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Editorials

Chagas Disease - Past and Future

Lung Ultrasound in COVID 19 Outbreak: Can we Reduce the Burden from the Overloaded CT Departments?

Original Article

Self-reported HIV/HAART-associated Lipodystrophy and Modifiable Risk Factors for Cardiovascular Disease

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Reliability between Cardiovascular Risk Assessment Tools: A Pilot Study

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What is the best cardiovascular risk score for the Brazilian population?

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Nuclear Medicine Methods for assessment of chronic Chagas heart disease

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Viewpoint

Dysautonomic Arrhythmogenesis: A Working Hypothesis in Chronic Chagas Cardiomyopathy

Letter to the Editor

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Case Reports

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SUMARY

- **Editorials**

Chagas Disease - Past and Future 601
Aurea Lúcia Alves de Azevedo Grippa de Souza and Claudio Tinoco Mesquita

Lung Ultrasound in COVID 19 Outbreak: Can we Reduce the Burden from the Overloaded CT Departments? 604
Filipe Penna de Carvalho and Alex dos Santos Felix

- **Original Article**

Self-reported HIV/HAART-associated Lipodystrophy and Modifiable Risk Factors for Cardiovascular Disease 606
Thiago Veiga Jardim, Rodrigo de Castro Cardoso, Annelisa Silva e Alves de Carvalho Santos, Marianne de Oliveira Falco, Erika Aparecida Silveira

- **Editorial**

Lipodystrophy Associated with HIV/ART and Cardiovascular Risk Factors 616
Claudio Leinig Pereira da Cunha

- **Original Article**

Reliability between Cardiovascular Risk Assessment Tools: A Pilot Study 618
Rodrigo Conill Marasciulo, Ana Maria Nunes de Faria Stamm, Guilherme Thomé Garcia, Antônio Carlos Estima Marasciulo, Ariel Córdova Rosa, Alexandre Augusto de Costa Remor, Cristian Battistella

- **Editorial**

What is the best Cardiovascular Risk Score for the Brazilian Population? 627
Bruno Ferraz de Oliveira Gomes and Gláucia Maria Moraes de Oliveira

- **Original Article**

Prevalence of Malnutrition and Its Association with Clinical Complications in Hospitalized Cardiac Patients: Retrospective Cohort Study 629
Natally Gonçalves de Ávila, Juliana Umbelino Carneiro, Fernanda Donner Alves, Izabele Vian da Silveira Corrêa, Juliana Paludo Vallandro

- **Editorial**

Hospital Malnutrition, Inflammation, and Cardiovascular Diseases 635
Camila Weschenfelder and Aline Marcadenti

- **Original Articles**

The Clinical Course of Takotsubo Syndrome Diagnosed According to the InterTAK Criteria 637
Nelson Henrique Fantin Fundão, Henrique Barbosa Ribeiro, Carlos de Magalhães Campos, Vinicius Bocchino Seleme, Alexandre de Matos Soeiro, Marcelo Luiz Campos Vieira, Wilson Mathias Jr, Ludhmilla Abraão Hajjar, Expedito E. Ribeiro, Roberto Kalil Filho

Evaluation of the Autonomic Nervous System in Chronic Chagasic Cardiopathy: A Systematic Review of the Literature 648
Lorena dos Santos Marreto Rimolo, Roberto Magalhães Saraiva, Ademir Batista da Cunha

Mortality Trends from Cardiovascular Diseases in the State of Bahia, Brazil, between 2000 and 2015 656
Yana Mendonça Nascimento and Adriana Lopes Latado

Prognosis of Heart Failure with Preserved Ejection Fraction in Primary Care by the H2FPEF Score 666
Antonio Jose Lagoeiro Jorge, Maria Luiza Garcia Rosa, Wolney de Andrade Martins, Adson Leite, Dayse Mary da Silva Correia, Maria Auxiliadora Nogueira Saad, Humberto Villacorta, Sergio Chermont, Ronaldo Altenburg Gismondi, Breno Macedo Almeida, Evandro Tinoco Mesquita

Factors Predicting Heart Failure in Children Admitted to a Pediatric Emergency Ward in a Developing Country 673
Uchenna Onubogu

- **Review Articles**

Nuclear Medicine Methods for assessment of chronic Chagas heart disease 686
Marcus Vinicius Simões, Denise Mayumi Mayumi Tanaka, José Antonio Marin-Neto

Heart Transplantation for Chagas Cardiomyopathy 697
Maria da Consolação Moreira, Fabio Morato Castilho, Renato Braulio, Guilherme Ferraz Messina de Pádua Andrade, José Renan da Cunha Melo

Cardiac Magnetic Resonance in the Assessment of Chagas Disease and its Complications 705
Ariane Binoti Pacheco, Rodrigo de Jesus Louzeiro Melo, Carlos Eduardo Rochitte

- **Viewpoint**

Dysautonomic Arrhythmogenesis: A Working Hypothesis in Chronic Chagas Cardiomyopathy 713
Roberto Coury Pedrosa

- **Letter to the Editor**

Effectiveness of Rapid Response Teams and the Importance of Preprints 721
Hermano Alexandre Lima Rocha, Sabrina Gabriele Maia Oliveira Rocha, Antônia Célia de Castro Alcântara

- **Case Report**

Coxiella Burnetti Infective Endocarditis – Detection and Cure 723
Manuel Martins Barbosa, Carla Dias, Elsa Araújo, Raquel Costa

Iatrogenic Complications During the Diagnostic Work-Up of an Inflammatory Cardiomyopathy 729
Hugo Antunes, Júlio Gil, Bruno Marmelo, Maria Luísa Gonçalves, Maria Inês Pires, João Miguel Santos, Miguel Correia, José Costa Cabral

- **Erratum** 734

- **See in the Next Edition** 735

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EDITORIAL

Chagas Disease - Past and Future

Aurea Lúcia Alves de Azevedo Grippa de Souza and Claudio Tinoco Mesquita

Hospital Universitário Antônio Pedro, HUAP-EBSERH-UFF, Niterói, RJ – Brazil

"Remember to look up at the stars and not down at your feet. Try to make sense of what you see and wonder about what makes the Universe exist. Be curious."

Stephen Hawking

After 111 years of its discovery, Chagas disease remains a major public health challenge in Brazil and in other Latin American countries, reason why it continues to be a relevant topic in discussion panels worldwide.[1] The disease was first described in 1909 by Carlos Justiniano Ribeiro das Chagas after his observations during an expedition to eradicate malaria in the rural areas of the state of Minas Gerais, in the city of Lassance.[2] Carlos Chagas' magnificent life journey makes him a unique figure in the history of medicine, as he alone described all the stages of a new infectious disease: pathological findings, means of transmission (*Triatoma infestans*), etiology, clinical manifestations, and epidemiology. For this reason, he was one of the few Brazilians to be nominated for a Nobel Prize, which, unfortunately, he did not win. This issue of the International Journal of Cardiovascular Sciences (IJCS) focuses on Chagas disease and its repercussions on the cardiovascular system.

Carlos Chagas graduated in 1904 in Rio de Janeiro and began his professional life in the city of Niterói as a physician of the Public Hygiene Committee at Santa Isabel Maritime Hospital, after declining Oswaldo Cruz's invitation to work at Manguinhos. The Maritime Hospital, a beautiful architectural complex (**Figure 1a**) built during the 19th century from an old farm, was considered a reference for the treatment of infectious diseases until the end of the 4th decade of the 20th century.[3] Sailors, immigrants and local residents with bubonic plague, yellow fever or tuberculosis were treated at the institution. In this hospital, the Italian physician Camillo Terni, from the Serum Therapy Institute of Messina, conducted pioneering studies on a plague vaccine (**Figure 1b**).[4] After working for 1 year at the Maritime Hospital, Chagas left to Manguinhos, where he began his journey to eradicate yellow fever and malaria, which led him to discover the disease caused by the insect known as *barbeiro* (kissing bug).[2]

Currently, Chagas disease is endemic in the Americas, with sporadic cases in Europe and Asia resulting from migratory processes. Bolivia, Argentina, Paraguay and Ecuador are the countries with the highest prevalence rates. Public policies implemented to control the disease since the 1980s have resulted in a decrease in prevalence in Brazil, dropping from 7% in the 1970s to 0.17% nowadays. However, it is estimated that Argentina and Brazil (with about 1.3-1.5 million people infected) and Mexico and Bolivia (with about 0.6-0.8 million people infected) are the countries with the largest infected populations, for a total of more than 40 000 new annual cases due to vector transmission and more than 14 000 due to congenital transmission,[5-8] In Brazil, efforts to control the spread of the disease have been intensified since the 1980s with the implementation of a national program. With the development of studies on *Trypanosoma sp* prevention and contamination, actions have been implemented in blood product transfusions, organ transplants, laboratory sample-handling procedures, and food-handling practices associated with transmission as well as in congenital transmission.[5] These actions have also been implemented in other Latin American countries, especially regarding the prevention of congenital

Keywords

Chagas disease, Carlos Chagas, Trypanosoma Cruzi, Heart Failure; Percutaneous Coronary Intervention; Platelet Aggregation; Women; Aging; Myocardial Infarction.

Mailing Address: Aurea Lúcia Alves de Azevedo Grippa de Souza
Hospital Universitário Antônio Pedro
Rua Marquês de Paraná, 303. Postal Code: 24070-035, Centro, Niterói, RJ - Brazil
E-mail: aureagrippa@cardiol.br

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transmission, which is currently an important form of transmission. Therefore, resources have been directed toward, but not limited to, molecular diagnosis in order to develop algorithms representative of the situation of infecting *Trypanosoma cruzi* strains in pregnant women and their potential maternal-fetal transmission.[8]

The World Heart Federation (WHF) has included Chagas disease in its roadmap project in view of serious cardiac complications, constant migratory flows of populations, and the need to prevent the spread of the disease not only in the Americas but also in the rest of the world. This action also aims to improve the allocation of resources for research into the development of new forms of laboratory diagnosis, vaccines, and drugs for treatment. The roadmap project proposes, by identifying roadblocks along the way, strategies and evidence-based solutions for health care professionals, health authorities, and governments to help overcome the barriers to a better understanding and comprehensive care in Chagas disease.[9]

In the last 20 years, approximately 12 000 documents on Chagas disease, including articles and guidelines, have been published in MEDLINE journals. The importance of this topic is also reflected in special journal issues dedicated entirely to Chagas disease.[10] The changes bring to light individual susceptibility to *T. cruzi* infection, development of biomarkers to monitor disease progression, production of new drugs, and control of transmission. These actions should be extremely effective in controlling the disease, with a great socioeconomic impact in Latin America.[11] Research in this field will certainly contribute to the development of a vaccine by providing a better understanding of the diversity of the more than 140 subtypes of *T. cruzi* and the effects triggered in autoimmunity. Many needs are yet to be met in Chagas disease (Table 1).

Greater investment is needed in the Americas to increase awareness of the silent progression of Chagas disease, since symptoms of chronic impairment may take decades to manifest, especially cardiac complications. Improvements in general sanitation and housing conditions should form the basis of government public policies. However, the socioeconomic implications of this silent disease are often underestimated due to neglected observation, support and treatment for populations living with the disease, whether endemic or not. Efforts to eradicate Chagas disease require a multidisciplinary approach, tailored to local conditions and supported by medical and lay societies, which recognizes that reducing poverty, improving housing conditions and promoting cultural and educational actions have a direct impact on the incidence and prevalence not only of the disease itself but also of the chronic conditions associated with it, such as heart failure. In this special issue, the IJCS promotes a forum for a better understanding of Chagas disease and encourages continued basic and clinical research in the topic by using the above-quoted words of the physicist Stephen Hawking as a guide.

Table 1: Areas in Need of Research and Development in Chagas Disease

Research and Development Area	Expected impact
More accurate diagnostic tests	Reduction in the need to repeat tests and in diagnostic uncertainty
Techniques to monitor the progression of Chagas disease	Improvements in risk stratification and follow-up to aid in intervention decision-making
Vaccine development	Disease prevention in high-risk areas
Development of more effective drugs	Improvement in clinical outcomes with reduced side effects
Development of strategies for better management of advanced cases of heart disease	Reduction in the risk of disease reactivation after transplant and in morbidity and mortality with device therapies

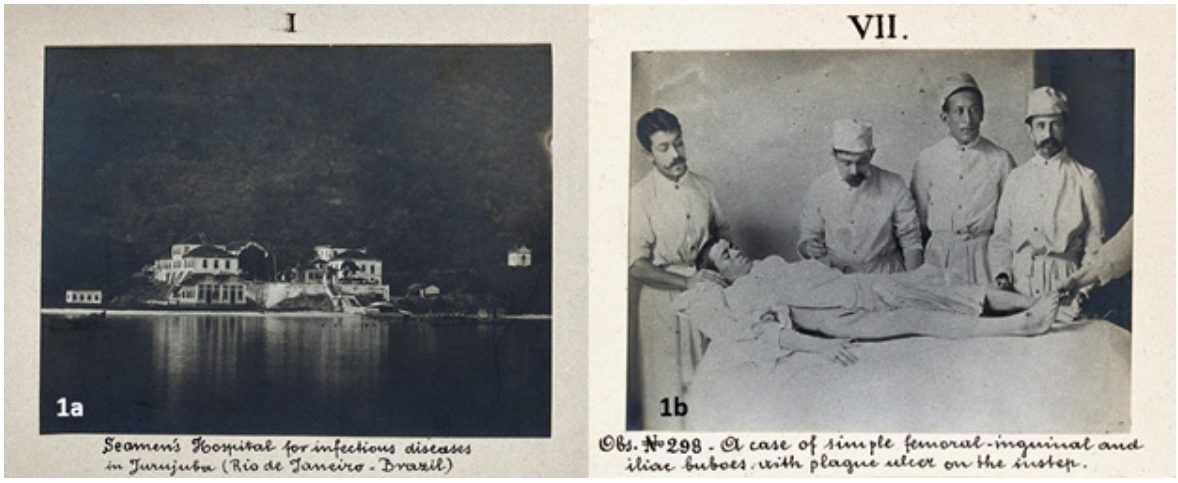

Figure 1 – Photographs from the collection of the University of Cambridge, with permission for reproduction. The photographs are personal records of Professor Camillo Terni during his stay at Santa Isabel Maritime Hospital between 1901 and 1905. 1a - View of the architectural buildings, known today as *Casa da Princesa* (Princess House). 1b - Photographic record of a bulb biopsy – Professor Camillo Terni at the center and his work team, which included Carlos Chagas.

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EDITORIAL

Lung Ultrasound in COVID 19 Outbreak: Can we Reduce the Burden from the Overloaded CT Departments?

Filipe Penna de Carvalho[1,2] and Alex dos Santos Felix[1,2,3,4]

Américas Serviços Médicos,[1] Rio de Janeiro, RJ – Brazil.
Diagnósticos da America SA (DASA),[2] Rio de Janeiro, RJ – Brazil.
Clínica São Vicente,[3] Rio de Janeiro, RJ – Brazil.
Instituto Nacional de Cardiologia,[4] Rio de Janeiro, RJ – Brazil.

Editorial related to the article: Lung Ultrasound as a Triage Tool in an Emergency Setting during the Covid-19 Outbreak: comparison with CT Findings

Since the first descriptions on the use of lung ultrasound (LUS) for bedside evaluation of critically ill patients,[1] important publications have underscored the utility of LUS for the detection of a wide array of pulmonary and pleural diseases, as well as for the differential diagnosis of acute respiratory failure,[2] proving to be an important tool for a point-of-care based examination and an extended resource for examining critical patients, cited by many as the "new stethoscope".[3,4]

The coronavirus disease-2019 (COVID-19) outbreak has emerged as a global health burden since late 2019, challenging healthcare systems around the world due to the constant need for intensive care support and isolation of patients, many of whom evolve with severe hemodynamic involvement, leading to high morbidity and mortality.[5] This critical scenario highlights the importance of appropriateness and best appliance of all diagnostic and therapeutic resources. In this regard, the use of point-of-care ultrasound (POCUS) is proving to be a cost-effective tool for the management of these potentially critical patients, from the initial presentation (triage) to in-hospital management and post-discharge follow-up[6].

Chest computed tomography (CT) has a high sensitivity in the detection of findings compatible with COVID 19 pneumonia,[7] and some scores derived from CT-findings have a good correlation with short term outcomes, with a higher mortality in cases of a higher percentage of lobar involvement.[8] Considering the fact that CT scans are not available in all emergency clinics, especially in underdeveloped countries or remote locations, and that, in a pandemic scenario, the sheer number of patients needing evaluation may surpass the actual capacity of the system, alternative diagnostic modalities are a good reinforcement to aid in patient evaluation and severity assessment.

This issue of the International Journal of Cardiovascular Sciences presents the results of an interesting study entitled "Lung Ultrasound as a Triage Tool in an Emergency Setting during the Covid-19 Outbreak: comparison with CT Findings" written by Alcantara et al.[9] This study sheds new light on the discussion of this important topic, adding relevant information about the value of LUS for triage of suspected COVID-19 patients examined at the emergency clinic (EC), as compared to CT findings.

The authors performed LUS in 20 patients admitted to the EC with clinically suspected COVID-19 and registered the number of abnormal segments detected by LUS. Each lung segment was also scored based on the degree of severity of LUS findings and a final summed score was calculated for each patient. The number of affected segments and the summed score was then compared to standardized CT findings.

Interestingly, patients with a low LUS score (≤1) or number of affected segments (≤1) showed an excellent correlation with minor pulmonary involvement illustrated in the CT scan, thus correctly classifying these patients into a lower risk group. Conversely, more

Keywords

COVID-19/complications, Pandemics, Acute Failure Respiratory; Morbidity; Mortality; Pleural Diseases/Diagnosis; Critic care; Ultrasonography/methods; Computed, Tomography.

Mailing Address: Filipe Carvalho
Avenida Ataulfo de Paiva, 669. Postal Code: 22640-102, Leblon, Rio de Janeiro, RJ – Brazil.
E-mail: filipepenna@me.com

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extensive lung abnormalities seen on LUS, defined as the presence of ≥3 abnormal segments or a score >7 showed good sensitivity and excellent specificity (81.8% and 100%, respectively) in predicting extensive lung involvement via CT scans (≥6 CT segments), with AUCs of 0.980 for a number of affected segments via LUS and a LUS score of 0.975.

Characteristic LUS lesions suggestive of COVID-19 pneumonia have been described since the initial stages of the outbreak.[10] The sensitivity of LUS in detecting a alveolo-interstitial pattern in COVID-19 patients was even greater than that detected by CT, as shown in the findings from Yang et al.,[11] demonstrating the potential applicability of this technique to early diagnosis and treatment. A study conducted by Zieleskiewicz et al.[12] showed an association of a high LUS score with the use of mechanical ventilation, and with a SpO2/FiO2 ratio below 357, also indicating a prognostic value of LUS findings. A greater extent of pulmonary involvement in the CT scan was correlated with severe COVID-19 presentations ($p < 0.0001$), CRP levels ($p < 0.0001$, $r = 0.6204$), and D-dimer ($p < 0.0001$, $r = 0.6625$). An increased risk of mortality was observed in patients with extensive disease, as shown via a CT scan, both in univariate (HR, 8.33; 95% CI, 3.19–21.73; $p < 0.0001$) and multivariate (HR, 3.74; 95% CI, 1.10–12.77; $p = 0.0348$) analyses.[8]

Findings from Alcantara et al.[9] adds new insight to this issue by demonstrating the potential power of LUS as a triage tool for COVID-19 in ECs, since LUS showed a good correlation with both minor and extensive pulmonary involvement, as defined via CT scans. Further studies with larger cohorts and external validation are still required to answer whether LUS as a triage tool translates into an improved workflow and a safe hospital discharge for patients in the EC setting.

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ORIGINAL ARTICLE

Self-reported HIV/HAART-associated Lipodystrophy and Modifiable Risk Factors for Cardiovascular Disease

Thiago Veiga Jardim, Rodrigo de Castro Cardoso, Annelisa Silva e Alves de Carvalho Santos, Marianne de Oliveira Falco, Erika Aparecida Silveira

Programa de Pós-graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Goiás, Goiânia, GO – Brazil

Abstract

Background: Patient self-report is the most common diagnostic tool in the literature to detect HIV/HAART-associated lipodystrophy. However, data on the association of cardiovascular risk factors with HIV/HAART-associated lipodystrophy assessed by self-report are still missing.

Objectives: To determine the prevalence of self-reported HIV/HAART-associated lipodystrophy and to identify independent associations between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy.

Methods: We conducted a retrospective observational study at an outpatient infectious disease clinic in the Central-West of Brazil to identify the association between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy. Sedentary lifestyle, smoking status, family history of cardiovascular disease, hypertension, diabetes, dyslipidemia, increased waist circumference and overweight were the cardiovascular risk factors assessed. Self-reported HIV/HART-associated lipodystrophy was categorized as: mild (noticeable by patients' close inspection), moderate (easily noticeable by patient and physician) or severe (readily noticeable by a casual observer). Prevalence ratio (PR) and 95% confidence interval (CI95%) were calculated. Multivariate Poisson's regression was used to analyze factors associated to HIV/HAART-associated lipodystrophy assessed by self-report considering a significance level of 5%.

Results: A total of 183 patients were included, with a mean age of 39.3±10.9 years. Most of the sample were male (77.6%), non-white (50.8%) and single (53.0%). The overall prevalence of HIV/HAART-associated lipodystrophy was 52.5% (95% CI 44.96 - 59.88). Severe lipodystrophy was observed in more than half patients (55.2%). No traditional modifiable cardiovascular risk factor was independently associated with lipodystrophy. Female sex (PR 1.49; 95% CI 1.15 – 1.95; p=0.003), time of HIV infection diagnosis of 1-3 years (PR 1.83; 95% CI 1.09 - 3.08; p=0.002) and a positive family history of CVD (PR 1.62; 95% CI 1.11 - 2.36; p<0.001) were independently associated with lipodystrophy.

Conclusion: HIV/HAART-associated lipodystrophy assessed by patient self-report was not associated with traditional modifiable cardiovascular risk factors. (Int J Cardiovasc Sci. 2020; 33(6):606-615)

Keywords: Retroviridae; Antivirals/therapeutic use; Cardiovascular Diseases/complications; Risk Factors; Metabolic Diseases/complications; Lipodystrophy.

Introduction

Antiretroviral therapy (ART) has significantly increased the survival and quality of life of people living with HIV/AIDS. Since the introduction and widespread use of combination ART, referred to as highly active antiretroviral therapy (HAART), HIV-related mortality has been reduced from 50 to 80%.[1] However, the long-term use of ARTs has been associated with metabolic abnormalities, including increased serum lipids, glucose, and insulin resistance. The combination of these disorders leads

Mailing Address: Erika Aparecida Silveira
Primeira Avenida, s/n. Postal Code: 74605-220, Goiânia, GO – Brazil.
E-mail: erikasil@terra.com.br

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to a highly atherogenic profile, increasing the risk of cardiovascular disease (CVD).[2]

The interaction between host factors, HIV, and HAART is strongly associated with the accumulation or loss of body fat in specific body sites,[3] which has been identified as lipodystrophy.[4] Lipodystrophy is characterized by fat redistribution, with subcutaneous fat loss (lipoatrophy), mainly in the face, limbs, and buttocks, or fat accumulation (lipohypertrophy) in the abdomen, breast or posterior neck, or a combination of both.[4] The HIV-associated body fat redistribution in individuals receiving ART (HIV/HAART-associated lipodystrophy) by itself is associated to dyslipidemia and hypertriglyceridemia, low-HDL-cholesterol, reduced insulin sensitivity, and diabetes.[5] Subjects with HIV/HAART-associated lipodystrophy may have increased Framingham risk scores and higher coronary calcium scores and thus are at increased risk of coronary heart disease.[6,7]

The most common diagnostic tool reported in the literature to detect HIV/HAART-associated lipodystrophy is the self-reported body fat distribution.[8-10] It is an accurate, reproducible and easy-to-implement method, adding almost no costs to the usual care of HIV/AIDS patients.[10-12] Despite the common use of patients' self-reported methods to identify lipodystrophy, to our knowledge, there are no available data on the association of cardiovascular risk factors and HIV/HAART-associated lipodystrophy assessed exclusively by this method. Therefore, we assessed subjects attending an HIV/AIDS outpatient care center of a capital city in Brazil (a middle-income country) to determine the prevalence of self-reported HIV/HAART-associated lipodystrophy and possible independent associations between traditional modifiable cardiovascular risk factors and self-reported lipodystrophy.

Materials and methods

Study design and ethical aspects

This is a retrospective observational study conducted at the Outpatient Clinic of Infectious and Parasitic Diseases in Goias State, Brazil. Methodological details have been published elsewhere, since this is part of a large epidemiological study.[13-15] Data collection occurred between October 2009 and July 2011. The study was approved by the Research Ethics Committee under the approval number 163/2009.

Inclusion and exclusion criteria

Inclusion criteria were age ≥ 19 years, HIV infection and HAART. All patients willing to participate signed the informed consent form.

Pregnant and lactating women, subjects with an opportunistic infection diagnosed less than two months before recruitment or longer but without clinical resolution within that period, and those with cognitive incapacity to fulfill the self-perception instrument were excluded.

