysis of parasympathetic autonomic function using the Holter method has demonstrated parasympathetic dysfunction in low-risk individuals with loss of parasympathetic protection (PEÑA MM, et al., 2018; ALBERTO AC, et al., 2020). The correlation between metabolic alterations, such as high levels of leptin and adiponectin, and HRV has been studied in patients with Chagas' disease, with the observation of a sympathovagal imbalance and an increase in leptin and adiponectin, characterizing an inflammatory milieu in patients with Chagas' disease.

In a cohort of elderly people, phenotypic metabolic changes such as increased BMI and abdominal girth did not show a correlation with HRV indices (DABARIAN AL, et al., 2019). The persistent inflammatory milieu, even if of low intensity, favors endothelial dysfunction and is fed by autonomic dysfunction. This association has been studied, and it has been observed that the flow-mediated vasodilator response correlates with increased sympathetic activity or sympathovagal imbalance, independent of left ventricular contractile deterioration (CHEVILLARD C, et al., 2018; BELEIGOLI AM, et al., 2012).

In another study investigating coronary and myocardial microvascular flow and autonomic dysfunction, a loss of coronary flow control capacity was observed in the face of stimuli with a consistent response to cardiac parasympathetic denervation without correlation with loss of left ventricular contractile function (TRUCCOLO AB, et al., 2013). HRV assessed during long recordings using the Holter methodology and machine learning showed the ability to predict echocardiographic alterations, correlating with the RASSI score, a predictor of mortality risk, in cardiomyopathies with or without associated digestive development (VASCONCELOS DF e JUNQUEIRA-JUNIOR LF, 2012; NASSARIO-JUNIOR O, et al., 2015; RABELO DR, et al., 2014).

FINAL CONSIDERATIONS

Autonomic nervous system dysfunction is one of the main mechanisms of injury in Chagas disease, and heart rate variability is one of the ways to detect this condition. However, the use of heart rate variability should be incorporated into clinical practice for the assessment of patients diagnosed with Chagas' disease. There is a need to incorporate this measure into clinical practice, as well as to operationalize it in order to make it even easier to use.

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