Data collection

Patients who met eligibility criteria to participate in the study were invited to participate. A multidisciplinary team with cardiologist, nutritionists, and undergraduate students of health sciences composed the research group. Data collection on sociodemographic, clinical and smoking status variables occurred during the interview with the cardiologist. Subsequently, the cardiologist referred the patients to a nutritionist, who applied an interview on self-perception of changes in body composition, alcohol consumption and physical activity level. Finally, trained investigators performed the anthropometric assessment of the patients.

Sociodemographic data collection

Sociodemographic variables (age, gender, skin color, income, marital status and schooling years) were assessed using a pre-tested standardized questionnaire.

Age was stratified in four categories: 19-29, 30-39, 40-49 and ≥ 50 years. Skin color was defined as white or non-white. Number of schooling years was divided in four groups: ≤ 4 years, 5-8 years, 9-11 years and ≥ 12 years. Marital status was defined as single, married and widow/divorced.

The income in the previous month was clustered into quartiles (1st quartile ≤ U$ 170.00; 2nd quartile from U$ 170.01 to U$ 240.00; 3rd quartile from U$ 240.01 to U$ 400.00 and 4th quartile ≥ U$ 400.01).

HIV-related clinical and laboratorial data

Clinical characteristics were time since diagnosis of HIV infection, duration of ART use and class of antiretroviral drug (nucleoside reverse-transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI).

The time since HIV diagnosis and the time of ART use were calculated based on the difference in years from the date of data collection and both events dates informed by the patient. Both variables were categorized in: <1 year, 1-3 years and >3 years. Information on CD4 T + lymphocytes count and viral load were obtained from the patient's medical chart, as these tests are performed routinely in the outpatient clinic. CD4 count was determined by flow cytometry and viral load by branched DNA (bDNA) assays for HIV-1 (Versante HIV-1 RNA 3.0 assay). CD4+ lymphocyte count (cells/mm3) was classified as ≤350 and >350.[14]

Biochemical tests

Biochemical tests were performed after 12 hours fasting and no alcohol consumption for at least three days. The enzymatic colorimetric method was used to determine total cholesterol (TC), HDL-cholesterol (HDL), serum triglycerides (TG) and blood glucose. The LDL-cholesterol (LDL) level was estimated with the Friedewald formula: LDL = TC - (HDL + TG/5)[16].

Anthropometric measurements

Anthropometric measurements were collected following standardized techniques,[16,17] and researchers were trained to make precise and accurate measurements.[18] To measure body weight, a digital scale with 150 kg capacity and 100 g accuracy was used (Tanita BC-558 Ironman). Height was measured to the nearest 0.1 cm with a 150 cm length non-elastic tape, at 50 cm from the ground, fixed to a wall without a baseboard. Patients were instructed to be barefooted during weight and height measurements.

BMI was calculated as weight (kg) divided by the square of height (m^2). Nutritional status was classified as: 1) underweight or normal weight (BMI < 18.5 kg/m^2 and between 18.5–24.9 kg/m^2, respectively); 2) overweight (BMI between 25.0-29.9 kg/m^2); and 3) obesity (BMI ≥ 30.0 kg/m^2).

Waist circumference (WC) was measured at the largest extension of the abdomen in a horizontal plane with a non-elastic measuring tape. Values of less than 80 cm for women and 94 cm for men were considered normal.

Cardiovascular risk factors

The short version of the International Physical Activity Questionnaire (IPAQ) was used to assess physical activity level. Subjects who reached ≥ 600 MET-min/week score were considered physically active, corresponding to 30 minutes of moderate physical activity five days a week, a total of 150 min/week. Subjects with score <600 MET-min/week were considered sedentary.[19]

Smoking status was investigated according to the Pan American Health Organization (OPAS—Organización Panamericana de la Salud)[20]. "Smoker" was defined as a current smoker or who had quit smoking for less than six months; "former smoker" who had quit smoking for more than six months; and "nonsmoker" who had never smoked.

Family history of cardiovascular disease is a non-modifiable risk factor for CVD. It was assessed by patient report and considered positive if an early event has happened in a first-degree relative (males before 55 years and females before 65 years)[21].

Subjects with systolic blood pressure (BP) ≥ 140 mmHg and diastolic BP ≥ 90 mmHg (mean of three office measurements) and/or on treatment were considered hypertensive.[22]

Diabetes was defined when fasting blood glucose was ≥ 126 mg/dl and/or on treatment.[23]

Dyslipidemia was defined when the cutoff points for TC, LDL-c, TG and/or HDL-c were met and/or on lipid lowering drugs. The cutoff points were: TC ≥ 200 mg/dL, LDL-c ≥ 160 mg/dL, TG ≥ 150 mg/dL, and HDL-c <40 mg/dL in men and <50 mg/dL in women.[24]

Increased WC was defined as ≥ 80 and <88 cm for females and ≥ 94 and <102 cm for males; and greatly increased when ≥ 88 cm in women and ≥ 102 cm in males.[21] These two categories were grouped for analysis.

BMI ≥ 25.0 kg/m^2 was considered as a cardiovascular risk factor.[21]

HIV/HART-associated lipodystrophy

A standardized, self-reported questionnaire was used to evaluate lipodystrophy.[13,25,26] First, patients were asked if their body appearance changed since the initiation of HIV treatment. If not, the degree of body fat redistribution was rated as absent and, if the answer was positive, HIV/HART-associated lipodystrophy was rated as present. Lipodystrophy was than categorized as: mild (noticeable by patients' close inspection), moderate (easily noticeable by patient and physician) or severe (readily noticeable to a casual observer).

Sample calculation and statistical analyses

The sample size was calculated with the software Epi-Info 3.0, with a confidence level of 95% and 80% power; 150 patients would be required to study the associations between lipodystrophy and cardiovascular risk factors.

The dataset was structured in Epi-Data 3.1 with double entrance to avoid inconsistencies. Statistical analyses were performed with the software Stata 12.0. Absolute and relative frequencies were estimated. Pearson's chi-squared test was used to study sex differences regarding the prevalence of lipodystrophy and its severity. The simple Poisson regression was used to calculate prevalence ratio (PR), 95% confidence interval (CI95%) and *p* values. All variables with a p-value ≤ 0.20 in simple regression were included in multivariate Poisson's regression analyses in three hierarchical levels as follow: 1st level – sociodemographic data; 2nd level - HIV-related clinical and laboratorial data; 3rd level – cardiovascular risk factors; and 4th level – anthropometric data. Variables that remained with a p < 5% after the adjustments were kept in the final regression model. The Wald`s test was used to measure the significance level of each Poisson coefficient, in both simple and multivariate regressions. It is a test similar to the chi-squared test and is the standard test of the Poisson regressions in the statistical package used. Statistical significance was established at 5%.

Results

A total of 183 patients met eligibility criteria and were included in this study, with a mean age of 39.3 ± 10.9 years. The prevalence of HIV/HAART-associated lipodystrophy in the overall sample was 52.5% (96/183). Most of the sample was male (77.6%), non-white (50.82%) and single (53.0%); sociodemographic characteristics of the sample as well as the prevalence of lipodystrophy by subgroups are described in Table 1. There was a significantly higher percentage of female subjects with lipodystrophy (*p*=0.003).

The distribution of the different levels of lipodystrophy is presented in Figure 1. No differences were observed between males and females (Table 1). Severe lipodystrophy was observed in more than half of the individuals (55.2%).

When we assessed the prevalence of HIV/HAART-associated lipodystrophy by HIV-related clinical and laboratorial variables, a higher prevalence of lipodystrophy (66.7% - PR 1.88; 95% CI 1.12 – 3.14; *p*=0.025) was observed among those with a time of diagnosis of HIV infection between 1 and 3 years. No other HIV-related clinical or laboratorial data evaluated were associated with lipodystrophy. All patients were using NRTI (Table 2).

The prevalence of HIV/HAART-associated lipodystrophy was assessed by the presence of cardiovascular risk factors. In this analysis, lipodystrophy was associated with a family history of CVD (PR 1.70; 95% CI 1.22 – 2.39; *p*=0.002) and increased/greatly increased WC (PR 1.39; 95% CI 1.06 – 1.82; *p*=0.018), as shown in Table 3.

After including the clinical and laboratorial HIV-related variables, and the cardiovascular risk factors in the model, female sex, 1-3 years of HIV infection diagnosis and a positive family history of CVD remained associated with lipodystrophy in the multiple regression analysis (Table 4).

Discussion

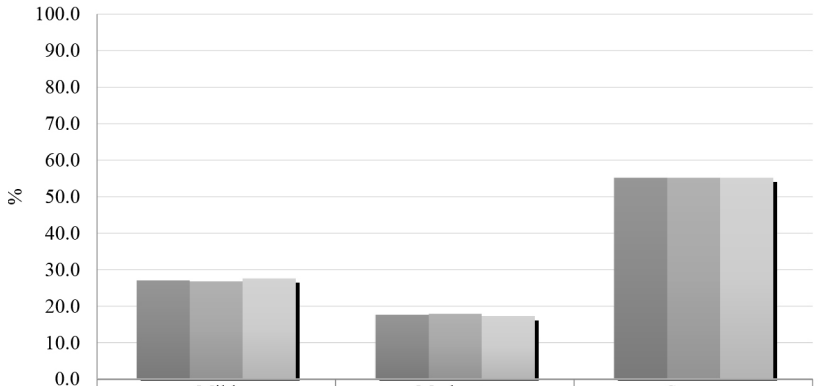
In a relatively large group of patients living with HIV/AIDS receiving HAART, the prevalence of HIV/HAART-associated lipodystrophy assessed exclusively by patient self-report was 52.5%. Most of these patients (55.2%) reported their lipodystrophy as severe, as opposed to mild or moderate. HIV/HAART-associated lipodystrophy was independently associated with female sex, 1-3 years of HIV infection diagnosis and a positive family history of CVD.

No association was found between self-reported HIV/HAART-associated lipodystrophy with traditional modifiable cardiovascular risk factors. In contrast, marked elevation of cardiovascular risk factors in HIV-infected patients with fat redistribution was previously reported by Hadigan *et al.*,[27] Some differences between the two studies need to be discussed. In the study by Hadigan *et al.*,[27] the population was older, had a longer time of HIV infection diagnosis and longer ART exposure. Additionally, and most importantly, the presence of lipodystrophy was determined by examiners rather than self-report. A difference in time course, considering ART prescriptions, between the two studies needs to be highlighted as well. In the last decade efforts have been made to reduce the use of drugs that are more strongly related to lipodystrophy such as stavudine and zidovudine and increase prescriptions of better tolerated drugs,[12] changing the

Table 1 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and associated sociodemographic factors

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	95% CI	
Sex							0.003
Male	142	77.60	67	47.18	1.00		
Female	41	22.40	29	70.73	1.50	1.15 – 1.95	
Age							0.952
19-29 years	35	19.13	18	51.43	1.01	0.67 – 1.52	
30-39 years	61	33.33	32	52.46	1.03	0.73 – 1.46	
40-49 years	59	32.24	30	50.85	1.00		
≥50 years	28	15.30	16	57.14	0.51	0.75 – 1.69	
Skin color							0.598
White	90	49.18	49	54.44	1.07	0.82 – 1.42	
Non-white	93	50.82	47	50.54	1.00		
Schooling (years)							0.808
≤4 years	30	16.39	18	60.00	1.20	0.79 – 1.81	
5-8 years	42	22.95	22	52.38	1.05	0.70 – 1.58	
9-11 years	65	35.52	33	50.77	1.01	0.70 – 1.48	
≥12 years	46	25.14	23	50.00	1.00		
Marital Status							0.434
Single	97	53.01	50	51.55	1.07	0.76 – 1.52	
Married	50	27.32	24	48.00	1.00		
Widowed/Divorced	36	19.67	22	61.11	1.27	0.86 – 1.88	
Monthly income							0.864
1st quartile	59	32.24	31	52.54	1.07	0.74 – 1.55	
2nd quartile	35	19.13	18	51.43	1.05	0.68 – 1.61	
3rd quartile	51	27.87	25	49.02	1.00		
4th quartile	38	20.77	22	57.89	1.18	0.79 – 1.74	

*PR: prevalence ratio; 95% CI: 95% confidence interval. *Wald's Test.*



	Mild	Moderate	Severe
Total	27.1	17.7	55.2
Male	26.9	17.9	55.2
Female	27.6	17.2	55.2

Figure 1 – Distribution of patients with HIV/HAART-associated lipodystrophy by severity levels assessed by self-report (n=96)

lipodystrophy patterns over time.[28,29] Individuals in the study by Hadigan et al.,[27] were assessed in 2000, therefore not subject to this new prescription pattern, while our study was conducted in 2009.

The decision to use a self-report method alone instead of using evaluations performed by healthcare providers or combined methods relied on the fact that body changes related to HIV/HAART-associated lipodystrophy are more likely to be noticed by the patients themselves and their families, then by third parties.[30] This situation is particularly relevant in the HIV/AIDS clinics of Brazil and other developing countries, where the healthcare provided is mainly public, with high staff rotation in different work shifts. Therefore, the patient is rarely followed by the same physician throughout time. Moreover, the self-report method plays an important role in lipodystrophy diagnosing, since it is validated, low-cost for implementation, and widely applicable, especially in low-income countries.[10]

This study shared similarities with other studies regarding HIV/HAART lipodystrophy. The prevalence of HIV/HAART-associated lipodystrophy can range from 9% to 83%,[31] and depends on the criteria adopted for the diagnosis and on the characteristics of the studied population. Studies where lipodystrophy was assessed, either by a self-report method alone or by a combination of self-report method and observer evaluation, found a prevalence ranging from 45.9% to 64.3%,[11,12,32,33] which is similar to the 52.5% found in the present study.

Other similarities in the clinical characteristics of our population compared with other studies on HIV/HAART-associated lipodystrophy were found, such as a higher prevalence of lipodystrophy in females and patients living with HIV for a relatively longer time.[34-37] The higher prevalence of lipodystrophy among women might be explained by the higher body fat percentage in females when compared to males,[38] enabling a more noticeable fat redistribution related to the HAART. Additionally, women may have a better self-perception of body changes[39] than men.

Lipodystrophy prevalence was higher in patients living with HIV for 1 to 3 years. Since there is a dose-response relationship between the time of ART and lipodystrophy,[40] one would expect that the longer the HIV infection time, the higher the prevalence of lipodystrophy. Since the time of diagnosis does not necessarily coincide with treatment initiation, and ART time was not shown to be associated with lipodystrophy prevalence in our analysis, further investigations addressing exclusively the initiation time of ART are necessary.

Our study has some limitations. Despite the fact that lipodystrophy represents a continuum of fat redistribution over time, the study had a cross-sectional design, which allowed this temporal perspective. No control group was used for comparison. Also, no other method for the diagnosis of lipodystrophy was used for comparison with the self-reported method.

This study provides an important contribution to the knowledge of HIV/HAART-associated lipodystrophy identified by patient self-report. To our knowledge, this is the first time that this diagnostic approach was assessed focusing on associations between lipodystrophy and

Table 2 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and HIV-related clinical and laboratorial variables

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	95% CI	
CD4 lymphocyte count							0.564
≤ 350 cells/mm^3	64	36.36	36	56.25	1.09	0.82 – 1.44	
> 350 cells/mm^3	112	63.64	58	51.79	1.00		
Time of HIV infection diagnosis							0.025
< 1 year	31	18.24	11	35.48	1.00		
1 - 3 years	51	30.00	34	66.67	1.88	1.12 – 3.14	
> 3 years	88	51.76	45	51.14	1.44	0.86 – 2.42	
ART time							0.131
< 1 year	58	35.58	25	43.10	1.00		
1 - 3 years	41	25.15	26	63.41	1.88	1.01 – 2.14	
> 3 years	64	39.26	36	56.25	1.31	0.90 – 1.88	
Drug classes							
NRTI							-
Yes	173	100.00	93	53.76		-	
No	0	0.00	0	0.00			
NNRTI							0.436
Yes	133	76.88	69	51.88	1.00		
No	40	23.12	24	60.00	1.16	0.85 – 1.56	
PI							0.799
Yes	47	27.17	26	55.32	1.04	0.77 – 1.41	
No	126	72.83	67	53.17	1.00		

*PR: prevalence ratio; 95% CI: 95% confidence interval; ART: antiretroviral therapy. *Wald's Test. NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor*

traditional cardiovascular risk factors. Future studies using the same methodology in different clinical contexts are necessary to continue developing this accessible, accurate, reproducible and easy-to-implement tool.[10-13]

Conclusion

HIV/HAART-associated lipodystrophy assessed by patient self-report was not associated with traditional modifiable cardiovascular risk factors in HIV/AIDS patients attending an outpatient care center in a capital city of a middle-income country.

Author contributions

Conception and design of the research: Jardim T, Cardoso RC, Silveira EA. Acquisition of data: Cardoso RC, Santos ASAC, Falco MO, Silveira EA. Analysis and interpretation of the data: Jardim T, Cardoso RC, Santos ASAC. Statistical analysis: Santos ASAC, Silveira EA. Obtaining financing: Falco MO, Silveira EA. Writing of the manuscript: Jardim T, Cardoso RC, Santos ASAC, Falco MO, Silveira EA. Critical revision of the manuscript for intellectual content: Jardim T, Cardoso RC, Santos ASAC, Falco MO, Silveira EA.

Table 3 – Prevalence of HIV/HAART-associated lipodystrophy assessed by self-report and cardiovascular risk factors

Variables	Total		Lipodystrophy prevalence				p-value*
	n	%	n	%	PR	CI 95%	
Sedentary lifestyle							0.087
No	105	57.38	61	58.10	1.29	0.96 – 1.74	
Yes	78	42.62	35	44.87	1.00		
Smoking							0.646
No	89	48.63	44	49.44	1.00		
Yes	49	26.78	26	53.06	1.07	0.77 – 1.50	
Former smoker	45	24.59	26	57.78	1.17	0.84 – 1.62	
Family history of CVD							0.002
No	173	96.11	87	50.29	1.00		
Yes	7	3.89	6	85.71	1.70	1.22 – 2.39	
Hypertension							0.230
No	166	90.71	85	51.20	1.00		
Yes	17	17	11	64.71	1.26	0.86 – 1.85	
Diabetes							0.905
No	177	96.72	93	52.54	1.05	0.46 – 2.37	
Yes	6	3.28	3	50.00	1.00		
Dyslipidemia							0.132
No	65	35.52	29	44.62	1.00		
Yes	118	64.48	67	56.78	1.27	0.93 – 1.74	
Waist circumference							0.018
Normal	123	71.93			1.00		
Increased or very increased	48	28.07			1.39	1.06 -1.82	
Overweight							0.306
No	122	71.35	62	50.82	1.00		
Yes	49	28.65	29	59.18	1.16	0.87 – 1.56	

*PR: prevalence ratio; 95% CI: 95% confidence interval. CVD: cardiovascular disease. *Wald's Test.*

Table 4 – Multivariate Poisson's regression analysis of factors associated with HIV/HAART-associated lipodystrophy assessed by self-report

Variables	Lipodystrophy		p-value*
	[a]PR	95% CI	
Sex			0.003
Male	1.00		
Female	1.49	1.15 – 1.95	
Time of HIV infection diagnosis			0.002
< 1 year	1.00		
1 - 3 years	1.83	1.09 – 3.08	
> 3 years	1.39	0.83 – 2.33	
Family history of CVD			<0.001
No	1.00		
Yes	1.62	1.11 – 2.36	

*[a]PR: adjusted prevalence ratio; 95% CI: 95% confidence interval; CVD: cardiovascular disease. *Wald's Test.*

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Rodrigo de Castro Cardoso, from *Universidade Federal de Goiás*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital de Clínicas da Universidade Federal de Goiás* under the protocol number 163/2009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Lipodystrophy Associated with HIV/ART and Cardiovascular Risk Factors

Claudio Leinig Pereira da Cunha

Universidade Federal do Paraná, Paraná, PR – Brazil

Editorial referring to the article: Self-reported HIV/HAART-associated lipodystrophy and modifiable risk factors for cardiovascular disease

Before effective antiretroviral therapy (ART) became available, patients with advanced acquired immunodeficiency syndrome had devastating losses and their metabolic profile was characterized by reduced cholesterol levels. Since introduction of ART, numerous studies have reported changes in body composition with accumulation of central fat and loss of peripheral fat. The term "human immunodeficiency virus (HIV)-associated lipodystrophy syndrome" was then coined, which was soon recognized as several phenotypes that varied from person to person, rather than a unique syndrome. While some individuals had solely lipoatrophy, others had fat accumulation with varied presentation or a mixed condition of the two morphological patterns.[1]

Lipoatrophy involves loss of subcutaneous fat in the face, arms, legs, abdomen, and buttocks. Abdominal fat accumulation is featured mainly by excess visceral fat and consequent increased waist circumference, but also in the dorsal cervical region ("buffalo hump"), trunk, breasts (in both women and men), and lipomas of the upper extremities.[2]

The prevalence of lipodystrophy syndrome is controversial, varying from 10% to 80% of HIV patients.[3] This wide variation may be due to conceptual and methodological issues (e.g. self-reports or objective measures), characteristics of the patients (age, genetics, lifestyle), or treatment (type and duration).[3]

In an interesting study conducted by Jacobson et al.[4] on 452 HIV-infected patients, the prevalence of lipoatrophy, fat accumulation, and a mixed lipodystrophy was 35%, 44% and 14%, respectively. Body fat was measured objectively. Lipoatrophy was defined as a triceps skinfold measurement less than the tenth percentile for sex and age, according to the National Health and Nutrition Examination Survey. Fat accumulation was defined as a waist-to-hip ratio of > 0.95 for men and of > 0.85 for women as a surrogate for intra-abdominal fat.[4]

Several factors may influence the occurrence of different forms of lipodystrophy. Data have suggested that the main risk factor for lipodystrophy is the exposure to nucleoside reverse transcriptase inhibitors (NRTIs), especially stavudine and zidovudine.[5] Other characteristics of the patients and the virus can also affect lipodystrophy phenotypes, such as low fat mass, advanced age, high viral load, and low CD4 counts in the beginning of therapy.[4] Fat accumulation was not associated with any retroviral therapy regimen, and showed a relationship with increasing age and female sex.[2]

Lipodystrophy and fat accumulation have been associated with abnormalities of lipid and glucose metabolism.[6] The development of visceral obesity, insulin resistance and atherogenic lipid profile reinforces the concept of an increased cardiovascular risk in HIV-infected individuals, since these are well-recognized risk factors.[7]

The association between lipodystrophy and metabolic dysfunction can be related to adipokines. Adipokines, such as adiponectin, leptin, and resistin are involved in many metabolic pathways. Patients with HIV infection and lipodystrophy have low adiponectin levels, favoring the development of insulin resistance.[8] Lipoatrophy is also associated with hypoleptinemia, which, in turn, is related to insulin resistance. Lipoatrophy and diabetes mellitus have been observed in HIV patients in ART and attributed to genetic changes in resistin.[9] In patients with HIV and lipodystrophy, the waist-hip ratio was the main indicator of fasting hyperinsulinemia.[10]

Keywords

Lypodystrophy; Retroviridae; HIV-Associated Lypodystrophy Syndrome; Cardiovascular Diseases; Risk Factors.

Mailing Address: Claudio Pereira da Cunha
Rua Olavo Bilac, 181. Postal Code: 80440-040, Curitiba, Paraná, PR - Brazil
E-mail: cpcunha@cardiol.br

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Atherogenic lipid profiles have been associated with changes in body fat in HIV-infected patients.[11] A study on the relationship between regional body fat distribution and lipid levels has shown that the atherogenic profile was more common in HIV patients, particularly in those with increased visceral fat, reduced subcutaneous fat in the legs, increased triglyceride levels and reduced HDL cholesterol levels.[12]

Arterial hypertension seems to be more prevalent in HIV-infected than in HIV-uninfected individuals, especially in HIV patients using ART for at least two years. No specific therapeutic agent has been associated with hypertension.[13]

Individuals with HIV infection have lower rates of smoking compared with the general population (42% vs. 21%).[14] HIV-infected smokers have higher cardiovascular mortality rates, with estimates of 12.3 years of life lost to smoking compared with HIV-infected non-smokers.[14]

The data presented in the study by Jardim et al.15 in the present issue of the International Journal of Cardiovascular Sciences describe well this association between lipodystrophy and HIV/ART. The study presents the prevalence of this syndrome in Brazil and the results indicate that lipodystrophy is not associated with modified cardiovascular risk factors, but rather with female sex, family history of cardiovascular disease and time of HIV infection. The authors did not compare the occurrence of cardiovascular risk factors to that in the general population and did not evaluate the influence of lipodystrophy on the clinical course of these patients. Since data collection was made approximately 10 years ago, it would be useful if these patients were reevaluated to define the influence of lipodystrophy on survival.

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ORIGINAL ARTICLE

Reliability between Cardiovascular Risk Assessment Tools: A Pilot Study

Rodrigo Conill Marasciulo,[1] Ana Maria Nunes de Faria Stamm,[1] Guilherme Thomé Garcia,[1] Antônio Carlos Estima Marasciulo,[2] Ariel Córdova Rosa,[1] Alexandre Augusto de Costa Remor,[1] Cristian Battistella[1]

Universidade Federal de Santa Catarina,[1] Santa Catarina, SC – Brazil.
Hospital Universitário Polydoro Ernani de São Thiago,[2] Florianópolis, SC – Brazil

Abstract

Background: The prevention of cardiovascular disease (CVD) is important in clinical practice due to its high morbidity and mortality. Different guidelines have recommended the use of different cardiovascular risk assessment tools, which may have implications on therapeutic decisions.

Objective: To evaluate the agreement rate between the Framingham risk score (FRS) and the Systematic Coronary Risk Evaluation (SCORE) tool on CVD risk assessment in disease-free subjects.

Methods: Cross-sectional study with a sample of 51 subjects treated at the outpatient clinic of a university hospital in Brazil between January 2014 and January 2015. The FRS and two versions of the European SCORE (SCORE-High and SCORE-Low) were used to assess CVD risk; patients were classified as low/moderate risk (< 20% and <5%, respectively) or high risk (≥ 20% and ≥5%, respectively). The agreement rate was evaluated using kappa statistics, a test for interrater reliability that ranges from -1 to 1, and results above 0.6 represent a high agreement rate.

Results: The FRS classified a higher proportion of subjects as high risk for CVD (35.3% [18/51] vs. 23.5% [12/51] with the SCORE-High and 13.7% [7/51] with SCORE-Low). However, there was a high agreement rate between FRS and SCORE-High (k=0.628). The agreement between FRS and SCORE-Low was poor (k=0.352).

Conclusions: There was a high agreement rate between FRS and SCORE-High in cardiovascular risk assessment in the study sample. (Int J Cardiovasc Sci. 2020; 33(6):618-626)

Keywords: Cardiovascular Diseases/prevention and control; Risk Factors; Mortality; Morbidity; Hypertension; Diabetes; Risk Assessment; Cross-Sectional Studies.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality and cause of 17.1 million deaths worldwide, which corresponds to 45% of deaths for chronic noncommunicable diseases.[1] In Brazil, CVD is responsible for approximately 20% of deaths in people older than 30 years, and in 2015 it represented an estimated total cost of BR 37.1 billion.[2,3]

Therefore, CVD prevention is crucial in clinical practice, and identifying asymptomatic subjects at high risk is essential for an effective prevention.[4,5] To meet this demand, cardiovascular risk assessment tools, and risk scores, including the Framingham risk score (FRS), have been the most widely used worldwide.[6] However, it is known that these tools have limitations and may overestimate the risk in certain populations, which prompted the development of other scores.[7,8] For example, the Systematic Coronary Risk Evaluation (SCORE), created based on the results of 12 European cohort studies, has been recommended since 2003 by the European CVD Prevention Directive.[5] This score estimates the 10-year risk of fatal CVD relying on a model that encompasses countries with high and low incidence of CVDs (SCORE-High and SCORE-Low, respectively).[8]

Mailing Address: Rodrigo Conill Marasciulo
Rua Vento Sul, n: 306. Postal code: 88063-070, Campeche, Florianópolis, Santa Catarina, SC – Brazil.
E-mail: rodrigomarasciulo@gmail.com

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In Brazil, the Brazilian Cardiovascular Prevention Guideline recommends the use of the 2008 FRS, which estimates the 10-year risk of global CVD.[4,7] However, some studies indicate that there may be differences in risk stratification between the FRS and the SCORE, which could lead to different therapeutic approaches for the same patient, especially with regard to beginning treatment with hypolipidemic drugs.[6,9,10]

Given the need to identify asymptomatic subjects at high risk of developing CVD, and effects of using different scores on treatment decision making, the aim of this study was to assess the degree of agreement between the FRS and the SCORE in cardiovascular disease risk stratification of a disease-free population at a teaching hospital.

Methods

Study design

This was a cross-sectional, observational, descriptive and analytical pilot study.

Population and sample

We interviewed 121 patients attending the internal medicine outpatient clinic of a university hospital in Southern Brazil, from January 2014 to January 2015. From this convenience sample, 51 patients of both sexes aged between 40 and 65 years (the widest age range common to both scores), without a diagnosis of CVD met the inclusion criteria. Patients with CVD and patients with incomplete data for risk score application were excluded. The study was approved by the human research ethics committee (project number 1973.8713.8.0000.0121) (Annex IV) and conducted after the consent form was signed (Brazilian National Health Council Resolution 196/96/MS).

Study variables

Using a standard form, trained medical students collected participants' sociodemographic and clinical data by interview and by review of medical records.

The sociodemographic variables were age, gender, self-reported race (white and non-white), per capita family income – self-declared income in Brazilian reais divided by the number of residents of the same household, classified as 'low' and 'high' in relation to the average of the population of the state of Santa Catarina, Brazil, in 2014 (BRL1,245[11]) – and education level, categorized into 'low' (from no education to elementary school) and 'high' (from some high school to college graduate).

The following clinical characteristics were evaluated – presence of systemic arterial hypertension (previous diagnosis and/or use of antihypertensive medication), type 1 and 2 diabetes mellitus (DM) (previous diagnosis and/or treatment), smoking habit ('non-smoker' and 'smoker', i.e., current smokers or those who had stopped smoking less than two years before);[12] and lipid profile – total cholesterol (TC) (mg/dL) and HDL cholesterol (HDL-c) (mg/dL) during the last 12 months (nine of the 51 participants had no recent lipid profile). In addition, weight (kg) and height were determined using an anthropometric scale, and systolic blood pressure (SBP) (mmHg) was measured in the upper limbs after five minutes of rest, in supine position, using an automatic oscillometric sphygmomanometer; the highest measure between both arms was considered for analysis. [13] Body mass index (BMI) was calculated, and a BMI ≥ 25 kg/m²and > 30 kg/m² considered overweight and obesity, respectively.[14]

Application of CVD risk scores

The FRS uses the variables gender, age, SBP, hypertension treatment, smoking habit, DM, HDL-c and TC for calculating the global 10-year CVD risk, using the online calculator available on the Framingham Heart Study website.[15] According to this tool, subjects were classified as having low (<10%), moderate (10-20%) or high risk (> 20%).[6]

The SCORE, in turn, classifies individuals at low (<1%), moderate (≥1% and <5%), and high risk (≥5%) of having fatal CVD in 10 years, using the variables gender, age, SBP, TC, HDL-c and smoking status for its calculation.[5] The SCORE was calculated using the online calculator available on the HeartScore website, and both versions of the SCORE for high- and low-risk European countries were applied to the participants of our study.[16]

For participants with no recent lipid profile, risk calculation was performed using models in which lipid variables are replaced by BMI in both FRS and SCORE (Table 1).

Table 1 – Characteristics of 10-year cardiovascular risk stratification tools

Score	Location/Studies for tool derivation	Age	Sex	Variables	Outcomes	Risk
FRS, total CVD in 10 years: two versions used; FRS w/lipids & FRS by BMI (non-laboratory)	8,491 participants, city of Framingham, Massachusetts, USA, 12 years follow-up	30-74 years	Male & female	Age, sex, SBP, treatment for SAH, TC, HDL-c, DM, smoker, BMI	Risk in 10 years for acute myocardial infarction, coronary insufficiency, angina pectoris, ischemic stroke, hemorrhagic stroke, peripheral arterial occlusive disease, heart failure	0-6% low; 6-20% moderate; ≥ 20% high risk
SCORE, fatal CVD in 10 years; 2 models for countries with high & low incidence of CVD; 2 versions: SCORE with HDL-c & SCORE by IMC (non-laboratory)	205,178 participants of 12 prospective studies in 11 European countries, 2.7 million people/ year of follow-up	40-65 years	Male & female	Age, sex, smoker, SBP, TC, HDL-c, BMI	10-year risk of fatal CVD, including CAD, arrhythmias, heart failure, stroke, aortic aneurysm & PAOD.	≤1% low; 1-5% moderate; 5-10% high risk; ≥10% very high risk

Source: Framingham Heart Study[15], HeartScore®[16], 2016 European Guidelines on cardiovascular disease prevention in clinical practice[5]
FRS: Framingham risk score; CVD: cardiovascular disease; BMI: body mass index; SBP: systolic blood pressure; SAH: systemic arterial hypertension; TC: total cholesterol; HDL-c: HDL cholesterol; DM: diabetes mellitus; PAOD: peripheral arterial occlusive disease; CAD: coronary artery disease

Statistical analysis

Normality of the data was visually verified by analysis of histograms and no specific statistic test was needed for such evaluation. Continuous variables were described as mean and standard deviation, and categorical variables as proportion and absolute frequency. Risk strata were divided into low/moderate risk and high risk for comparison of sociodemographic and clinical variables. The proportion of individuals in each stratum was calculated with a 95% confidence interval (CI). Parametric and non-parametric statistics were used to complement the descriptive analysis and to identify the associations between the variables included in the scores and the high-risk stratum of the different tools studied. Unpaired Student's t test was used for analysis of continuous variables and Chi-square test or Fisher's test, when appropriate, for categorical variables, and a p value <0.05 was considered statistically significant. The agreement rate between risk scores was assessed by kappa statistics, a correlation statistic used to test for interrater reliability. It ranges from -1 to 1 and is interpreted as follows:[17] <0, no level of agreement; 0-0.19, poor agreement; 0.20-0.39, weak agreement; 0.40-0.59, poor agreement; 0.60-0.79, high agreement; 0.80-0.99, almost perfect agreement; 1, perfect agreement. Analyses were performed using IBM's SPSS (Statistical Package for the Social Sciences) version 21.0 and OpenEpi version 3.01.[18]

Results

A total of 51 patients met the inclusion criteria, and Table 2 summarizes the sociodemographic and clinical characteristics of the sample. The proportion of hypertension was similar between genders {female and male [45.5% (15/33) vs. 50% (9/18), p = 0.96]}; however, a higher prevalence of DM was observed in men [44.4% (8/18) vs. 18.2% (6/33), p = 0.057].

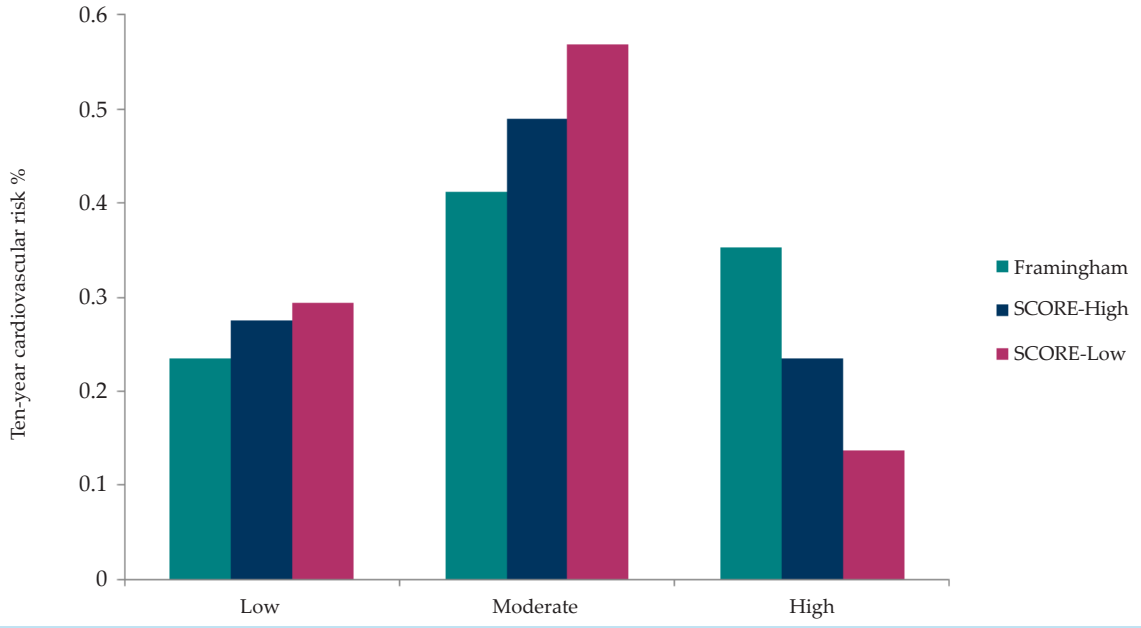
According to the FRS, 35.3% [18/51 (95% CI = 23.15 - 49.07)] of the participants had a high cardiovascular risk, whereas 23.5% [12/51 (95% CI = 13.42 - 36.57)] of the subjects were classified as having a high risk of fatal CVD in 10 years according to the SCORE-High. This value dropped to 13.7% [7/51 (95% CI = 6.21 - 25.27)] when the SCORE for low-risk European countries (SCORE-Low) was used (Graph 1).

A moderate agreement was observed between the FRS and SCORE-Low stratification (K = 0.516); however, when the same analysis was performed comparing the subgroups "low/ moderate risk" vs. "high risk", these two scores showed poor agreement (K = 0.352). On the other hand, there was a high agreement between the FRS and the SCORE-High (K = 0.638), with similar results in the comparisons between the subgroups (K = 0.628). There was an excellent agreement between the two SCORE models (K = 0.807); however, this value

Table 2 – Sociodemographic and clinical characteristics of 51 patients attending the internal medicine outpatient clinic of a university hospital, Florianopolis, Brazil, 2015

Variables	Males (n=18) %[n]	Females (n=33) %[n]	Total (n=51) %[n]
Age	54.0 ± 6.6	52.0 ± 7.3	52.7 ± 7.1
Race			
White	94.4 [17]	90.9 [30]	92.2 [47]
Non-white	5.6 [1]	9.1 [3]	7.8 [4]
Income			
High	22.2 [4]	18.2 [6]	19.6 [10]
Low	72.2 [13]	78.8 [26]	76.5 [39]
Education			
High	27.8 [5]	21.2 [7]	23.5 [12]
Low	72.2 [13]	78.8 [26]	76.5 [39]
SAH			
Yes	50.0 [9]	45.5 [15]	47.1 [24]
No	50.0 [9]	54.5 [18]	52.9 [27]
DM			
Yes	44.4 [8]	18.2 [6]	27.5 [14]
No	55.6 [10]	81.8 [27]	72.5 [37]
Smoker			
Yes	22.2 [4]	12.1 [4]	15.7 [8]
No	77.8 [14]	87.9 [29]	84.3 [43]
Overweight/Obesity			
Yes	77.8 [14]	78.8 [26]	78.4 [40]
No	22.2 [4]	21.2 [7]	21.6 [11]
SBP†‡	143.8 ± 26.0	143.8 ± 25.4	143.8 ± 25.3
Total cholesterol†‡	190.4 ± 51.7	207.1 ± 43.8	201.2 ± 46.8
HDL-c†‡	45.3 ± 13.9	55.5 ± 15.3	51.9 ± 15.5
LDL-c†‡	119.1 ± 40.7	127.8 ± 34.2	124.7 ± 36.4
Triglycerides†‡	126.9 ± 98.0	116.1 ± 62.3	120.0 ± 75.9

Source: Marasciulo, 2018
** Values in square brackets indicate the absolute number of participants; † mean ± standard deviation; ‡ 9 participants had no recent lipid profile; SAH: systemic arterial hypertension; DM: diabetes mellitus; SBP: systolic blood pressure; HDL-c: High density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol*



Graph 1 – Ten-year cardiovascular risk stratification in 51 patients attending the internal medicine outpatient clinic of a university hospital in Florianopolis, Brazil, from January 2014 to January 2015.

decreased when the comparison was made between the low/ moderate risk" vs. "high risk" subgroups, although a high agreement was maintained (K = 0.682).

Most patients in the high-risk category was men, white, hypertensive, non-smokers, overweight or obese in all scores used; there was a higher prevalence of diabetic patients in the FRS compared with the SCORE. In all tools, there was a statistically significant relationship between the high-risk stratum and the variables age and SBP. Participants in this category was older and had higher average SBP compared with individuals at low/moderate risk. In addition, SCORE-High and FRS also showed a significant relationship between the high-risk group and male participants, but only the FRS showed a significant relationship between this group and the presence of DM and SAH (Table 3).

When comparing the distribution of variables in the high-risk stratum of FRS versus the SCORE-High (which showed higher agreement according to kappa statistics), the *p* value ranged from 0.28 to >0.99 (Table 4).

Discussion

The FRS classified a higher proportion of subjects as at high risk for CVD compared with the SCORE (35.3% versus 23.5% by SCORE-High, and 13.7% by SCORE-Low), suggesting the tendency of this score to overestimate the risk in certain populations.[7,8] with possible implications in therapeutic decisions. When assessing the degree of agreement between the 10-year cardiovascular risk stratification using these three tools, a high degree of agreement was observed between the FRS and the SCORE-High, both when comparing the three risk groups (low, moderate and high) and in the two groups "low/ moderate risk" vs. "high risk" (K = 0.638 and K = 0.628, respectively). When FRS was compared with the SCORE-Low, the degree of agreement was moderate (K = 0.516), but the result of the dichotomized (low/ moderate risk vs. high risk) analysis was poor (K = 0.352).

The literature indicates poor to high degree of agreement between FRS and SCORE, and this variation is observed depending on where the comparison was performed and/or on the methodology used.[7, 9, 10, 19, 20]

In a Spanish study, there was poor agreement between the FRS version recommended by the Adult Treatment Panel III (ATP III) and the SCORE-Low,[10, 21] while a research in Germany showed moderate agreement between an older version of the FRS (1991) and both SCORE models (High and Low).[7] In an Iranian study using a different methodology for assessing the degree of agreement, the result was similar (high agreement between FRS vs. SCORE-High) when compared to the present series.[9]

Table 3 - Distribution of variables for cardiovascular disease risk stratification according to the Framingham risk score and the SCORE-High/Low in 51 patients attending the internal medicine outpatient clinic of a university hospital in Florianopolis, Brazil, 2015

	Framingham			SCORE-high			SCORE-low		
Variables	**High risk [n=18]**	**Moderate/ low risk [n=33]**	**p**	**High risk [n=12]**	**Moderate/ low risk [n=39]**	**p**	**High risk [n=7]**	**Moderate/ low risk [n=44]**	**p**
Age†	57.9 ± 4.7	49.9 ± 6.6	.000	58.2 ± 6.2	51 ± 6.5	.002	59 ± 6.8	51.7 ± 6.7	.01
Male sex	61.1 [11]	21.2 [7]	.011	66.7 [8]	25.6 [10]	.015‡	57.1 [4]	31.8 [14]	.226‡
White	100 [18]	87.9 [29]	.284‡	100 [12]	89.7 [35]	.561‡	100 [7]	90.9 [40]	1.0‡
SAH	77.8 [14]	30.3 [10]	.003	66.7 [8]	41.0 [16]	.220	71.4 [5]	43.2 [19]	.232‡
DM	55.6 [10]	12.1 [4]	.002‡	41.7 [5]	23.1 [9]	.272‡	42.9 [3]	25.0 [11]	.376‡
Smoker	11.1 [2]	18.2 [6]	.696‡	25 [3]	12.8 [5]	.372‡	14.3 [1]	15.9 [7]	1.0‡
SBP†	161.2 ± 28.9	134.4 ± 17.4	.002	167.9 ± 32.3	136.5 ± 17.5	.007	174.3 ± 24.9	139.0 ± 22.1	.000
High BMI	94.4 [17]	69.7 [23]	.072‡	91.7 [11]	74.4 [29]	.422‡	100 [7]	75 [33]	.323‡
Total cholesterol†§	204.3 ± 52.8	199.5 ± 44.3	.752	230.6 ± 67.4	192 ± 33.8	.120	248.9 ± 72.4	191.7 ± 34.1	.083
HDL-c†§	47.1 ± 14.2	54.5 ± 15.8	.140	49.5 ± 16.7	52.6 ± 15.3	.582	53.1 ± 18.9	51.7 ± 15.1	.820

Source: Marasciulo, 2018
** Values in square brackets indicate the absolute number of participants; † mean ± standard deviation; ‡ Fisher's test was more appropriate for these analyses; § 9 participants had no recent lipid profile; SAH: systemic arterial hypertension; DM: diabetes mellitus; SBP: systolic blood pressure; BMI: body mass index; HDL-c: HDL cholesterol*

In Brazil, in a population of HIV-positive patients, there was poor to moderate agreement between the models, and poor agreement in women who survived breast cancer. However, no studies comparing the 2008 FRS with the SCORE model was found.[19,20]

Given the findings from this series, in accordance with previous studies,[7,9,10] it can be inferred that we may use both the FRS 2008 and the SCORE-High to stratify cardiovascular risk, without this meaning the need to adopt different therapeutic measures.

The comparison of the FRS' and SCORE-High's high-risk groups (Table 4) corroborates that these two models are similar in terms risk stratification, since there was no statistically significant difference in the distribution of the variables analyzed between the tools, indicating that both groups had a similar composition.

The degree of agreement between SCORE-High and SCORE-Low ranged from excellent (K = 0.807) to high (K = 0.682) – the latter being obtained from the dichotomized risk classification – as these two models were derived from the same cohorts.[8]

It is important to mention that although the FRS and the SCORE assess different cardiovascular outcomes – risk of global CVD and fatal CVD, respectively – we believe that the comparison between both instruments is valid, since they both stratify patients at low, moderate or high risk.[4,6,8] In addition, the equivalence of risk estimates is mentioned in the literature; the values obtained by the SCORE stratification, when multiplied by three for men and by four for women, are equivalent to the FRS stratification.[5,9]

In many European countries, cardiovascular mortality data are easy to obtain, allowing SCORE calculators to be calibrated according to the cardiovascular mortality in each country, regardless of existing cohort studies to validate the risk stratification tools.[8] When comparing the results of the FRS and the SCORE in the studied sample, we observed a risk pattern similar to that of European countries with high cardiovascular risk. Therefore, it is possible to adjust these calculators to the Brazilian population, since there are no calibrated scores for this population so far, despite indicators of cardiovascular mortality comparable to those of countries of the SCORE-High group.[2,22]

Table 4 - Distribution of variables in the high-risk stratum: Framingham risk vs. SCORE-High in patients attending a teaching hospital, Florianopolis, Brazil, 2015

Variables	Framingham [n=18]	SCORE-High [n=12]	p
Age†	57.9 ± 4.7	58.1 ± 6.2	0.62
Sex			
Male	61.1 [11]	66.7 [8]	>0.99‡
Female	38.9 [7]	33.3 [4]	
Race			
White	100 [18]	100 [12]	§
Nonwhite	0.0 [0]	0.0 [0]	
SAH			
Yes	77.8 [14]	66.7 [8]	0.79‡
No	22.2 [4]	33.3 [4]	
DM			
Yes	55.6 [10]	41.7 [5]	0.46
No	44.4 [8]	58.3 [7]	
Smoker			
Yes	11.1 [2]	25 [3]	0.61‡
No	88.9 [16]	75 [9]	
Overweight/Obesity			
Yes	94.4 [17]	91.7 [11]	>0.99‡
No	5.6 [1]	8.3 [1]	
SBP†	161.1 ± 28.8	167.9 ± 32.3	0.6
Total cholesterol†	204.3 ± 52.7//	230.6 ± 69.3¶	0.28
HDL-c†	47.1 ± 14.2//	49.5 ± 16.6¶	0.73

Source: Marasciulo, 2018
** Values in square brackets indicate the absolute number of participants; † mean ± standard deviation; ‡ Fisher's test was more appropriate for these analyses; § could not perform the analysis; // three participants had no recent lipid profile; ¶ two participants had no recent lipid profile; FRS: Framingham risk score; SAH: systemic arterial hypertension; DM: diabetes mellitus; SBP: systolic blood pressure; HDL-c: HDL cholesterol*

However, the comparison of the high risk versus low/moderate risk stratum showed that when using the FRS assessment, a greater number of traditional cardiovascular risk factors had a statistically significant relationship with the high-risk stratum (Table 3). Higher mean age and SBP, and male sex were related to the SCORE-High, and in the FRS, in addition to these variables, hypertension and DM were also present in the high-risk group. This suggests that the FRS is a more appropriate risk stratification score to the population studied, since a statistically significant relationship was indeed expected between the traditional cardiovascular risk variables (age, male sex, hypertension, DM, dyslipidemia, and smoking) and the high-risk group.[6] However, this may be a result of the non-inclusion of DM in the SCORE models and also of the sample's low power.

The prevalence of individuals classified as at high cardiovascular risk by both FRS and SCORE was higher in our study (35.3% and 25.3%, respectively) compared to the literature, which reported a prevalence ranging from 1.9 to 15.1%, depending on the instrument used and the group of patients analyzed.[10,19,23] This result can be explained by the characteristics of the sample, composed

of patients attending a tertiary university hospital, which treats patients with more complex needs.[24] In addition, the high prevalence of the cardiovascular risk factors[25-27] – hypertension (47.1%), DM (27.5%) – as well as overweight and obesity (78.5%) which was higher than that observed in the Brazilian (18.9%) and North American (33.8%) populations,[28,29] in the sample may also have influenced this result.

The inclusion of diabetic patients in the study can be considered a limitation, since according to the Brazilian and European guidelines, these patients are already considered at high cardiovascular risk.[4,5] The main objective of this study, however, was to compare other risk stratification models than those proposed by the guidelines; this motivated the inclusion of diabetic participants, since the FRS includes diabetes in its regression model, although the SCORE does not consider this variable (as this information was not consistently collected in the cohorts used in its development).[6,8] In addition, the sample size and composition can be seen as limitations, as a small number of participants and the convenience sampling make it difficult to extrapolate these results to the general population.

Considering the characteristics of the cardiovascular risk assessment tools studied, we understand the repercussions of the use of these tools in clinical practice. On the other hand, further studies are needed to validate cardiovascular risk scores in the Brazilian population.

Conclusion

In the study population, a higher number of patients were classified in the high cardiovascular risk group according to the FRS compared with European models. However, there was a high agreement between the FRS and the SCORE-high regarding risk stratification, although the agreement between the FRS and the SCORE-low ranged from moderate to poor.

Author contributions

Conception and design of the research: Marasciulo RC, Stamm AMNF, Garcia GT, Rosa AC, Marasciulo AC. Acquisition of data: Marasciulo RC, Garcia GT, Rosa AC, Remor AAC, Battistella C. Analysis and interpretation of the data: Marasciulo RC, Marasciulo AC, Stamm AMNF. Statistical analysis: Marasciulo RC, Marasciulo AC. Obtaining financing: None. Writing of the manuscript: Marasciulo RC, Stamm AMNF. Critical revision of the manuscript for intellectual content: Marasciulo RC, Stamm AMNF.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the UFSC under the protocol number CAAE 1973.8713.8.0000.0121. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

What is the best Cardiovascular Risk Score for the Brazilian Population?

Bruno Ferraz de Oliveira Gomes[1,2] and Gláucia Maria Moraes de Oliveira[2]

Rede D'Or São Luiz,[1] Rio de Janeiro, RJ – Brazil.
Universidade Federal do Rio de Janeiro,[2] Rio de Janeiro, RJ – Brazil.

Editorial referring to the article: Reliability between Cardiovascular Risk Assessment Tools: A Pilot Study

Although the cardiovascular disease mortality rates in Brazil still reach high numbers, they have decreased significantly in recent years. In the early 1990s, the country presented approximately 350 deaths per 100 000 inhabitants per year, and the most recently published rates were reduced to just over 200 deaths per 100 000 inhabitants. Mortality rates due to coronary artery disease are higher in men: between 1990 and 2017, the annual mortality rate due to coronary artery disease was approximately 100 deaths per 100 000 inhabitants. Disability-adjusted life years (DALYs) went from more than 6000 years per 100 000 inhabitants in the 1990s to just over 4000 years per 100 000 inhabitants in the past decade.[1]

Strategies for measuring cardiovascular risk have changed clinical practice by promoting effective preventive measures that reduce the occurrence of major cardiovascular events and improve quality of life. Among them, the most commonly used are simple clinical criteria, clinical prediction scores, imaging examinations, and biomarkers. The clinical application of a cardiovascular risk score should be assessed for its ability to affect the therapeutic management and prognosis of individuals. A risk prediction model must be evaluated in several subsequent phases, such as the initial concept, its prospective validation in independent populations, the incremental information provided in relation to the currently available models, the confirmation of its effects in modifying the clinical conduct and prognosis of patients, and its cost-effectiveness.[2]

Keywords

Cardiovascular Diseases/mortality; Risk factors; Demography; Epidemiology; Population Characteristics, Propensity Score; Socioeconomic Factors; Ethnic Groups.

A patient may be allocated in different categories depending on the cardiovascular risk score used, but therapeutic measures should not differ substantially. Therefore, the health care team should discuss which type of patient would benefit the most from the information provided by the risk prediction model. A current line of thought states that patients at intermediate risk need to be reclassified. However, in the primary prevention of cardiovascular disease, intermediate-risk patients already receive the same type of preventive care as high-risk patients.[3]

The Brazilian Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology[4] recommends the Framingham global risk score, which includes a 10-year estimate of coronary and cerebrovascular events, peripheral arterial disease, or heart failure. The guideline also considers that cardiovascular additional risk factors, significant atherosclerosis, or subclinical atherosclerosis should lead to a risk reclassification regardless of the Framingham risk score. The early identification of patients at higher risk could allow for several interventions aimed at reducing the occurrence of cardiovascular events, especially by implementing population measures in a multidisciplinary approach.[4]

The Framingham studies in Massachusetts started at the end of last century and are based on higher cardiovascular mortality rates, with an overestimation of current risk in different populations worldwide, as is the case in Europe and Brazil. Furthermore, this score does not take into account factors that are currently considered relevant, such as body mass index and obesity, ethnicity, socioeconomic factors, family history, presence of comorbidities such as concomitant kidney disease, physical inactivity, and the prevalence of cardiovascular disease among different populations. More recent studies suggested

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. Andar – Sala 6, UFRJ. Postal Code 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com

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adjustments to recalibrate this score, but were not able to sufficiently improve its performance. However, they can better predict the risk for a given continent, such as the Systematic Coronary Risk Evaluation (SCORE) that was designed for the European population. In order to extend the risk prediction, some models are able to estimate 30-year or lifelong risks, but they require validations in different populations.[3]

Marasciulo et al.[5] compared the use of SCORE with the Framingham risk score in a Brazilian population.[5] The SCORE tool used data from more than 250 000 individuals in 12 European countries to predict cardiovascular death in 10 years, with different models for countries with high or low incidence of cardiovascular disease (SCORE-High and SCORE-Low, respectively).[6] The study was conducted at a university hospital with 51 patients aged between 40 and 65 years and without a diagnosis of cardiovascular disease. Most patients had low levels of income and education, and the population presented a high prevalence of hypertension, diabetes, overweight, and dyslipidemia. Framingham, SCORE-High, and SCORE-Low scores were applied to these patients, and a higher proportion of high-risk classifications was observed when using the Framingham score. Finally, the Framingham score showed a good correlation with the SCORE-High but not with the SCORE-Low, suggesting that the SCORE-High may be a good alternative in the Brazilian population.[5]

No risk score has ever been designed for the Brazilian population, leading physicians to use scores that were created using populations with different characteristics. In addition to the traditional risk factors, economic and social factors also interfere with cardiovascular mortality[7], hence scores based on European populations are expected to underestimate the real cardiovascular risk in Brazilian people.

Patients with diabetes are at high cardiovascular risk regardless of the score used.[4] In the study by Marasciulo et al.[5] people with diabetes represented 27.5% of the sample. The Framingham score classified 71.4% of these patients as high-risk. In comparison, the SCORE-High and SCORE-Low identified 35.7% and 21.4% of high-risk patients, respectively; this demonstrated the superiority of the Framingham score in characterizing risk in patients with diabetes.

The small sample size represents an important limitation of the described study, as well as the lack of follow-up for verifying the actual occurrence of cardiovascular events. The identification of the best score to be applied to the Brazilian population must be based on a long-term follow-up that allows the observation of the real rate of occurrence of events. Nevertheless, the study presents an alternative regarding the Framingham risk score that deserves to be further studied in the Brazilian population.

In conclusion, several risk prediction models have independent predictive values, but this criterion is not enough to guarantee clinical utility. An increased prognostic capacity, the prediction of therapy benefits, and clinical efficacy are criteria required when assessing the predictive value of a risk score to be used in the Brazilian population.

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ORIGINAL ARTICLE

Prevalence of Malnutrition and Its Association with Clinical Complications in Hospitalized Cardiac Patients: Retrospective Cohort Study

Natally Gonçalves de Ávila,[1] Juliana Umbelino Carneiro,[1] Fernanda Donner Alves,[1] Izabele Vian da Silveira Corrêa,[2] Juliana Paludo Vallandro[1]

Centro Universitário Ritter dos Reis – Uniritter,[1] Porto Alegre, RS – Brazil
Instituto de Cardiologia – Fundação Universitária de Cardiologia (IC-FUC),[2] Porto Alegre, RS – Brazil

Abstract

Background: Malnutrition can affect the clinical course of hospitalized patients, increasing hospital stay, infections, mortality, and hospital costs. Among heart disease patients, the malnutrition prevalence ranges from 25 to 51.9%.

Objective: To assess the prevalence of malnutrition and its association with clinical complications in cardiac patients admitted to a cardiology hospital.

Method: Retrospective cohort study with patients evaluated within 48 hours of admission to the ward of a referral center for cardiology in Porto Alegre, Brazil. Patients were aged 18 years or older. Malnutrition was assessed by Subjective Global Assessment. Length of hospital stay, transfer to the intensive care unit (ICU), hospital discharge and in-hospital death were collected from medical records. Statistical analysis was performed using the SPSS 22.0 program. Comparisons between groups with and without malnutrition were made by unpaired Student's t-test and chi-square test with adjusted residuals, and multivariate Poisson regression used for analysis of outcomes. The significance level considered was 5%.

Results: We evaluated 130 patients aged 63 ± 13 years, 63% were male, and the most frequent cause of hospitalization was angina (25%). The prevalence of malnutrition was 27% and, after statistical adjustment for age, malnutrition was positively associated with ICU transfer and length of hospital stay longer than seven days.

Conclusion: The prevalence of malnutrition found in this sample was 27% and this nutritional diagnosis was positively associated with ICU transfer and length of hospital stay longer than seven days. (Int J Cardiovasc Sci. 2020; 33(6):629-634)

Keywords: Cardiovascular Diseases/complications; Malnutrition; Patient Care; Mortality; Hospitalization; Cohort Studies.

Introduction

Annually, approximately 17.9 million people die from cardiovascular disease worldwide, representing nearly 31% of global deaths.[1] In cardiac patients, the prevalence of malnutrition varies according to the cause of the disease and the malnutrition screening tool, ranging from 25 to 51.9%.[2] However, no study has been found in the literature over the past 10 years investigating the prevalence of malnutrition and its association with clinical outcomes in stable ischemic heart disease patients.

In hospital practice, impaired nutritional status and malnutrition are possible complications among cardiac patients[3,4] leading to increased morbidity and mortality rates and impact on clinical outcomes.[4,5] Studies have shown that cardiac patients with moderate or severe energy-protein malnutrition have higher mortality risks,[3,6,7] and hospitalization, per se, is an important predictor of nutritional risk.[8]

The assessment of nutritional status of hospitalized cardiac patients is essential to diagnose nutritional

Mailing Address: Juliana Paludo Vallandro
Rua Fernando Abbott, 455/901. Postal Code: 91040-360, Bairro Cristo Redentor, Porto Alegre, RS - Brazil
E-mail: jujupaludo@hotmail.com

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disorders that may be additional risk factors for heart disease.[3,5] Different parameters, such as dietary history, anthropometric measures, biochemical data, clinical history and physical examination, have been used in the nutritional assessment of hospitalized patients,[9,10] and the Subjective Global Assessment (SGA) has been a widely used tool due to its practicality[3,11] and sensitivity in detecting impaired nutritional status.[3,7]

Identifying the nutritional profile of hospitalized cardiac patients is essential to determine the most appropriate dietary treatment and to optimize health professionals' and institutional managers' planning. As malnutrition is an important risk factor for clinical complications, the aim of the present study was to identify the prevalence of malnutrition and its association with the need for intensive care, with death and longer hospital stay in cardiac patients admitted to a referral center for cardiology.

Materials and methods

Study design

It was a retrospective cohort study performed at the Institute of Cardiology - University Foundation of Cardiology (IC - FUC) of Porto Alegre - RS, Brazil. Collection of data referring to the period from May 2016 to September 2017 was made in June and July 2018, following the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE)[12] recommendations. The IC-FUC is a tertiary level hospital specialized in cardiac diseases, that provides emergency, outpatient and inpatient care, with approximately 300 beds, 60% of which for users of the Brazilian Unified Health System and 40% for patients covered by private health insurance and private patients.

Population

The study included hospitalized patients aged 18 years or older, of both genders, whose underlying disease was ischemic heart disease. All patients were prescribed oral diets. Patients on enteral or parenteral nutrition were excluded, since the SGA includes parameters for assessment of oral intake only; patients admitted to the emergency room, to the Intensive Care Unit (ICU) or to the operating room were not included.

Nutritional Status Assessment

Assessment of nutritional status was conducted using the SGA[11] tool, applied by experienced and trained nutritionists of the hospital within 48 hours of admission. The SGA questionnaire contains subjective information obtained by anamnesis and simplified physical examination. The SGA includes taking a history of body weight change (weight loss percentage calculated from patient's usual and current weight), eating habits (changes in food intake in the last two weeks), gastrointestinal symptoms, functional capacity (defined as the ability to walk and perform daily activities) and degree of metabolic stress (classified according to type and stage of the disease).

Subcutaneous tissue loss, muscle mass loss, presence of edema in the ankle, sacral region and ascites were evaluated by physical examination. Then, After the evaluator's subjective evaluation, patients were subjectively classified as being (A) well-nourished, (B) moderately malnourished or (C) severely malnourished.[11]

Variables related to clinical outcomes were obtained from patients' electronic medical records and included length of hospital stay (days), transfer to ICU and in-hospital death.

Statistical analysis

For statistical analysis purposes, SGA categories B and C were grouped in one category, and analysis was made based on two groups: Group 1: well-nourished and Group 2 (categories B and C): malnourished. Furthermore, multivariate analysis with Poisson regression was performed in an adjusted and unadjusted way for the variable age.

The WINPEPI program (version 11.65) was used for sample calculation, based on the prevalence of malnutrition reported in the systematic review by Correia et al.,2 of 25-52% in cardiac patients. Therefore, to estimate the prevalence of malnutrition with an acceptable difference of 0.1 and a significance level of 95%, the number of patients for this study would be from 97 (25%) to 105 (52%). To ensure sampling, 130 patients were included.

The variables collected were compiled into an Excel database and analyzed using the Statistical Package for the Social Science 22.0 (SPSS) software. Continuous variables were expressed as means and standard deviations and categorical variables were described in absolute frequencies and percentage. The Kolmogorov-

Smirnov normality test was performed to assess sample distribution. For comparisons between patients with different nutritional status assessed by SGA, continuous variables were compared by unpaired Student's t-test. Multivariate analysis was also performed with age-adjusted Poisson regression for death, length of hospital stay and need for intensive care. Categorical variables were compared with chi-square test and adjusted residual analysis greater than 1.96 indicated statistical difference. The level of significance adopted was 5%.

Ethical aspects

The research project was submitted and approved by the Research Ethics Committee of the Teaching Unit of IC-FUC (approval number UP 5496.18 and CAAE number 90618818.2.0000.5333). The study was conducted and developed according to the Declaration of Helsinki and CNS Resolution No. 466 of 2012 of the Brazilian Ministry of Health. Considering the retrospective nature of data collection and review of patients' electronic medical records, patient confidentiality was preserved.

Results

Data of 130 patients were analyzed. Mean age of patients was 63 ± 13 years, most of patients was male (n = 82, 63%), and angina was the main cause of hospitalization (n = 33, 25%). The prevalence of malnutrition according to the SGA was 27% (n = 35). Table 1 describes the characteristics of the sample and SGA classification.

Table 2 describes the frequency of the SGA components, and a low frequency of severe malnutrition was found. Most patients were classified as having low metabolic stress (n = 48, 37%). Weight loss in the last 6 months was identified in 15 patients (11%), and reduced food intake in 20 (15%) patients.

Table 3 shows the comparison of well-nourished patients (SGA group A) with patients grouped as SGA B + C (with some degree of malnutrition) for clinical variables and complications at admission. Patients classified as malnourished by SGA were older and had a higher frequency of hospital stay longer than 7 days.

In table 4 consolidates the multivariate analysis by Poisson regression models, adjusted and unadjusted for age. After this adjustment, statistical significance was observed for the variables ICU stay and hospital stay longer than 7 days.

Table 1 – Characteristics of the sample

Variables	N = 130
Age	63 ± 13
- elderly	56 (43.1%)
- adults	74 (56.9%)
Male	82 (63%)
Cause of hospitalization	
- angina	33 (25%)
- AMI	23 (18%)
- surgery	19 (15%)
Length of hospital stay	9 (5 – 14)
Need for intensive care	59 (45%)
In-hospital death	4 (3%)
SGA classification	
- A	95 (73%)
- B	32 (25%)
- C	3 (2%)

Data described as mean and standard deviation, absolute frequency and percentage. SGA: subjective global assessment; ICU: intensive care center; AMI: acute myocardial infarction;

Discussion

The present study found a low prevalence of malnutrition in the sample using SGA. Malnourished patients were older and had longer hospital stays. After age-adjusted multivariate analysis, a positive association of malnutrition with ICU transfer and length of hospital stay was observed.

Corroborating with the present study, findings in the literature indicate that malnutrition is more commonly observed in elderly patients,[8,13,14] where the more advanced the age, the greater the risk of malnutrition. Therefore, for assessment of malnutrition using clinical outcomes, age adjustment was necessary in the multivariate analysis. This research also revealed that 73% of the sample was well-nourished, which can be justified by the fact that most patients with ischemic heart disease are overweight or obese.[15,16] More severe patients and hemodynamically unstable patients were excluded to add data in the literature regarding the prevalence of malnutrition and associated clinical outcomes in patients with stable ischemic heart disease.

Table 2 – Frequency of patients by Subjective Global Assessment (SGA) components presence (n = 130)

SGA Variables	Frequency
Weight loss in the last 6 months	15 (11%)
Weight loss in the last 2 weeks	8 (6%)
Dietary intake change	20 (15%)
Presence of gastrointestinal symptoms	10 (7%)
Functional capacity dysfunction	12 (9%)
Underlying disease:	
- heart disease	67 (51%)
- two or more	22 (17%)
Metabolic stress:	
- low	48 (37%)
- moderate	2 (16%)
- high	5 (4%)
Slight fat loss	12 (9%)
Mild muscle loss	12 (9%)
Mild ankle edema	3 (2%)
Mild sacral edema	2 (1.5%)
Ascites	0 (0%)

SGA: subjective global assessment.

Malnourished patients in this study showed a higher percentage of hospitalization longer than 7 days. In the study of Karst et al.,[17] which evaluated 83 cardiac patients admitted to the ICU, mean hospital stay of malnourished patients was longer than that of well-nourished patients. Kang et al.,[18] evaluated 300 hospitalized patients with different diseases and identified a longer hospitalization time in the malnourished group. In contrast, the study by Veras et al.,[19] performed with 45 surgical patients with various diseases, found no significant difference in the length of hospital stay between well-nourished and malnourished groups according to SGA.

In addition, in-hospital mortality was not associated with malnutrition. However, a positive association of malnutrition with in-hospital mortality in heart failure has already been demonstrated,[20] which is expected for this patient's profile and which differs from ischemic heart disease. In the study by Yamauti et al.,[7] with two groups of cardiac patients, one consisting of several etiologies and the other only with decompensated congestive heart failure, malnutrition prevalence was significantly higher in the heart failure group.

To overcome the limitation that SGA is a method originally validated for surgical patients, we used the scored version of the instrument,[11] which is also validated and allows minimizing possible measurement biases, inherent to any subjective assessment methods. The evaluators were previously trained for its application; however, as it was a retrospective study,

Table 1 – Comparison between well-nourished and malnourished patients according to Subjective Global Assessment

	Well-nourished SGA A (n = 95)	Malnourished SGA B e C (n = 35)	*P value*
Age	60 ± 12	70 ± 13	< 0,001
Male	60 (63%)	22 (63%)	0.975
ICU admission	38 (40%)	21 (60%)	0.115
In-hospital death	1 (1%)	3 (8%)	0.075
Hospital stay > 7 days	50 (53%)	27 (77%)	0.012

Continuous data with normal distribution compared by Student's t-test and described as mean and standard deviation. Categorical data were described as absolute and percentage frequency and compared by chi-square test. SGA: global subjective assessment; ICU: intensive care unit

Table 4 – Multivariate analysis to assess the effect of malnutrition detected by Subjective Global Assessment (B / C classifications) on the study outcomes

Variables	PR (95% CI)	p	Adjusted PR* (95% CI)	p-value
ICU stay	1.48 (1.03 – 2.14)	0.034	1.55 (1.05 – 2.27)	0.026
In-hospital death	8.06 (0.87 – 74.9)	0.067	7.41 (0.49 - 112.4)	0.149
Hospital stay > 7 days	1.47 (1.13 – 1.91)	0.004	1.35 (1.01 – 1.79)	0.040

** Adjusted for age. SGA: subjective global assessment; ICU: intensive care unit; BMI: body mass index; PR: prevalence ratio; CI: confidence interval.*

intra-observer analysis was not possible. In addition, the exclusion of patients using enteral nutritional therapy may have underestimated the prevalence of malnutrition in our sample.

On the other hand, SGA allows for a consistent assessment of hospitalized patients, especially when objective measurements cannot be performed, which justifies its wide use in clinical practice.

Conclusion

The prevalence of malnutrition according to the SGA was 27% in hospitalized ischemic heart disease patients. There was a positive association of malnutrition with hospitalization stay longer than 7 days and referral to the intensive care unit. Studies evaluating body composition in cardiac patients can better elucidate the association of nutritional diagnosis with clinical complications and length of hospital stay.

Author contributions

Conception and design of the research: Ávila NG, Alves FD, Corrêa IVS, Vallandro JP. Acquisition of data: Ávila NG, Carneiro JU, Corrêa IVS, Vallandro JP. Analysis and interpretation of the data: Ávila NG, Alves FD, Corrêa IVS, Vallandro JP. Statistical analysis: Ávila NG, Alves FD, Corrêa IVS, Vallandro JP. Writing of the manuscript: Ávila NG, Carneiro JU, Alves FD, Corrêa IVS, Vallandro JP. Critical revision of the manuscript for intellectual content: Ávila NG, Carneiro JU, Alves FD, Corrêa IVS, Vallandro JP.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Instituto de Cardiologia - Fundação Universitária de Cardiologia* (IC-FUC) under the protocol number 5496.18. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

Hospital Malnutrition, Inflammation, and Cardiovascular Diseases

Camila Weschenfelder[1] and Aline Marcadenti[1,2]

Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia,[1] Rio Grande do Sul, RS - Brazil
Hospital do Coração (Hcor),[2] São Paulo, SP - Brazil

Editorial related to the article: Prevalence of Malnutrition and Its Association with Clinical Complications in Hospitalized Cardiac Patients: Retrospective Cohort Study

Malnutrition in hospitalized patients, whose prevalence ranges between 40% and 60% in Latin America,[1] is related to longer hospital stays, worse clinical outcomes,[2] and increased hospitalization costs.[3] The consequences related to hospital malnutrition have also been reported among patients diagnosed with cardiovascular disease (CVD).[4] In these individuals, an exacerbated inflammatory state is associated with malnutrition, loss of muscle mass, and cardiac cachexia, especially in the more advanced stages of the disease.[5]

Globally, there is a policy that aims to recognize the importance of hospital malnutrition and its consequences.[6] In Brazil, in 2018, the campaign "Say no to malnutrition" was published, composed of 11 steps to combat hospital malnutrition.[7] In this campaign, the first step involves risk stratification and nutritional assessment for subsequent implementation and monitoring of appropriate nutritional therapy.

In a retrospective cohort published by Ávila et al.,[8] 130 cardiac patients admitted to a referral hospital underwent nutritional assessment, among whom, 27% were malnourished. In comparison to well-nourished patients, these individuals were older, needed longer time in the intensive care unit (ICU), and stayed more than 7 days in the hospital – data in accordance with the literature.[2,4] In this study, the prevalence of malnutrition was lower than those reported in the literature among the general population,[1] which may have occurred due to the profile of the evaluated patients, who, for the most part, were classified as low metabolic stress. Patients using enteral and/or parenteral nutritional therapy, and patients admitted to the emergency room, ICU, or undergoing immediate surgery, were not included in the study. Thus, patients who were assessed for nutritional status may not have reflected the population with CVD with a more pronounced and/or severe inflammatory state, underestimating the frequency of malnutrition in this population.

Inflammation plays an important role at the time of nutritional diagnosis. Seeking to standardize the criteria used for the diagnosis of malnutrition, a consensus of the European Society for Enteral and Parenteral Nutrition (ESPEN)[9] proposes the use of the Global Leadership Initiative on Malnutrition (GLIM) tool. This tool includes phenotypic criteria (non-volitional weight loss, low body mass index, and reduced muscle mass) and etiologic criteria (reduced food intake or assimilation, and inflammation or disease burden). However, as this tool includes the measurement of the muscular compartment by validated body composition techniques, which may not be common in clinical practice, due to the necessary protocols or the costs involved, the GLIM tool ends up rarely being used in daily routines.

By contrast, the association between excess weight and CVD is widely recognized.[10] Patients evaluated in this study seem to reflect the population of wards in hospital cardiology units affected by ischemic diseases in milder forms and/or with a lesser degree of inflammation of the disease, for example, angina (25% of the sample evaluated).

Finally, malnutrition is frequent in the hospital environment and needs to be investigated early by nutritionists, especially among patients affected by CVD, whose mortality is high. Adequate nutritional diagnosis

Keywords

Cardiovascular Diseases; Hospitalized Patients; Hospitalization; Nutrition Service Hospitalar/ administration and organization; Cachexia; Desnutrition.

Mailing Address: Camila Weschenfelder
Av. Princesa Isabel, 395. Postal Code: 90040-371, Porto Alegre, RS – Brazil.
E-mail: camilawesche@gmail.com

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and the establishment of adequate nutritional therapy for treatment enable the improvement of the patient's quality of life, as well as a reduction in complications and costs related to hospitalization. The article published by Ávila et al.,[8] demonstrates the importance of the early identification of the nutritional status of hospitalized patients with CVD, for immediate implementation of appropriate nutritional therapy aimed at reducing hospital malnutrition and, therefore, the reduction of associated outcomes, such as ICU and hospital stay.

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ORIGINAL ARTICLE

The Clinical Course of Takotsubo Syndrome Diagnosed According to the InterTAK Criteria

Nelson Henrique Fantin Fundão,[1] Henrique Barbosa Ribeiro,[1,2] Carlos de Magalhães Campos,[1,3] Vinicius Bocchino Seleme,[1] Alexandre de Matos Soeiro,[1] Marcelo Luiz Campos Vieira,[1,3] Wilson Mathias Jr,[1] Ludhmilla Abraão Hajjar,[1,2] Expedito E. Ribeiro,[1,2] Roberto Kalil Filho[1,2]

Universidade de São Paulo - Instituto do Coração,[1] São Paulo, SP – Brazil.
Hospital Sírio-Libanês, São Paulo,[2] SP – Brazil.
Hospital Israelita Albert Einstein,[3] São Paulo, SP – Brazil.

Abstract

Background: There has been an increase in the number of cases of Takotsubo syndrome (TTS) and of scientific publications on the theme over the last years. However, little is known about the status of this disease in Brazilian hospitals.

Objective: To assess mortality and major adverse cardiovascular events (MACE) during hospitalization and follow-up of TTS patients seen in a tertiary hospital in Brazil.

Methods: This was a retrospective, observational study on 48 patients. Clinical data, signs and symptoms, complementary tests, MACE and all-cause mortality were assessed on admission and during follow-up. Kaplan-Meier curves were used for analysis of all-cause mortality and risk for MACE at median follow-up. The 95% confidence interval was also calculated for a significance level of 5%.

Results: Mean age of patients was 71 years (SD±13 years), and most patients were women (n=41; 85.4%). During hospitalization, four patients (8.3%) died and five (10.4%) developed MACE. At median follow-up of 354.5 days (IQR of 81.5-896.5 days), the risk of all-cause mortality and MACE was 11.1% (95% CI= 1.8-20.3%) and 12.7% (95% CI= 3.3-22.3%), respectively.

Conclusion: TTS was associated with high morbidity and mortality rates in a tertiary hospital in Brazil, which were comparable to those observed in acute coronary syndrome. Therefore, the severity of TTS should not be underestimated, and new therapeutic strategies are required. (Int J Cardiovasc Sci. 2020; 33(6):637-647)

Keywords: Acute Coronary Syndrome; Takotsubo Cardiomyopathy; Heart Failure; Shock, Cardiogenic; Ventricular Dysfunction.

Introduction

The term "Takotsubo syndrome" (TTS) emerged in the medical literature in the 1990s, in a Japanese book of medicine, to describe a syndrome of symptoms and electrocardiographic changes suggestive of acute myocardial infarction (AMI), but coronary arteries without significant obstructive lesions.[1,2] The name "takotsubo" comes from the similarity between the cardiac ventriculography in these patients and an old octopus trap used in Japan (in Japanese, "tako" means octopus and "tsubo" means pot/vase).[1,3]

The pathophysiology of TTS is essentially related to an exacerbated activation of sympathetic autonomic nervous system. However, the mechanism by which catecholamine excess triggers myocardial stunning, with a variety of motion segment dysfunction patterns that characterize this syndrome (dysfunctional apical mid-ventricular, basal or focal segments) is unknown.[1]

Despite the significant increase in the number of patients diagnosed with TTS,[4] and publication of international studies on the theme over the last years,[5] little is known about current reality of the disease in Brazil.

Mailing Address: Carlos de Magalhães Campos
Av. Dr. Enéas Carvalho de Aguiar, 44. Postal code: 05403-900, Cerqueira César, São Paulo, SP – Brazil
E-mail: carlosacampos1@gmail.com

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The aim of this registry was to assess mortality and major adverse cardiac events (MACE) – composed of stroke/transient ischemic accident (TIA), myocardial revascularization and cardiac mortality – in-hospital and during follow-up, in patients diagnosed with TTS according to InterTAK diagnostic criteria.

Methods

Since the first description of TTS, no widely accepted criteria for the diagnosis of TTS have been established. The most used criteria are the Mayo Clinic criteria, modified in 2008.[6] According to these criteria, although the presence of coronary obstructive lesion does not rule out the diagnosis of TTS, this information is not clearly defined and described as very rare.[7] However, other publications have evidenced that up to 10-29% of the patients diagnosed with TTS have concomitant obstructive coronary disease.[8-10] Therefore, in attempt to define a new consensus and based on the last available data, a new set of diagnostic criteria (InterTAK criteria) was proposed by experts in TTS in 2018 (Figure 1).[1]

Study Population

This was a retrospective observational study, approved by the institutional ethics committee

International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1. Patients with transient[a] left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or other left ventricular segmental (midventricular, basal, or focal) wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).[b]
2. An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (e.g. subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.[b]
8. Postmenopausal women are predominantly affected.

[a] Ventricular contraction abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured.

[b] Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of Takotsubo syndrome.[1]

Figure 1 – InterTAK diagnostic criteria

(approval number 3.279.964), conducted following best practices in research.

Electronic data of hospital admissions occurring between January 01, 2013 and December 31, 2018 (six year-period; 75,284 admissions) in the Heart Institute of the University of Sao Paulo (InCor – HCFMUSP) were analyzed. The following terms were searched in the electronic charts: "Takotsubo syndrome", "Takotsubo cardiomyopathy", "Broken Heart Syndrome", "Stress-Induced Cardiomyopathy" and "Adrenergic Cardiomyopathy".

One hundred and one patients older than 18 years of age were found in the search. Based on the InterTAK diagnostic criteria, TTS was excluded in 53 individuals, and 48 patients were included in the study. Forty-four patients met all diagnostic criteria (including one patient who developed TTS in the postoperative period of cardiac surgery), and four patients, despite fulfilling all the interTAK criteria in the postoperative of cardiac surgery, did not have an anatomical study of coronary artery for the event (all patients underwent preoperative cineangiography, with no evidence of coronary lesions) (Figure 2).

The InterTAK criteria, similar to previous diagnostic criteria for TTS, do not mention the occurrence of the syndrome in the postoperative period of cardiac surgery,[11] *i.e.*, do not confirm or exclude the diagnosis of TTS such case. However, due to the increasing number of TTS following cardiac surgery reported in the literature,[12-15] we decided to include these patients in the analysis.

Data Collection and Variables Analyzed

Data collection was made by review of electronic medical records of the 48 patients selected. When follow-up data after discharge were not available, patients were contacted by telephone to obtain information about new MACE and mortality.

At admission and during hospitalization, information on previous clinical data, signs and symptoms, complementary tests, MACE, all-cause mortality, length of hospital stay, signs of heart failure, signs of renal failure and new arrhythmias was assessed. In the out-of-hospital follow-up, data on MACE, overall mortality and left ventricular

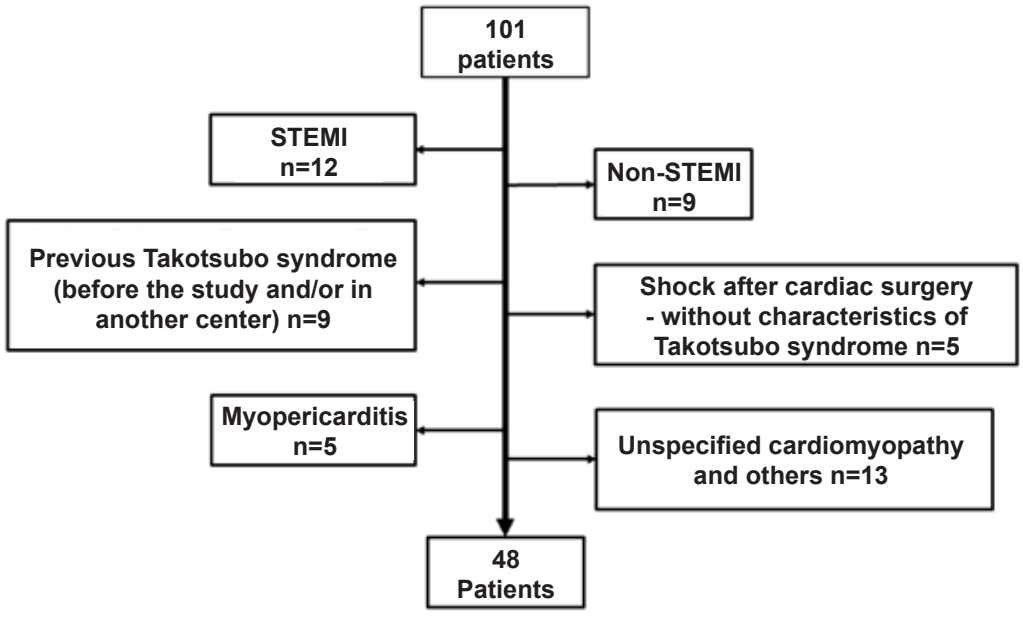

Figure 2 – Study population

ejection fraction values, determined by transthoracic echocardiography, were assessed.

Racial group classifications (white, black or "pardo") were collected from electronic medical records, which are usually filled with self-declared race.

The diagnosis of acute renal failure (ARF) was made based on the 'injury' definition of RIFLE criteria[16], which consider a two-fold increase of serum creatinine from baseline or a decrease of at least 50% in estimated glomerular filtration rate. RIFLE criteria define at least three grades of severity of ARF – 'risk', 'injury' and 'failure' – we adopted the 'injury' definition criteria for a balance between sensitivity and specificity for diagnosis of ARF.

Statistical Analysis

All variables were tested for normality using the Shapiro-Francia test. For continuous variables with normal distribution, mean and standard deviation were calculated, and for variables without a normal distribution, median and interquartile range (IQR) were determined. Categorical variables were expressed as absolute numbers and percentages of total population. Data analysis was performed using the IBM SPSS Statistics software package, version 25.0. The Kaplan-Meier survival curves were analyzed using MEDCALC®, version 19.

Kaplan-Meier survival curves were used to estimate the risk of all-cause mortality, and the risk of MACE was defined in the median follow-up time. A 95% confidence interval (95% CI) was calculated with a significance level of 5%.

Table 1 – Previous clinical characteristics

Age, years (mean ± SD)	**71 ± 13**
Sex, n (%)	
Male	7 (14.6)
Female	41 (85.4)
Race, n (%)	
White	35 (72.9)
Black	3 (6.3)
Pardo	10 (20.8)
Systemic arterial hypertension, n (%)	**34 (70.8)**
Dyslipidemia, n (%)	**16 (33.3)**
Diabetes, n (%)	**7 (14.6)**
Smoking, n (%)	
No	33 (68.8)
Yes	10 (20.8)
Ex-smoker	5 (10.4)
Previous atrial fibrillation, n (%)	**4 (8.3)**
Valvular disease, n (%)	**8 (16.7)**
Rheumatologic/Autoimmune disease, n (%)	**9 (18.8)**
Oncologic disease, n (%)	**6 (12.5)**
Previous stroke, n (%)	**2 (4.2)**
Previous CAD, n (%)	**7 (14.6)**
Previous heart failure, n (%)	**8 (16.7)**
Chronic kidney disease, n (%)	**7 (14.6)**
Previous pulmonary disease, n (%)	**10 (20.8)**
Family history of early CAD, n (%)	**6 (12.5)**
Total, n (%)	**48 (100)**

CAD: coronary artery disease

Results

Table 1 describes the clinical features of patients at admission. Most patients were women (85.4%); 70.8% had systemic arterial hypertension and 14.6% were diabetic.

Most of the cases (75%) manifested with chest pain on presentation, mainly chest pain with anginal characteristics - 47.9% of the study population (Table 2). Regarding the triggering factor, there is a preponderance of physical causes (such as bronchospasm, neoplasia under treatment, surgeries and other concomitant diseases), corresponding to 47.9% of individuals included in the registry.

Regarding complementary tests (Table 2), what draws attention is that almost all patients (97.9%) had electrocardiographic changes, mainly T-wave inversion (47.9% of the cases). Cineangiography was available during the TTS event for most patients (91.7%), except for four patients (8.3%) who underwent valve replacement surgery and had undergone the test prior to the surgery, and had no evidence of coronary obstructive lesions. In most of TTS patients, there was involvement of the left ventricular apex (87.5%), which is in agreement with the typical presentation of the disease, where apical dysfunction is predominant.

In addition, 10.4% of patients had left ventricular outflow tract obstruction, which increases the severity of the disease due to the increase in the incidence of hypotension and cardiogenic shock.[17,18]

Table 2 – Clinical presentation and complementary tests

Clinical manifestations	
Chest pain, n (%)	**36 (75)**
Atypical pain	23 (47.9)
Typical pain	13 (27.1)
Dyspnea, n (%)	**10 (20.8)**
Syncope, n (%)	**2 (4.2)**
Triggering factors, n (%)	
Physical triggers	23 (47.9)
Psychological triggers	15 (31.3)
Not reported	10 (20.8)
Heart rate, Mean ± SD	82.16±17.7
Systolic blood pressure, median (IQR)	121.5 (110-139.2)
Complementary tests	
Electrocardiographic changes, n (%)	
ST-elevation	**18 (37.5)**
Anterior wall	13 (27.1)
Lateral wall	9 (18.8)
Inferior wall	4 (8.3)
ST-depression	**4 (8.3)**
T-wave inversion	**23 (47.9)**
Nonspecific changes	**5 (10.4)**
Normal	**1 (2.1)**
Cineangiography during the event, n (%)	**44 (91.7)**
Coronary obstructive lesion ≥ 50%	**13 (27)**
Type of Takotsubo cardiomyopathy, n (%)	
Apical	42 (87.5)
Mid-ventricular	2 (4.2)
Basal	0
Focal	4 (8.3)
Echocardiography during the event, n (%)	**41 (85.4)**
LVEF (%), mean ± SD	**42.73±9.3**
Left atrial diameter (mm), mean ± SD	**37.5±5.2**
LV diastolic diameter (mm), mean ± SD Left ventricular systolic diameter (mm), mean ± SD	**47.4±4.3**
Pericardial effusion, n (%)	**32.1±4.8**
Moderate/severe mitral insufficiency, n (%)	**4 (8.3)**
LV outflow tract obstruction, n (%)	**5 (10.4)**
	5 (10.4)
Cardiac nuclear magnetic resonance, n (%)	**18 (37.5)**
Involvement of the right ventricle at Echo or NMRi, n (%)	**2 (4.2)**
LV thrombus on Echo or NMRi, n (%)	**0**
High-sensitivity troponin I* (ng/mL), Median (IQR)	
Baseline	3.41 (1.90-5.78)
Peak	5.38 (3.45-17.44)
CK-MB Mass† (ng/mL), Median (IQR)	
Baseline	11.3 (6.03-20.05)
Peak	16.6 (12.6-26.85)
BNP‡ (pg/mL), Median (IQR)	**1788 (501.5-2478.5)**
Creatinine (mg/dL), Median (IQR)	
Baseline	0.98 (0.77-1.37)
Peak	1.27 (0.89-2.26)

*Reference values: *Troponin I ≤ 0.04 ng/mL / †CK-MB Mass ≤ 4.4 ng/mL / ‡BNP < 100 pg/mL. BNP levels were available for 13 (27%) of the 48 patients included in the study. BNP: brain natriuretic peptide; CKMB: creatine phosphokinase-MB; SD: standard deviation; LVEF: left ventricular ejection fraction; Echo: echocardiogram; IQR: interquartile range; NMRi: nuclear magnetic resonance imaging; LV: left ventricular*

Left Ventricular Function

Figure 3A shows left ventricular circumferential dysfunction, and Figure 3B displays a comparative analysis between left ventricular function on admission and on echocardiographic follow-up (in-hospital or our-of-hospital) (n=30). Almost all patients (96.6%) showed recovery of the LVEF, which makes clear the temporary nature of ventricular dysfunction. In this analysis, only one patient did not show improvement of LVEF, which may be explained by the short time from diagnosis to transthoracic echocardiography (four days), *i.e.*, probably, there was no enough time for recovery of the left ventricular function. This patient progressed to death.

Clinical Course

In-hospital outcomes and medications are described in Table 3. A significant proportion of patients (41.7%) developed heart failure during hospitalization, which is the main complication of TTS.[19] High in-hospital mortality (8.3%) and MACE rates (10.4%) were also observed.

Median follow-up was 354.5 days (IQR = 81.5 – 896.5 days), with an all-cause mortality of 11.1% (95% CI: 1.8-20.3%), and prevalence of MACE of 12.7% (95% CI> 3.3-22.3%) (Figure 4). Interestingly, all MACE occurred during the first three months of follow-up after the diagnosis.

Discussion

The main findings of this study were: (1) the use of the InterTAK diagnostic criteria helped in the establishment of the correct diagnosis of TTC in 47.5% of the 101 patients enrolled in the study; (2) there is a considerable number of TTS patients with concomitant coronary artery disease (CAD); (3) a normalization of ventricular function was detected by echocardiographic follow-up in almost all patients; and (4) there was a high prevalence of clinical events in short-term follow-up.

With respect to diagnosis, the TTS diagnosis was initially considered for 101 patients and, after application of the InterTAK criteria, the diagnosis was confirmed in 48 patients (47.5%). This finding reinforces that a correct diagnosis of STT is not easy and requires a systematic approach to the diagnostic criteria, which have evolved over the years.

Some years ago, little attention was paid to the possibility of a TTS patient having important coronary

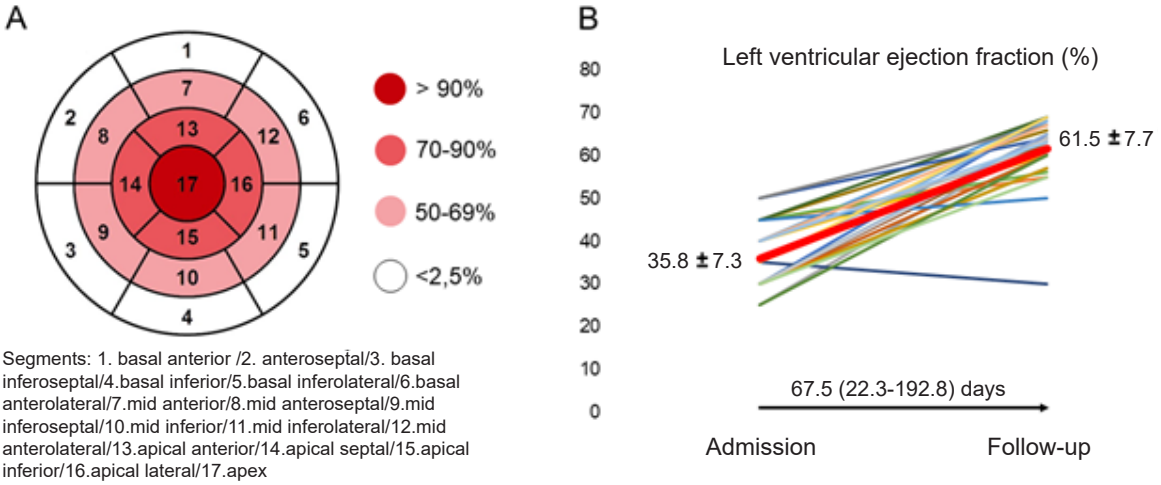

Figure 3 – A. Percentage of patients (n=41) showing an involvement of each of the left ventricular segments on transthoracic echocardiography. B. Left ventricular function of patients who underwent transthoracic echocardiography on admission and during follow-up (n= 30)

Figure 3A. Adapted and modified from Cerqueira et al. (36). Figure 3B. Mean (thick red line) left ventricular ejection fraction ± standard deviation of patients, on admission and follow-up. Median time and interquartile range (days) between the tests above the arrow

Table 3 - Hospitalization data and medications

Length of hospital stay, days, median (IQR)	**5.5 (3.0-12.0)**
Acute renal failure, n (%)	**11 (22.9)**
Acute decompensation of CKD, n (%)	**3 (6.3)**
All-cause in-hospital mortality, n (%)	**4 (8.3)**
In-hospital MACE, n (%)	**5 (10.4)**
Cardiac mortality, n (%)	1 (2.1)
AMI, n (%)	0
Revascularization, n (%)	2 (4.2)
TIA/stroke, n (%)	2 (4.2)
Non-cardiac mortality, n (%)	**3 (6.3)**
Mechanical ventilation requirement, n (%)	**6 (12.5)**
Heart failure, n (%)	**20 (41.7)**
Killip classification, n (%)	
1	28 (58.3)
2	6 (12.5)
3	4 (8.3)
4	10 (20.8)
New arrhythmia, n (%)	**8 (16.7)**
VF/TV, n (%)	2 (4.2)
Atrial fibrillation, n (%)	3 (6.3)
Medications administered	
Acetylsalicylic acid, n (%)	**22 (45.8)**
Clopidogrel, n (%)	**10 (20.8)**
Beta blocker, n (%)	**28 (58.3)**
Statin, n (%)	**31 (64.6)**
ACEI, n (%)	**30 (62.5)**
ARBs, n (%)	**3 (6.3)**
Spironolactone, n (%)	**14 (29.2)**

CKD: chronic kidney disease; MACE: major adverse cardiac events AMI: acute myocardial infarction; TIA: transient ischemic accident (TIA), VF: ventricular fibrillation; AF: atrial fibrillation; ACEI: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; IQR: interquartile range

obstructive disease, which has been corrected by the new criteria proposed (Figure 1). Usually, the association between TTS and CAD is not a cause-effect relationship. Despite the rare cases of TTS patients in whom acute coronary syndrome was the cause of TTS,[20-22] it is believed that, in most cases, the coronary obstructive lesions found in TTS patients are complementary test findings, since the main population affected by the syndrome (postmenopausal women) is also a group with a significant prevalence of CAD.[23] In the present study, in line with the complementary tests' results (Table 2), there was a significant prevalence of patients (27% of the study population) with coronary obstructive lesion ≥50% of vessel lumen diameter. This is in agreement with more recent literature data, showing a prevalence of 10-29% of TTS patients with concomitant obstructive coronary disease[8-10]

Another important issue is the development of electrocardiographic abonrmalities, circumferential dysfunction of ventricular contraction at transthoracic echocardiography, and clinical signs/symptoms (precordial pain and/or hypotension/circulatory shock) in the immediate post-operative period after cardiac surgery. These are possible manifestations of TTS, probably caused by extracorporeal circulation and surgical trauma. In the present study, these patients represented 10.4% of the cases. For the next diagnostic criteria updates, the inclusion of cardiac surgery as trigger for TTS should be considered.

The transient character of left ventricular dysfunction in TTS patients has been consolidated in previous studies and is one of the disease characteristics included in the diagnostic criteria for TTS.[1,6,24-26] This feature was corroborated by our findings of the analysis of ventricular function (Figure 3 B), which supports the correct diagnosis of TTS in our study group.

Regarding morbidity and mortality of TTS, the mortality rate in previous series was lower – in-hospital mortality of 1-2%,[27-28] – which generated an erroneous idea of the benign character of the disease. More recent studies, including a greater number of patients and longer follow-up, have shown much higher mortality rates (in-hospital mortality 4-5%), compatible with the mortality rate of acute coronary syndrome treated according to current recommendations.[8, 29-32]

The largest registry of TTS available, including 1,750 patients, reported an in-hospital mortality rate of 4.1% and overall mortality of up to 5.6% per patient/year and MACE of 9.9% during follow-up.[8] Similar mortality and MACE rates were found in our study, reinforcing the severity of the disease.

Another finding that deserves attention is the fact that the events occurred within three months after the diagnosis of TTS. Since ventricular dysfunction

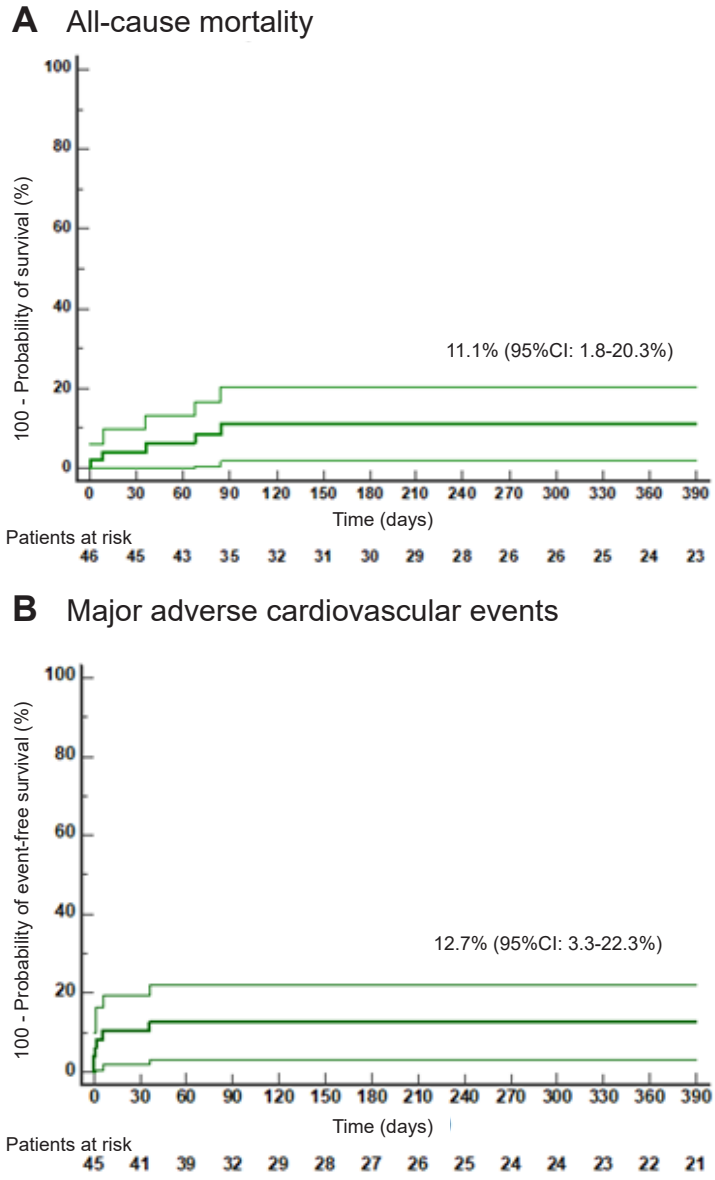

Figure 4 – Kaplan-Meier curves of overall mortality (A) and major adverse cardiovascular events after the diagnosis of Takotsubo syndrome, including both in-hospital and post-discharge events thin lines represent the 95% confidence interval

is potentially reversible in TTS, we may infer that morbidity and mortality of the disease are concentrated in the first months after the event and, if survives the acute phase, with LVEF recovery, the patient will have an excellent prognosis. However, studies with a larger number of patients and longer follow-up have shown that TTS morbidity and mortality are not limited to the first months after diagnosis, and that MACE may occur for years following the first event, at a rate higher than in general population and similar to CAD patients.[8, 29, 33] The different results obtained in our study may be due to the relatively small number of patients (n=48) and shorter follow-up, of approximately one year.

The reasons why patients with diagnosis of TTS have higher morbidity and mortality compared with the general population and similar to CAD patients, even in acute phase, are not fully understood. First, it was thought that the fact that some of TTS patients also have CAD could have caused this bias. This was explored by Tornvall et al.,[29] who compared a group

of patients with TTS and without CAD with further two groups: (a) controls without CAD and TTS; and (b) patients with CAD without TTS. The results were similar to those previously obtained – mortality rate in TTS patients was higher than in controls and similar to the CAD group. Thus, the hypothesis that the concomitance of CAD and TTS would cause higher morbidity and mortality (as compared to healthy controls) became less likely.

Another hypothesis for the high mortality rates after acute phase in TTS patents was based on a population-based study that reported that TTS patients have more comorbidities than patients with previous CAD, including higher rates of past history of stroke/transient ischemic attack, drug abuse, psychiatric disorder, oncologic disease, chronic liver disease and sepsis.[34] Therefore, TTS may be seen as a disorder that often affects already ill patients, with higher morbidity and mortality than the general population.

The treatment of TTS is controversial, and based on clinical experience and experts consensus (level of evidence C), since there are no prospective, randomized clinical trials evaluating therapeutic approaches of these patients.[19] Figure 5 summarizes the main recommendations for treatment of the TTS today. In the present registry, most patients received heart failure medications during hospitalization and after discharge, including beta-blockers (58.3%) and angiotensin converting enzyme inhibitors (62.5%).

One of the key issues in TTS treatment is to determine the presence or absence of left ventricular outflow tract obstruction. The presence of this condition changes the therapeutic approach, including the possibility of using short-acting beta-blockers in patients with cardiogenic shock.[19,35] The detection of left ventricular outflow tract obstruction is usually made by echocardiography or hemodynamic measures during cardiac catheterization.

Limitations

The present study has some limitations that need to be considered. First, the study had a short follow-up period (median 354.5 days) and a small number of patients (n=48) compared with international multicenter registries.[8] This may explain the occurrence of MACE only in the early phase after the diagnosis, as discussed above. Second, not all patients underwent transthoracic echocardiography during the syndrome; 41 (85.4%) underwent the test, and seven were assessed by other methods – three underwent ventriculography during cardiac catheterization and cardiac magnetic resonance; three underwent ventriculography only; and one underwent cardiac magnetic resonance only.[36] The transthoracic echocardiographic follow-up allows the comparative assessment of ventricular function and of the segments involved, contributing to a better understanding of the syndrome. Also, the test enables the appropriate detection of left ventricular outflow tract obstruction, which is a key point in the TTS treatment. However, despite these limitations, this is the largest registry on the theme conducted in Brazil.

Conclusion

The present study evidenced the high morbidity and mortality of TTS, diagnosed according to the new InterTAK criteria, in a tertiary center in Brazil, especially during hospitalization and within 90 days after the diagnosis. Based on these findings, further research is urgently needed, mainly to establish the most appropriate therapy for this population.

Author Contributions

Conception and design of the research: Fundão NHF, Ribeiro HB, Campos CM. Acquisition of data: Fundão NHF, Seleme VB, Soeiro AM, Vieira MLC, Mathias W, Ribeiro EE. Analysis and interpretation of the data: Fundão NHF, Ribeiro HB, Campos CM. Statistical analysis: Campos CM. Writing of the manuscript: Fundão NHF, Ribeiro HB, Campos CM. Critical revision of the manuscript for intellectual content: Hajjar LA, Filho RK.

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.

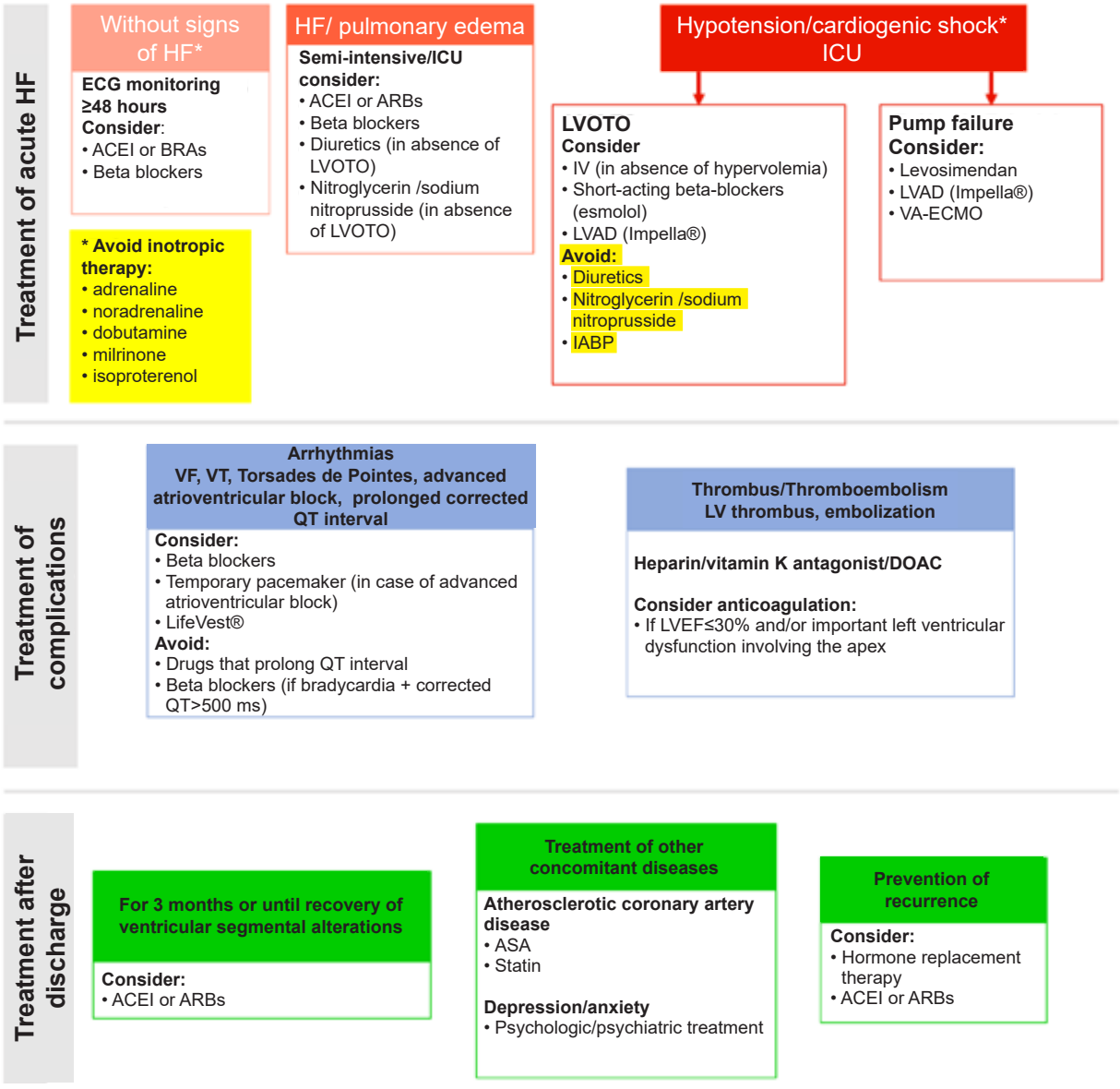

Figure 5 – Current treatment options in Takotsubo syndrome
ACEI: angiotensin converting enzyme inhibitors; ASA: acetylsalicylic acid; AV: atrioventricular; IABP: intra-aortic balloon pump; ARBs: angiotensin II receptor blockers; DOAC: Direct Oral Anticoagulant; ECG: Electrocardiogram; ICU: intensive care unit; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; VF: ventricular fibrillation; IV: intravenous therapy; HF: heart failure; LVOTO: Left Ventricular Outflow Tract Obstruction; LVAD: Left Ventricular Assist Device;; VT: ventricular tachycardia; VA-ECMO: venoarterial extracorporeal membrane oxygenation
Modified and adapted from Ghadri et al.(19)

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - USP* under the protocol number 3.279.964. All procedures in this study were in accordance with the Helsinki Declaration of 1975, updated in 2013. No consent form was obtained from the study participants, as it was a retrospective study, only with the collection of secondary data obtained from the analysis of material already collected and review of medical records and without new clinical interventions, the ethics committee waived the need to obtain a free and informed consent form.

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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

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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).

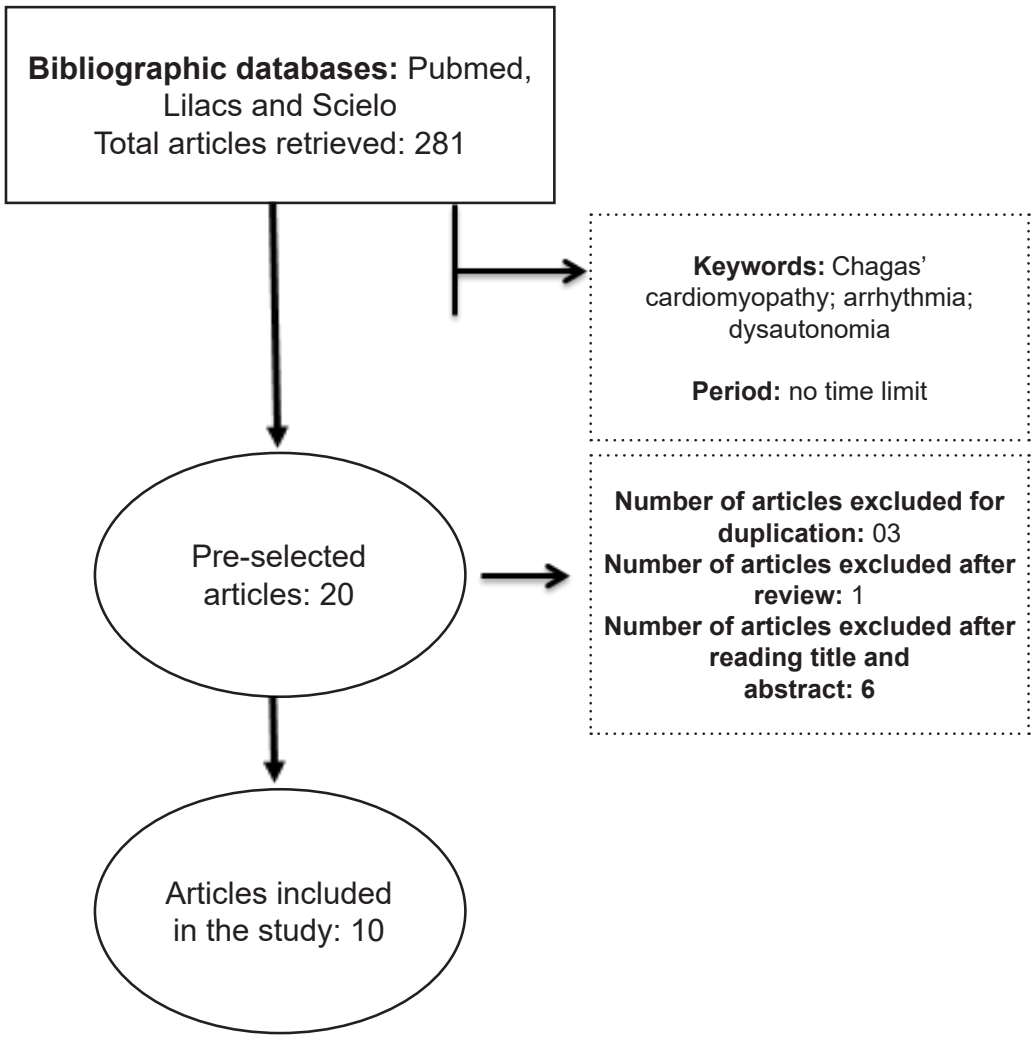

Figure 1 – Selection process of the studies in the systematic mapping of the literature.

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.

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Study Association

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Ethics approval and consent to participate

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

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ORIGINAL ARTICLE

Mortality Trends from Cardiovascular Diseases in the State of Bahia, Brazil, between 2000 and 2015

Yana Mendonça Nascimento and Adriana Lopes Latado

Universidade Federal da Bahia - Faculdade de Medicina de Bahia, Salvador, BA – Brazil.

Abstract

Background: Mortality from cardiovascular diseases has reduced in Brazil in recent decades, but this phenomenon is not clear in the northeast region of the country.

Objectives: To describe the mortality trends from cardiovascular disease in Bahia from 2000-2015, in total population and by sex and age groups, and by specific causes (ischemic heart disease, cerebrovascular diseases, rheumatic heart disease and heart failure).

Methods: This was a time series study. Data were obtained from SIM-DATASUS and IBGE, and the 10th revision of the ICD used for disease classification. Mortality rates (per 100,000 inhabitants) were calculated from total cardiovascular disease and specific causes, by sex and age groups. Direct standardization was used to adjust for age, using the population of 2010 as reference. Linear regression models estimated percentage variation. The significance level of 5% was adopted.

Results: In Bahia, crude mortality rates from cardiovascular disease increased in the period; however, after standardization by age, mortality rates became stable for the total and female populations, with a slight reduction for the male population. An increase in mortality rates from cardiovascular disease was found in the elderly groups. For ischemic heart disease, a progressive increase in adjusted mortality rates was observed: 43%, 24% and 29% for the total, male, and female population, respectively. There was a progressive reduction in crude and age-standardized mortality rates from heart failure in all groups, a modest reduction in age-adjusted mortality rates from cerebrovascular diseases, and a slight reduction in age-standardized mortality rate from rheumatic heart disease, especially in the subgroup <40 years.

Conclusions: Mortality from cardiovascular disease in Bahia did not follow the decreasing trend of other Brazilian states, especially in relation to ischemic heart disease, which showed an increase in mortality rates. (Int J Cardiovasc Sci. 2020; 33(6):656-665)

Keywords: Cardiovascular Diseases/mortality; Heart Failure; Rheumatic Fever; Rheumatic; Rheumatic Heart Disease; Myocardial Ischemia; Cerebrovascular Disorders.

Introduction

In Brazil and worldwide, chronic non-communicable diseases are the health problem with the greatest impact on population morbidity and mortality. Cardiovascular diseases are the most frequent causes of death in many countries, accounting for 31.8% of deaths from chronic diseases in Brazil. [1-4]

From 1980 to 2012, there was a progressive decline in mortality rates from ischemic heart disease and cerebrovascular disease for the total population and by sex in Brazil. However, mortality from ischemic heart disease remained stable between 2007 and 2012, differently from the mortality rates from cerebrovascular disease, which maintained the downward trend.[5] Despite these observations, the state of Bahia, as well as the

Mailing Address: Adriana Lopes Latado Braga
Rua Reitor Miguel Calmon, s/n, Postal Code: 40110-100, Canela, Salvador, Bahia - Brazil
E-mail: adrianalatado@cardiol.br

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northeast region of Brazil, showed a tendency of trend of increased mortality from cardiovascular disease in the same period.[6]

Despite the recognition of the relevance of cardiovascular diseases throughout the country and in the northeast region, there are few studies evaluating mortality trends in patients with cardiovascular diseases in the state of Bahia. Bahia is the largest and most populous state in the northeast region[7] and the fourth most populous state of Brazil. Given the above, the present study aims to analyze the mortality trend from cardiovascular diseases in the state of Bahia by specific causes of death, by sex and age and in the total population between 2000 and 2015.

Methods

Design and Data Source

This is an ecological time series study, that analyzed trends in mortality from cardiovascular diseases in the state of Bahia, in the period between 2000 and 2015. Disease data were collected using their specific 10th Revision International Classification of Diseases (ICD 10) codes and analyzed separately or in combination, depending on the disease classification

Data on deaths were obtained from the Mortality Information System (SIM) of DATASUS (SUS Informatics Department), a public domain website,[1] which covers vital statistics of the entire Brazilian population. Data on Bahia's population were obtained from the website of the Brazilian Institute of Geography and Statistics (IBGE)[2], considering census years and population estimates of the analysis period.

For calculation of mortality rates, the total number of deaths by cause of death (numerator) was divided by the total population at risk (denominator) and then multiplied by 100,000 inhabitants (mortality rate/100,000 inhabitants). The calculations were made for the total population of Bahia State, and by sex groups. In addition, rates of mortality from all cardiovascular causes and specific components were calculated, defined as ischemic heart disease, cerebrovascular disease, rheumatic heart disease and heart failure, as described below in "defining diagnostic criteria". Mortality rates were also calculated by the age groups: <40 years, 40-59 years, 60-69 years, 70-79 years and ≥80 years. Data were stored in Excel® spreadsheets for further analysis.

Defining Diagnostic Criteria

1. ICD 10 codes for ischemic heart disease: angina pectoris (I20), acute myocardial infarction (I21), subsequent myocardial infarction (I22), other acute ischemic heart diseases (I24) and chronic ischemic heart disease (I25);
2. ICD 10 codes for cerebrovascular disease: subarachnoid hemorrhage (I60), intracerebral hemorrhage (I61), other nontraumatic intracranial hemorrhages (I62), cerebral infarction (I63), stroke, not specified as hemorrhagic or infarction (I64) and other cerebrovascular diseases (I67);
3. ICD 10 codes for rheumatic heart diseases: acute rheumatic fever with heart involvement (I01, I02), chronic rheumatic heart diseases (I05 to I09); and
4. ICD 10 Codes for heart failure: I50.

Search Variables

1. Death rate from total cardiovascular diseases and from ischemic heart disease, cerebrovascular disease, rheumatic heart disease and heart failure;
2. Cardiovascular disease mortality rate in total, male and female population, and according to age groups for: ischemic heart disease, cerebrovascular disease, rheumatic heart disease and heart failure; and
3. Standardized (age-adjusted) mortality rates for cardiovascular diseases and by specific cause group, for the total population and for male and female populations.

For the purposes of the present study, total cardiovascular disease was defined as the sum of deaths resulting from the four groupings of specific causes of death, as already reported.

Statistical Analysis

Data were presented as mortality rates per 100,000 inhabitants. In addition to crude mortality rates, a method of direct standardization of mortality rates was applied to adjust the results for variations in the age structure of the population in the evaluated period. The population of Bahia in 2010 was used as standard population for the adjustment. Simple linear regression models were used to assess the percentage of variation in mortality rates adjusted for age over the evaluated period, through the *beta* coefficients, and the level of significance adopted was 5%. For this purpose, mortality rate was considered as a dependent variable and the year evaluated as an independent variable. All data and graph analyses were performed using the free "R" software, and the Excel® program.

1 http://www2.datasus.gov.br/DATASUS/index.php?area=0205&id=6937
2 https://www.ibge.gov.br/

Results

In Bahia, the mortality rate from cardiovascular diseases showed a progressive increase from 2000 to 2015, in the total population and in male and female groups (Table 1). For the total population, crude mortality rate from all cardiovascular diseases, considered as the sum of the specific causes described, was 65.85/100,000 inhabitants in 2000, against 87.05/ 100,000 inhabitants in 2015, which represented a relative increase of 32.2%. With regard to the female population, the relative increase was 33.1% (63.37/100,000 inhabitants in 2000, to 84.28/100,000 in 2015), similarly to what was observed for the male population (68.16/100,000 inhabitants in 2000 and 89.89/100,000 inhabitants in 2015, an increase of 31.7%).

Calculation of the age-standardized mortality rate showed that there was no variation in the study period for the total population (77.6/100,000 inhabitants in 2000 and 77.5/100,000 inhabitants in 2015). In the male population, there was a small relative reduction by 5.4%, the rates remained stable between 2000 and 2015 in the female population (Figure 1). Analysis of mortality trends from cardiovascular disease in Bahia's total population by age group showed an increase in the rates in the oldest subgroup (>80 years), with a slight reduction or no variation in the other age groups (Figure 2). The same pattern was observed for mortality from cardiovascular disease in the male population. In the female population, there was a trend towards more stable cardiovascular mortality rates over the period.

Specific Cardiovascular Causes of Mortality

1. Ischemic Heart Disease

In the study period, there was a progressive increase in crude and age-standardized mortality rates from ischemic heart disease. For the total, male and female populations, there was a relative increase by 75.5%, 76.3% and 75.3%, respectively, in the crude rates, and an increase by 43.0%, 24.4% and 29.2%, respectively, for age-standardized mortality (Figure 3). In the analysis

Table 1 – Crude mortality rates (per 100,000 inhabitants) from cardiovascular diseases in total, male and female populations in the state of Bahia, Brazil, from 2000 to 2015

	Total crude mortality rates	Crude mortality rates in men	Crude mortality rates in women
2000	65.85	68.16	63.37
2001	70.01	72.43	67.45
2002	71.66	74.34	68.91
2003	69.74	71.86	67.59
2004	70.19	72.47	67.87
2005	66.68	67.60	65.74
2006	85.25	88.14	82.35
2007	80.47	83.27	77.65
2008	80.00	82.02	77.96
2009	80.76	82.64	78.88
2010	82.34	85.83	78.86
2011	82.78	86.46	79.13
2012	83.92	85.76	82.11
2013	82.25	86.29	78.26
2014	85.18	90.41	80.03
2015	87.05	89.89	84.28

Source: DATASUS and IBGE

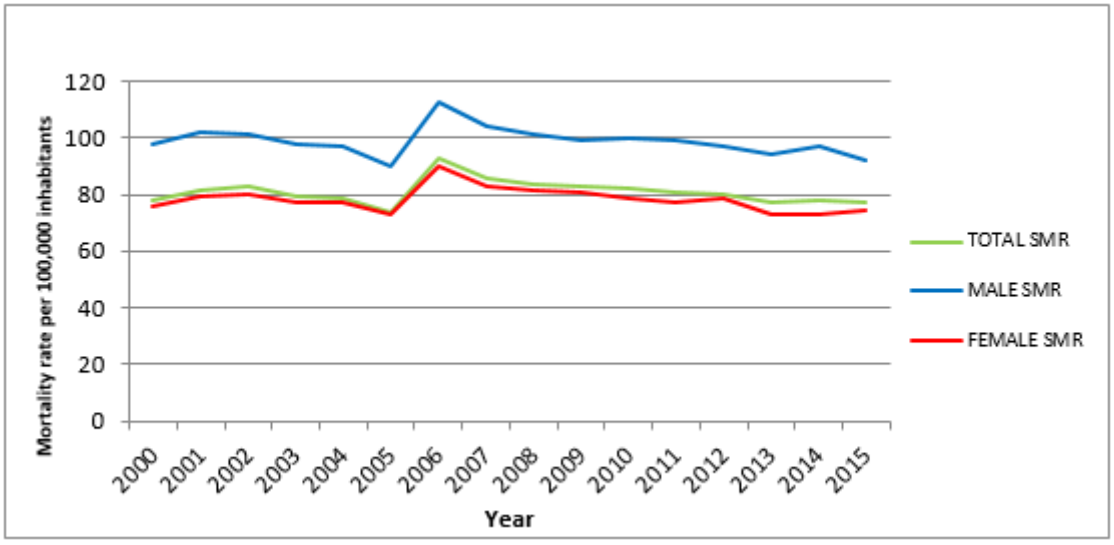

Figure 1– Age-standardized mortality curves from cardiovascular diseases in the population of Bahia, Brazil; SMR: standardized mortality rate
Source: DATASUS and IBGE

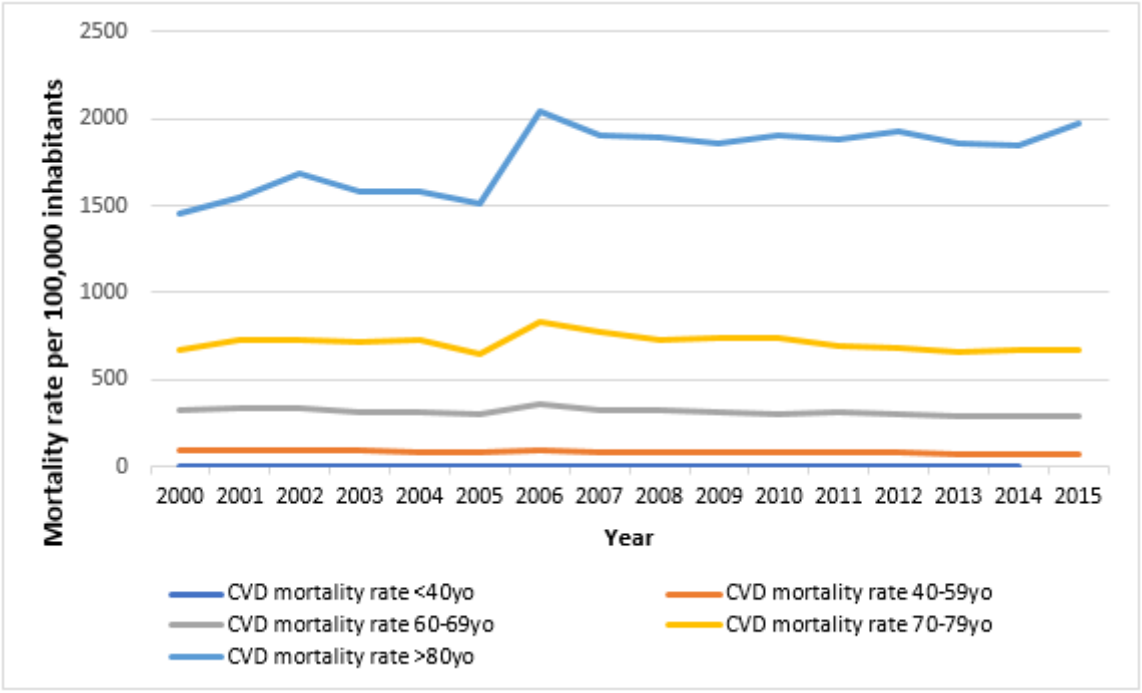

Figure 2 – Mortality curves from cardiovascular disease in the total population of Bahia, Brazil, by age groups
Source: DATASUS and IBGE

by age group, the mortality curves from ischemic heart disease progressively increased for individuals older than 60 years of age, in the total population and by sex. Linear regression models were developed, considering mortality as the outcome variable and the year as an independent variable, which showed an average annual increase in mortality rates of 0.59 (total population), 0.63 (male population) and 0.44 (female population).

2. Heart Failure

There was a progressive reduction in the crude and age-standardized mortality rates from heart failure in total, male and female populations. For the total population, the standardized rate declined from 16.67 to 10.96/100,000 inhabitants between 2000 and 2015, a decrease of 34.2%. The female and male populations showed a similar trend, with reductions of 37% in the period (Figure 4). It was observed that the phenomenon occurred in a more homogeneous way, in the different age groups and for total and female populations. Men over 80 years of age exhibited great variability in the annual rates of heart failure mortality, with even an increase in the values between 2000 and 2015 (387.9 to 446.5/100,000 inhabitants) (Figure 5). There was an average annual reduction in mortality rates for total, male and female populations (0.40; 0.47; 0.43, respectively).

3. Cerebrovascular Disease

For cerebrovascular diseases, there was a relative increase of 25.5% in the crude mortality rates from 2000 to 2015 in the total population. Among males, this increase was of 19.8% and, among females, of 31.2%. A reduction in age-standardized mortality rates was observed, with a fall of 5.2% in total population, 14.8% among men and 2.5% in women (Figure 6). For mortality by age groups, data showed a modest progressive decrease in the rates for all the populations, except for the subgroup over 80 years of age, in which there was an apparent increase in the incidence of deaths from cerebrovascular disease. Ederly women had a higher number of deaths from cerebrovascular disease than men in the same age group.

4. Rheumatic Heart Disease

Regarding rheumatic disease, crude mortality rates remained stable in the period from 2000 to 2015 for the total population, and for the female and male populations. After standardization, it was possible to observe a trend towards a modest but progressive reduction in mortality from 2008 onwards for the total population, for men and women (Figure 7). Considering that the subgroup at the highest risk of dying from rheumatic disease was the youngest, we analyzed the trend of mortality in individuals under 40 years old, and found a downward trend for the total, male and female populations, despite the high variability of the data .

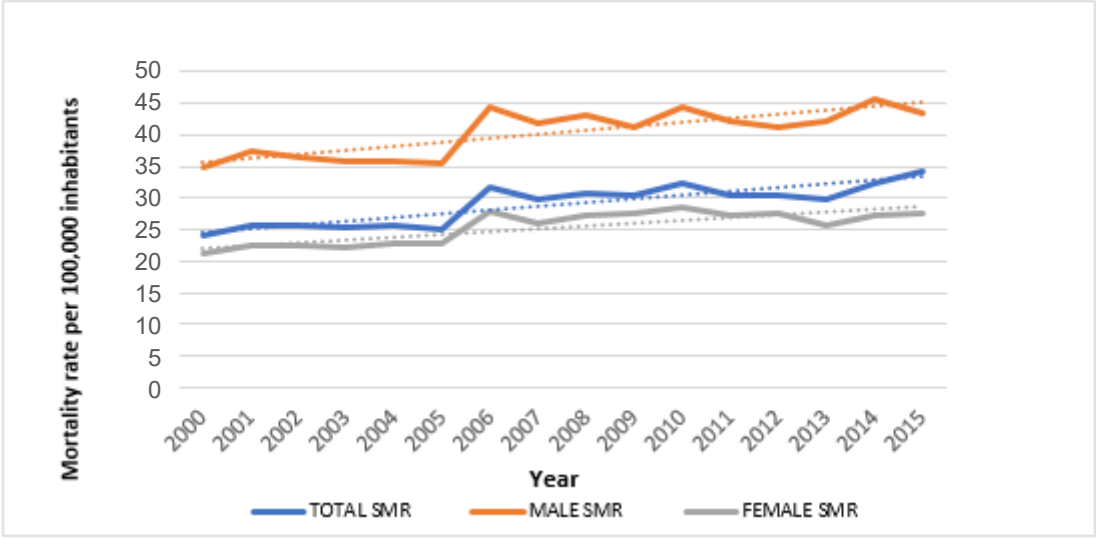

Figure 3 – Age-standardized mortality curves from ischemic heart disease in the population of Bahia, Brazil; SMR: standardized mortality rate
Source: DATASUS and IBGE

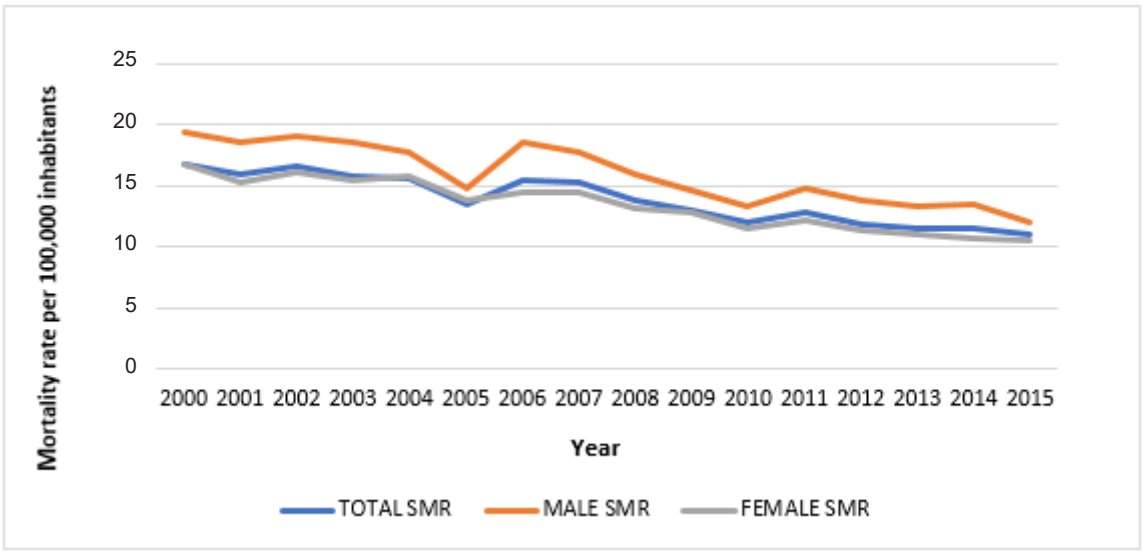

Figure 4 – Age-standardized mortality curves from heart failure in the population of Bahia State, Brazil; SMR: standardized mortality rate
Source: DATASUS and IBGE

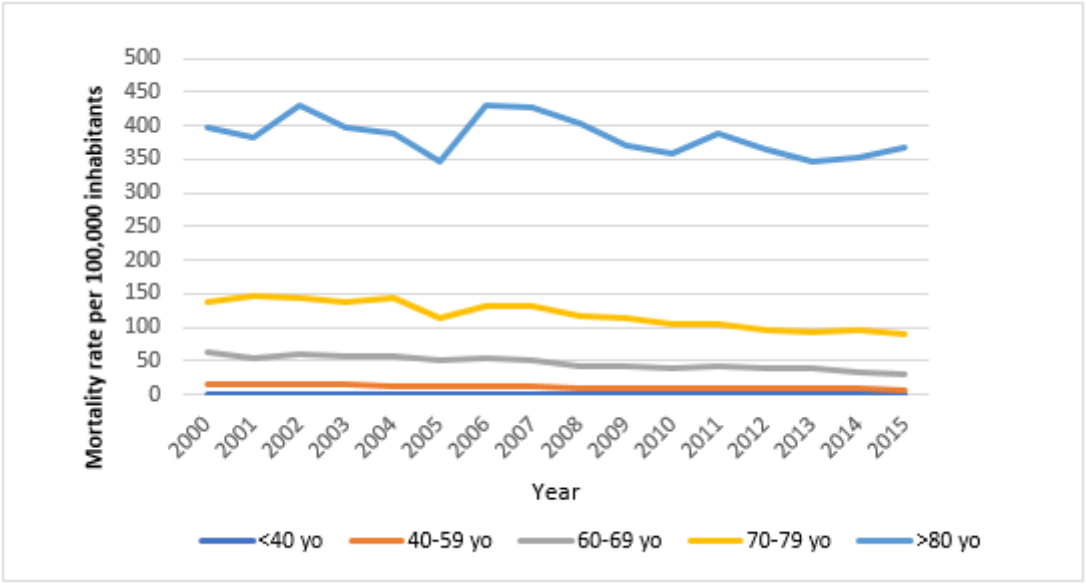

Figure 5 – Mortality curves from heart failure the population in Bahia State, Brazil, by age groups
Source: DATASUS and IBGE

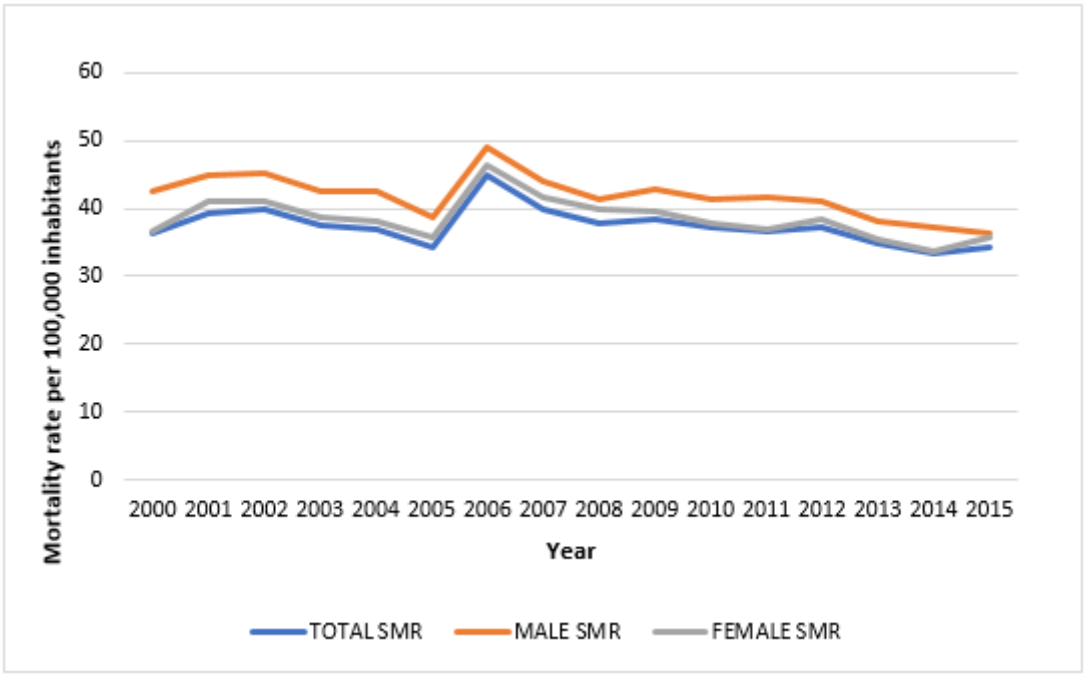

Figure 6 – Age-standardized mortality curves due to cerebrovascular diseases in the population of Bahia, Brazil; SMR: standardized mortality rate
Source: DATASUS and IBGE

Discussion

In the present study, trends in mortality from cardiovascular diseases in Bahia from 2000 and 2015 was described, to call attention to mortality patterns in a large state in the northeast of Brazil that differ from the south and southeast regions of the country. This may be related to socioeconomic and cultural inequalities, recognized in a continental country like Brazil.[8-10] The study showed stable mortality rates from cardiovascular diseases in Bahia, after standardization by age, in total and female populations, with a small tendency for reduction in males, in the evaluated period. Analysis of mortality by age groups showed a trend towards an increase in mortality rates in the very old (over 80 years old) male and female populations.

Studies on cardiovascular disease mortality have demonstrated a decrease in the rates all over the world, especially in developed countries in Europe and North America.[11-13] However, in one of these studies, Roth et al.,[12] assessing the correlation of epidemiological changes, population growth and aging with global mortality from cardiovascular disease in the period from 1990 to 2013, observed regional variations in relation to the studied factors, with a significant reduction in mortality only for the countries located in central or western Europe.

In Brazil, studies with similar methods to the present study showed a reduction in mortality from cardiovascular diseases.[5,8,9] According to Brant et al.,[8] from 1990 to 2015, this decreasing trend was more pronounced in the states of the south and southeast regions and was smaller in the states of the north and northeast regions. Guimarães et al.,[9] and Mansur and Favarato,[10] in studies that evaluated the trends in mortality from cardiovascular disease between 1980 and 2012, observed an increase in the rates only for the northeast region of Brazil. An analysis of the National Health Surveillance System showed a similar trend to that of the northeast region in the state of Bahia between 1996 and 2009.[6]

In relation to specific cardiovascular causes of mortality, there was a progressive increase in the crude and standardized (by age) mortality rates from ischemic heart disease in the period, which was justified by the increase in mortality in the population above 60 years

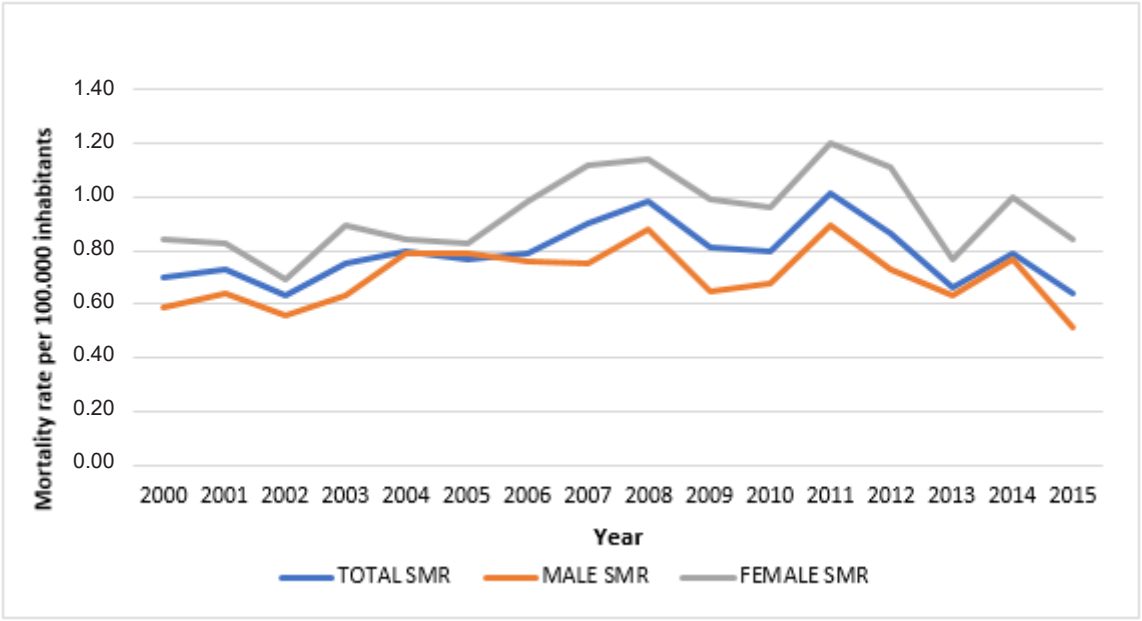

Figure 7 – Age-standardized mortality curves due to rheumatic heart disease in the population of Bahia, Brazil; SMR: standardized mortality rate.
Fonte: DATASUS e IBGE

of age. About heart failure, there was a reduction in crude and standardized mortality rates for the total, male and female populations during the study period. A reduction in standardized mortality rates was observed from cerebrovascular diseases in the total population, and in females and males. Finally, regarding rheumatic heart disease, while the crude mortality rates showed stability, the age-adjusted rates showed a slight decrease, progressive from 2008 on.

Roth et al.,[12] in a study on the main causal factors of the change in mortality between 1990 and 2013, pointed out that ischemic heart disease is the largest cause of death from cardiovascular diseases in several parts of the world. Despite this, they observed a significant decline in the mortality trends from this specific cause in most countries, as well as from cerebrovascular disease, heart failure and rheumatic heart disease. The same study showed a reduction in mortality from rheumatic heart disease worldwide in the period evaluated.[12] On the other hand, in 2014, the annual epidemiological update on cardiovascular diseases of the European Society of Cardiology showed a trend to increase or slight decrease in mortality from ischemic heart disease in some European countries.[13]

Some Brazilian studies have evaluated the patterns of mortality from cardiovascular diseases in different periods and according to different specific causes. Mansur and Favarato,[10] analyzing the mortality from cardiovascular disease in the five Brazilian regions from 1980 to 2012, observed a reduction in mortality rates from ischemic heart disease and cerebrovascular disease in the south and southeast regions, and an increase in these rates in the northeast region, in line with national studies that analyzed regional variations in mortality in the same period and between 1990 and 2015.[8,9] Gaui et al.,[14] in a study that evaluated mortality from two specific cardiovascular diseases between 1996 and 2011, found a decrease in standardized mortality rates from heart failure in all Brazilian regions. Brant et al.,[8] found a significant reduction in mortality rates from rheumatic heart disease between 1990 and 2015.

The increase in mortality from ischemic heart disease in Bahia observed in our study contrasts with other national and international studies. This may be explained by population aging and difficult treatment of several risk factors involved in the pathophysiology of atherosclerosis, such as dyslipidemia, smoking and

diabetes, and consequently more serious or recurrent clinical manifestations of ischemic heart disease.[5] In addition, regional variations in the management of acute ischemic syndromes may have contributed to the increase in mortality in Bahia, since studies revealed that the use of scientific evidence-based therapies in the treatment of patients with acute coronary syndromes seems to be below expectations in the northeast region, as is the case of myocardial reperfusion therapies (fibrinolytic therapy or primary percutaneous coronary intervention) for ST-elevation myocardial infarction.[15,16]

Regarding heart failure mortality observed in Bahia, there was a decreasing trend, which is in accordance with national and international scientific literature and can be justified, at least in part, by the expansion of available therapies proven to be effective in reducing case fatality rates among patients with heart failure, as is the case of beta blockers and renin-angiotensin-aldosterone system inhibitors.[14,17]

The stabilization or slight reduction in mortality rates due to rheumatic heart disease was an expected finding, since, despite the inequalities, there was an improvement in social conditions, and in the access to health care and to penicillin as primary and secondary prophylaxis to rheumatic fever, favoring the prevention of late cardiac complications caused by the disease. [18,19]

The present study has limitations. First, as an analysis of aggregated data, the internal validity of the results depends on the reliability of the databases used in the search. Our sources were DATASUS (Mortality Information Service - SIM) and the IBGE. Mortality information obtained from SIM/DATASUS depends on the accuracy of death certificates, which is directly or indirectly influenced by the access to health services, ability of health units to establish etiological diagnosis, ability of professionals to fill out death declarations correctly, among others. Depending on the city, the reliability of primary and secondary causes of death may vary; errors in diagnosis and the use of signs and symptoms to establish the basic cause of death are more frequently in less-favored areas in terms of health care, which is the case of many locations in the state of Bahia. In addition, using only the primary cause of death as a data source may hide relevant information and cause underestimation in mortality rates due to a specific cause.[5,9,10,20] However, DATASUS is a national reference source of information on mortality. Another limitation is the relatively short duration of the study (15 years); however, during this period, the 10th revision (ICD-10) was the only classification of diseases used in Brazil, preventing potential changes in the percentage of causes of deaths due to a shift in the diagnostic classification.

Despite these limitations, the present article contributes to the knowledge about cardiovascular mortality patterns in the state of Bahia, and provides important information for planning, management and development of health policies and actions.

Conclusion

The present study found that age-standardized mortality rates from cardiovascular disease remained stable in the state of Bahia between the years 2000 and 2015. Regarding specific causes of cardiovascular mortality, in contrast to other causes of death analyzed, there was an increase in the mortality rate from ischemic heart disease in the total population and by sex group, especially in the age groups above 60 years.

Potential Conflict of Interest

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

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Study Association

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Ethics Approval and Consent to Participate

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

Author Contributions

Conception and design of the research: Nascimento YM, Latado AL. Acquisition of data: Nascimento YM, Latado AL. Analysis and interpretation of the data: Nascimento YM, Latado AL. Statistical analysis: Nascimento YM, Latado AL. Writing of the manuscript: Nascimento YM, Latado AL. Critical revision of the manuscript for intellectual content: Latado AL.

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ORIGINAL ARTICLE

Prognosis of Heart Failure with Preserved Ejection Fraction in Primary Care by the H2FPEF Score

Antonio Jose Lagoeiro Jorge, Maria Luiza Garcia Rosa, Wolney de Andrade Martins, Adson Leite, Dayse Mary da Silva Correia, Maria Auxiliadora Nogueira Saad, Humberto Villacorta, Sergio Chermont, Ronaldo Altenburg Gismondi, Breno Macedo Almeida, Evandro Tinoco Mesquita

Universidade Federal Fluminense, Niterói, RJ – Brazil.

Abstract

Background: Primary care physicians have difficulty dealing with patients who have HF with preserved LVEF(HFpEF). The prognosis of HFpEF is poor, and difficult to predict on primary care.

Objective: The aim of the study is to apply the H2FPEF score to primary care patients and verify its power to assess the risk of death or hospitalization due to cardiovascular disease.

Methods: This longitudinal study included 402 individuals, with signs or symptoms of HF, aged≥45 years and, underwent an evaluation which included clinical examination, BNP and echocardiogram. The diagnosis of HFpEF was confirmed by the criteria of the European Society of Cardiology. After five years, the patients were reassessed as to the occurrence of the composite outcome, death from any cause or hospitalization for cardiovascular disease. H2FPEF used six variables: body mass index, medications for hypertension, age, pulmonary artery systolic pressure, atrial fibrillation and E/e' ratio ranged from 0 to 9 points. The level of statistical significance was $p<0.05$.

Results: HFpEF was diagnosed in 58(14.4%). Among patients with H2FPEF≥4, 30% had HFpEF and in those with a score≤4, HFpEF was present in 12%. Patients with HFpEF and H2FPEF≥4 had 53% of outcomes, whereas patients with HFpEF and a score ≤4 had a 21% of outcomes. BNP values were higher in patients with HFpEF compared to those without HFpEF($p<0.0001$).

Conclusion: H2FPEF≥4 indicated a worse prognosis in patients with HFpEF assisted in primary care. H2FPEF may be a simple and useful tool for risk stratification in patients with HFpEF at the primary care. (Int J Cardiovasc Sci. 2020; 33(6):666-672)

Keywords: Heart Failure; Stroke Volume; Risk Assessment; Morbidity; Mortality; H2FPEF Score.

Introduction

After 18 years of the classic pathophysiological characterization of what we currently call "heart failure (HF) with preserved ejection fraction (HFpEF)", its diagnostic criteria remain questionable and evolving.[1] Even with historically different diagnostic criteria, establishing its prevalence and assessing its prognosis is an increasing challenge in primary care. In 2016, the European Society of Cardiology (ESC) established the following as criteria for HFpEF: the presence of signs and or symptoms of HF; left ventricle ejection fraction (LVEF) greater than or equal to 50%; elevation of natriuretic peptides; and the presence of cardiac structural or functional alteration.[2] In general, primary care physicians find it difficult to deal with patients with multiple comorbidities, signs and symptoms of HF and preserved LVEF and, in such cases, easily accessible tools that assist the physician in diagnosis and prognosis can be extremely useful. Recently, a scoring system called the H_2FPEF score[3] was proposed to estimate the diagnostic probability of HFpEF in patients assisted in a specialized HF unit. However, the prognostic utility of this score remains

Mailing Address: Antonio Jose Lagoeiro Jorge
Avenida Marquês do Paraná, 303, 60 andar. Postal Code: 24030-215 ,, Niterói, RJ - Brazil.
E-mail: lagoeiro@globo.com

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unknown in primary care patients. The aim of the present study is to apply the H_2FPEF score to patients in primary care and to verify its predictive power of outcomes.

Methods

Study Design

We carried out a longitudinal study, derived from the DIGITALIS study, whose design has been previously published[4], which included 402 individuals consecutively, aged 45 years or over, enrolled in primary care, in a city of 400,000 inhabitants, in Rio de Janeiro State, Brazil. Initial data were collected from July 2011 to December 2012 and the revaluation took place between January and December 2017, that is, five years later.

Study Population

The selection of the primary care units and the population was performed through random sequence generated by a computer program, where the power of each unit was proportional to the number of individuals assisted. We sent letters to the health staff to invite 1,050 individuals to participate in this study, and 666 of these individuals attended the visit and signed the consent form. Of those, 264 individuals were excluded, 33 individuals who did not complete all of the research procedures, 37 because they had LVEF less than 50% and 194 because they did not present signs or symptoms of HF. The final study population was made up of 402 individuals (Figure 1).

Inclusion criteria were: age ≥45 years, LVEF measured by the Simpson technique ≥50%, signs or symptoms of HF and signing of the informed consent form. Individuals with disabilities to perform the procedures required for evaluation were excluded.

All subjects underwent anamnesis and clinical examination; laboratory tests, including B-type natriuretic peptide (BNP) dosing and tissue Doppler echocardiogram (TDE), all performed in a single visit.

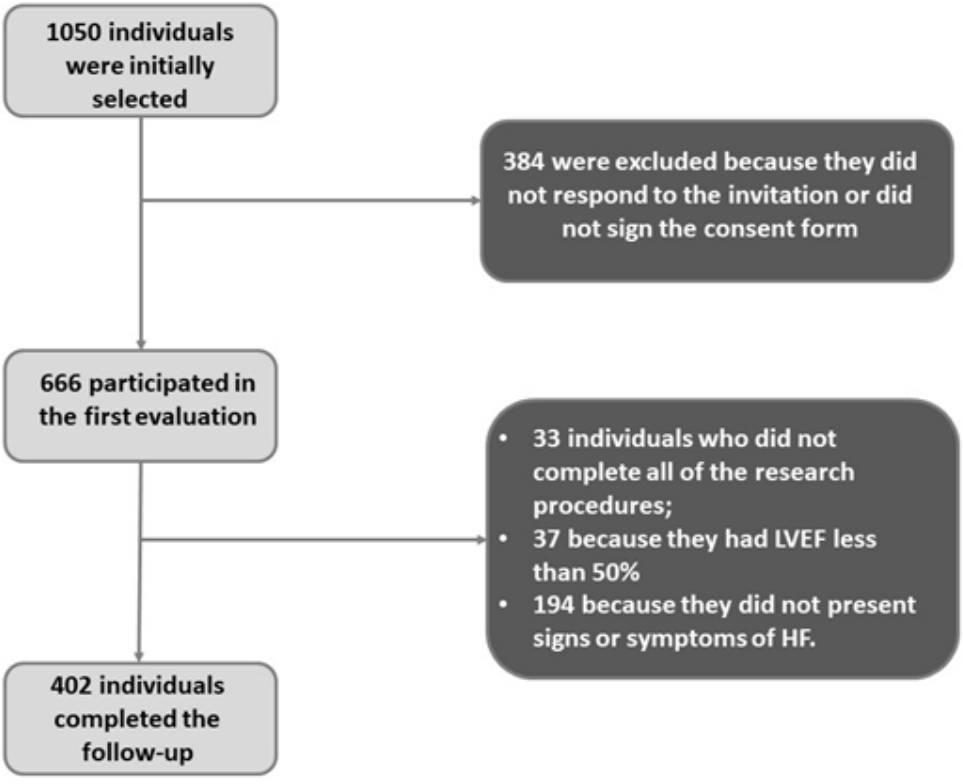

Figure 1 – Population selection flowchart.

The TDE exams were performed by two echocardiographists without previous knowledge of the results of the other tests using two devices: Cypress 20 (Acuson, Siemens, USA) and AU-3 Partner (Esaote, Italy). The examinations were performed according to the recommendations for quantification of chambers of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE)[5].

Outcome Measures

The diagnosis of HFpEF was confirmed in individuals with signs and symptoms of HF, LVEF ≥50%, elevation of BNP, and presence of structural alteration or diastolic dysfunction[2]. This evaluation was performed by two independent cardiologists who were blind to the study.

The H_2FPEF score uses six clinical and echocardiographic variables obtained in the evaluation of patients with HF symptoms. The variables were scored according to the strength of their respective association. The overall score of H_2FPEF ranged from 0 to 9. The variables used and their score were: body mass index >30kg/m^2 (2 points); use of two or more drugs to treat hypertension (1 point); atrial fibrillation (3 points); PASP >35 mmHg (1 point); age >60 years (1 point); and high left ventricular filling pressures, E/e'> 9 (1 point)[3] (Figure 2).

After five years, the patients in this study were reassessed as to the occurrence of the composite outcome: death from any cause or hospitalization for cardiovascular disease, including decompensated HF, coronary artery disease, stroke and vascular diseases.

Statistical Analysis

Statistical analysis was performed with SPSS v 21.0 software (Chicago, Illinois, USA). Continuous variables were expressed as median and interquartile range, as none of them was positive for normality when tested using the Kolmogorov-Smirnov test. Categorical variables were expressed in absolute numbers and/or percentages. For comparison between groups (categorical variables), we used chi-square tests with continuity correction and Fisher's exact test when necessary. The Mann Whitney test was used to verify the existence

	Clinical variable	Values	Points
H2	Heavy	Body mass index >30 kg/m2	2
	Hypertensive	2 or more antihypertensive	1
F	Atrial Fibrillation	Paroxysmal or persistent	3
P	Pulmonary hypertension	Pulmonary Artery Systolic Pressure >35 mmHg (echocardiographic)	1
E	Elder	Age >60 years	1
F	Filling Pressure	E/e' >9 (echocardiographic)	1

Figure 2 – H_2FPEF - score for each characteristic (maximum total of 9 points)[3]

of differences between continuous variables. In all comparisons, bilateral tests were performed and p-values <0.05 were considered statistically significant.

Ethical Considerations

This study was conducted in accordance with the principles set out in the Declaration of Helsinki, revised in 2000 (Scotland 2000). The study protocol was approved by the Institution's Research Ethics Committee under the number 0077.0.258.000-10.

Results

Among the 402 subjects (mean age = 60.2±10.0 years, 71% women) involved in the study, HFpEF was diagnosed in 58 subjects (14.4%) and these patients with HFpEF had a score H_2FPEF 2 (1-4). All the parameters used in the score model were significantly different between patients with and without HFpEF, except for body mass index (BMI) and pulmonary artery systolic pressure (PASP). The anthropometric, clinical and laboratory characteristics are shown in Table 1. Table 2 shows the main echocardiographic parameters.

Among patients with a H_2FPEF score ≥ 4, 30% had HFpEF and among patients with a score ≤ 4, 12% presented HFpEF. BNP values were higher in patients with HFpEF compared to those without HFpEF, regardless of the score obtained in the H_2FPEF. In patients with HFpEF and score ≤3, a lower outcome rate (21%) was observed compared to patients with HFpEF and a score ≥4 (53%), showing that the higher the H_2FPEF score, the greater the risk of death and/or hospitalization due to cardiovascular disease.

After a 5-year follow-up, 42 (10.4%) composite outcomes were observed, with 21% in patients with HFpEF and a score ≤4, and 53% in patients with HFpEF and a score ≥4. In patients without HFpEF, the rate of outcomes was 7% in patients with a score ≤4 and 6% in patients with a score ≥4 (Table 3).

Discussion

This study evaluates the H_2FPEF score in patients in primary care. Our data show that patients with HFpEF and a H_2FPEF score ≥4 are at increased risk of death from any cause or hospitalization for cardiovascular disease.

A secondary analysis of the TOPCAT study evaluated the association between the probability of HFpEF by the H_2FPEF score system and the primary endpoint composed of cardiovascular death, aborted cardiac arrest or HF hospitalization in patients with HFpEF using spironolactone or placebo. The high probability of HFpEF according to the H_2FPEF score was associated with worsening renal function, elevated natriuretic peptide values, increased left ventricle mass and left atrium (LA) size[6].

When comparing the patients with and without HFpEF according to the H_2FPEF score, we observed that in those with a score ≤4 there were significant differences between worsening renal function, increased left ventricle (LV) mass and LA volume index (LAV-I). However, in individuals with a score ≥4, the difference was only observed in relation to LAV-I.

Although natriuretic peptides are part of the diagnosis of HFpEF in the ESC guideline, their values did not contribute the score. NT-proBNP values were missed in 24% of the patients enrolled in the elaboration of the score because some cardiologists did not request the test during clinical evaluation[3]. Our data show that BNP was higher in patients with HFpEF compared to individuals without HFpEF, regardless of the H_2FPEF score.

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)[7], a risk score composed of 13 clinical variables, evaluated patients with HF across the spectrum of LVEF. Among the 13 variables used in the MAGGIC score, three were common to the H_2FPEF score (age, BMI and hypertension). The MAGGIC score did not use echocardiographic parameters and, like H_2FPEF, natriuretic peptides values were not considered. Of the patients defined with HFpEF (n = 407), followed during 3.6 ± 1.8 years, 28% died, 32% were hospitalized for HF and 55% had cardiovascular hospitalization and/or death. When compared to our assessment of the H_2FPEF score, we observed similar values in relation to the composite outcome observed in the MAGGIC score (55%) and in H_2FPEF, with a score ≥ 4 (53%). The H_2FPEF score, like the MAGGIC, is a simple score, but with a smaller number of variables, and shows to be useful for morbidity and mortality risk stratification in HFpEF.

The study has limitations related to a single center design, the relative small sample size, with female predominance, and the score was applied retrospectively. Multicenter studies with large populations are needed to confirm our data.

Table 1 - Anthropometric, clinical and laboratory characteristics of patients with and without heart failure.

Variable	Heart Failure *n= 58*	No Heart Failure *n= 344*	p-value
Age (years)	71(60.6-77.2)	57(51-64.7)	<0.0001
Women (%)	78	70	0,346
BMI (kg/m²)	27.7(23.3-30.6)	28.1(25.2-31.8)	0.111
SBP (mmHg)	143.3(129.3-167.2)	133(120-149)	0.001
DBP (mmHg)	80(71.7-91)	82(73.7-90)	0.689
HR (bpm)	70(61-80)	71.5(64.5-80)	0.349
Risk factors			
Smoking (%)	9	20	0.120
Diabetes (%)	29	29	0.523
Hypertension (%)	88	72	0.007
Obesity (%)	33	37	0.340
Metabolic Syndrome (%)	53	61	0.219
CKD (%)	53	15	<0.0001
CAD (%)	15	9	0.102
Anemia (%)	22	10	0.014
Laboratory			
Blood glucose (mg/dL)	99.5(94-119)	102(93-115)	0.718
Hemoglobin (g/dL)	13.2(12.4-14.5)	13.5(12.7-14.4)	0.445
Creatinine (mg/dL)	0.86(0.72-1.05)	0.82(0.70-0.96)	0.024
GFR (mL/min)	71.9((57.7-89.1)	83.5(71.2-96.1)	<0.0001
Total Cholesterol (mg/dL)	208(190-231)	215(188-244)	0.371
Triglycerides (mg/dL)	112(87-143)	120(88-179)	0.184
HDL-chol (mg/dL)	55(48-69)	51(44-62)	0.042
Albuminuria (mg/mL)	11.8(5.9-28.6)	12(6.6-25)	0.819
Uric acid (mg/dL)	4.9(4-6.1)	5.1(4.1-6.2)	0.714
BNP (pg/mL)	54.5(42-93)	14(10-23)	<0.0001
ACEI (%)	35	33	0.441
ARB(%)	14	11	0.362
Beta-blockers (%)	29	15	0.007
Diuretics (%)	50	34	0.017
H_2FPEF Score components			
Age >60 years n(%)	78	41	<0.0001
Hypertensive n(%)	53	38	0.018
BMI >30kg/m² n(%)	31	37	0.252
Atrial fibrillation n(%)	5	0	0.003
E/e' ratio >9 n(%)	28	12	0.003
PASP >35mmHg n(%)	3.5	0.5	0.056
H_2FPEF Score	2 (1-4)	2(1-3)	0.001

BMI: body mass index; BNP: B-Type natriuretic peptide; CAD: coronary artery disease; CKD: chronic kidney disease; DBP: diastolic blood pressure; GFR: glomerular filtration rate by the MDRD equation; HDL-chol: HDL cholesterol; HFpEF: heart failure with preserved ejection fraction; HR: heart rate; Hypertensive: 2 or more antihypertensive medicines; ACEI - angiotensin-converting-enzyme inhibitor; ARB - angiotensin receptor blocker; PASP: pulmonary artery systolic pressure; SBP: systolic blood pressure. Continuous variables as median and interquartile range (25 and 75%), overall p value for continuous variables performed with the Mann-Whitney-U-test; Categorical variables presented as percentage (%), p value for categorical variables performed with Pearson's chi-square test.

Table 2 - Echocardiographic characteristics of patients with and without symptoms of heart failure.

Variable	Heart Failure *n= 58*	No Heart Failure *n= 344*	p-value
LVEF – Simpson (%)	61(57.7-65.2)	61(58-65\0	0.790
LVMI (g/m²)	105.4(93-121)	88(75.9-120.4)	<0.0001
LAV-I (mL/m²)	24.7(19.9-33.5)	20.9(17.6-24.5)	<0.0001
E wave (cm/s)	65.5(51.5-78.7)	63(53.4-76)	0.901
A wave (cm/s)	79.5(58-93.8)	68(56-82)	0.019
E/A ratio	0.76(0.56-1.14)	0.95(0.71-1.20)	0.003
S' wave (cm/s)	8(6-9)	8.5(7-9.5)	0.021
e' wave (cm/s)	7.5(9.2-6.5)	10(8-12)	<0.0001
E/e' ratio	7.4(9.2-6.1)	6.6((7.8-5.5)	0.001

A wave: Mitral A velocity; E/A ratio: Mitral E/A ratio; e': Velocity of mitral annulus; E/e' ratio: Mitral E/e' ratio; E wave: Mitral E velocity; LAV-I: Left atrial volume index; LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index; S' wave: Peak annular systolic velocity. Continuous variables as median and interquartile range (25 and 75%), overall p value for continuous variables performed with the Mann-Whitney-U-test.

Table 3 - Outcomes in patients with and without heart failure with preserved ejection fraction according to H2FPEF score.

	Score H2FPEF 0-3 *(n= 352)*		P-value	Score H2FPEF ≥4 *(n= 50)*		p-value
	No HFPEF (n= 309)	HFPEF (n= 43)		No HFPEF (n= 35)	HFPEF (n= 15)	
Age (years)	56(51-63)	71(57-78)	<0.0001	64(61-67)	73(66-77)	0.002
Women n(%)	215(70)	31(72)	0.082	27(76)	14(93)	0.424
GFR (mL/min)	84.2(71.7-96.1)	74(58.3-88.9)	0.001	75(64.5-86.9)	64.4(45.5-90.1)	0.315
LVIM (g/m²)	87.7(75.4-102.3)	109.9(95.8-121.2)	<0.0001	93.5(80.6-105.8)	93.8(78.4-104.2)	0.874
LAV-I (mL/m²)	20.8(17.4-24.2)	23.7(19.1-30.7)	0.001	21.8(19-26.9)	26(21.4-36.1)	0.044
BNP (pg/mL)	14(10-23.5)	54(42-92)	<0.0001	11(10-23)	57(46-97)	<0.0001
Composite outcome n(%)(*)	23(7)	9(21)	0.009	2(6)	8(53)	<0.0001

GFR: Glomerular filtration rate by the MDRD equation; LAV-I: Left atrium volume index; LVIM: Left ventricular index mass; (*) Death from any cause and cardiovascular hospitalization.
Continuous variables as median and interquartile range (25 and 75%), overall p value for continuous variables performed with the Mann-Whitney-U-test; categorical variables presented as percentage (%), p value for categorical variables performed with Pearson's chi-square test.

Conclusion

A H_2FPEF score ≥4 indicates a worse prognosis in patients with HFpEF assisted in primary care. Our data show that a low-cost, easy-to-apply score, such as the H_2FPEF, can help physicians in primary care in the risk stratification of HFpEF patients.

Author Contributions

Conception and design of the research: Jorge AJL, Mesquita ET. Acquisition of data: Leite AR; Almeida BM; Correia D; Jorge AJL. Analysis and interpretation of the data: Jorge AJL; Martins WA. Statistical analysis: Rosa MLG; Jorge AJL. Writing of the manuscript: Jorge AJL; Villacorta Junior H; Martins WA. Critical revision of the manuscript for intellectual content: Martins WA; Mesquita ET; Saad MA.

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 study was approved by the Ethics Committee of the *Faculdade de Medicina da Universidade Federal Fluminense* under the protocol number 49637115.7.0000.5243. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Factors Predicting Heart Failure in Children Admitted to a Pediatric Emergency Ward in a Developing Country

Uchenna Onubogu

Rivers State University Teaching Hospital, Port Harcourt - Nigeria

Abstract

Background: Heart failure is an important cause of morbidity and mortality in children.

Objective: To determine the clinical characteristics of children with acute heart failure syndrome in the emergency ward of River state university teaching hospital, Nigeria and identify factors associated with poor outcomes.

Methods: This was an 18month retrospective review of the acute heart failure register. Poor outcome measures were defined as the persistence of heart failure after 4 days on admission or death.

Results: Ninety-two (4.1%) of 2,244 children admitted were in heart failure, Non-cardiac disorders [bronchopneumonia 32(36%), sepsis 21(24%), severe malaria 10(11%), sickle cell anaemia 8(9%) and tuberculosis 3(3%)] contributed to 74(83%) while congenital heart disease(CHD) was 15(17%). Seventy-four (83%) were discharged, 10(11%) died and 4(5%) left against medical advice. The median time to resolution of heart failure was significantly 24 hours longer for malnourished children than those with normal-nutritional status, 72Vs48hrs, log rank:0.001. Those with modified Ross score of >7 and sepsis were more likely to die, OR,8.8(95% CI,1.2 to 72.5,p = 0.02) and 3.9(95% CI,1.01 to 15.2;p =0.04). Age <2yrs(OR,3.1,CI,1.2 to 8.5,p = 0.02), and CHD (OR 3.6,95% CI,1.1 to 12,P=0.02) were associated with a higher likelihood of having a poor outcome. Each unit increase in weight for age Z score of 1, decreased the odds of having a poor outcome, OR,0.77 (95% CI,0.63 to 0.95)p=0.016.

Conclusion: Heart failure in our setting is predominantly caused by non-cardiac disorders. Modified Ross score of >7 and sepsis are risk factors for mortality in children with heart failure. (Int J Cardiovasc Sci. 2020; 33(6):673-685)

Keywords: Child; Heart Failure; Pediatric Emergency; Mortality and Morbidity; Critical Care Outcomes; Emergency Service, Hospital.

Introduction

Heart failure is a clinical syndrome that occurs when the heart is unable to meet the metabolic needs of the body in the presence of adequate ventricular filling.[1] It is an important cause of morbidity and mortality in children[2,3]. Heart failure accounted for 5971 (0.02%) annual pediatric emergency room visits in a U.S. national survey.[4] In Nigeria, heart failure accounted for 6 to 16% of hospital admissions in both emergency rooms and pediatric wards.[5-8]

In the emergency department, children with heart failure are a heterogeneous group of patients who could have a primary cardiac pathology or a secondary pathology of non-cardiac origin.[3] The emergency department acts as the first point of call for these children, and the emergency doctor has the primary responsibility of identifying these patients and promptly commencing management [9,10]. When children present with heart failure in developed countries, the most common reason is complications from a congenital or post-operative cardiac condition, while in developing countries, complications from non-cardiac conditions are the most predominant cause .[11]

Because acute heart failure syndrome is most often from secondary causes in developing countries, it tends to

Mailing Address: Uchenna Onubogu
6-8 Harley street, Forces Avenue. Postal code: 500241, Port Harcourt - Nigeria
E-mail: utchayonubogu@yahoo.co.uk

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be under-recognized, since it is obscured by the primary diagnosis. These children are very ill, and by the time acute heart failure complicates a primary pathology it is usually seen at the extreme spectrum of the disease. Early recognition of heart failure would prompt early commencement of cardiac support, which invariably leads to better outcomes in children presenting with heart failure.

There is limited data on the burden of acute heart failure in children in sub-Saharan Africa and factors associated with poor outcomes. There is also a need to understand the characteristics of acute heart failure and outline its management strategies in the pediatric age group.[11,12]

Thus, we set out to determine the prevalence of acute heart failure in the emergency ward of our hospital, describe the clinical characteristics and determine the outcomes of children admitted with acute heart failure. It is hoped that the results will help increase early recognition of acute heart failure syndrome in children, especially in emergency settings, and that the identification of factors associated with poor outcomes will improve the efficiency of clinical management and achieve better outcomes.

Materials and Methods

Aims and Objectives of the Research Project

To determine the clinical characteristics of children with acute heart failure syndrome in the emergency room and identify factors associated with poor outcomes.

Study Setting

Rivers State University Teaching Hospital (formerly known as Braithwaite Memorial Specialist Hospital) is a tertiary hospital located in Port Harcourt, Rivers State, Nigeria. The pediatric department contains 80 beds, including 12 in the emergency ward. The pediatric emergency department treats an average of 1724 children annually. Patients admitted through the emergency department are first evaluated by the resident physician, whose activity is overseen by a supervising consultant. Admitted patients are given urgent treatment, followed by transfer to the main pediatric ward within 48hrs of admission if they are determined to be clinically stable. Patients who respond to treatment can also be discharged from the emergency room within 24 hours.

Selection Criteria

This is a retrospective review of prospectively collected data from acute heart failure records of the pediatric emergency ward between March 2014 and July 2015. Children who presented in the emergency ward with the cardinal signs of heart failure were identified by the attending physician. The criteria for diagnosing heart failure were the presence of hepatomegaly with any two of the following:[8] 1) significant tachycardia, which is resting heart rate greater than the following cut-offs for different ages: 160bpm in infants, 150bpm in children >1-2 years of age, 140bpm in children >2-4 years, 120bpm in children >4-6 years and 100bpm in children >6 years (febrile children were allowed an additional 10bpm for every degree rise in temperature above normal); 2) tachypnea, which is resting respiratory rate above the following cut-offs; 60 bpm in infants <2 months old, 50 bpm in infants 2-12 months old, 40 bpm in children >1 year old; 3) cardiomegaly, which is a displaced apex beat in the presence of a central trachea or a cardiothoracic ratio of >60% in children ≤5 years of age and >50% in older children. Children diagnosed with heart failure whose parents gave consent were included in the study. Apart from excluding children whose parents who did not give consent, we also excluded neonates (children aged ≤ 28 days old), since they are usually admitted into the special-care baby unit, which is separate from the pediatric emergency ward.

Data Collection

After initial resuscitative treatment had been carried out to stabilize the patients, a member of the research team approached the parents and patient to inform them about the study and to receive formal consent for inclusion. Once recruited, the patients were followed up throughout their stay in the hospital, from the emergency room to the main hospital ward stay until discharge. An interviewer administered a questionnaire to the parents, and a study number was allocated to the patient. Data was collected using a structured proforma and was updated daily. The following information was collected: age, gender, referral pattern, social class, weight, temperature, respiratory rate, heart rate, presence of hepatomegaly, previous treatment, modified Ross score, packed cell volume, white blood cell count, primary diagnosis, treatments given, diagnosis, length of hospital stay, and outcome of admission.

Social class was categorized according to the parent's level of education and occupation, from class 1 (highest) to

class 5 (lowest).[13] A hemoglobin level of less than 8g/dl was described as severe anemia.[14] The modified Ross criteria were used to classify the severity of heart failure.

Nutritional status was classified using weight-for-age Z-scores[15-17]

Statistical Analysis

The data were entered into an Excel spreadsheet and analyzed using IBM SPSS statistics version 23. Univariate descriptive statistics were used to explain the patient's characteristics with measures of central tendency and dispersion. Kaplan-Meier survival curves were generated for resolution of heart failure by 1 week (168 hrs) after admission, and a log rank test was performed to compare the time to resolution of heart failure in different sub groups. P-values ≤0.05 were considered significant. Post hoc identification of risk factors for poor outcomes was performed using univariate logistic regression for all variables. Variables with a p-value <0.1 or with a clinical application relevant to children with a non-cardiac cause of heart failure were put into a multivariate logistic regression model. Backward stepwise elimination was used to determine variables included in the final model. The final model was internally validated using the Hosmer and Lemeshow goodness-of-fit test, with an acceptable fitness set at a p >0.05, and a ROC curve of the new model was constructed to assess its discriminatory accuracy.

The primary outcome measures were the persistence of heart failure >4 days after admission or death. The results are reported as odds ratio with 95% confidence interval.

Informed consent was required from all participating patients, although refusal did not affect the patient's hospital management. Ethical clearance was obtained from the ethics committee of the Rivers State Hospital Management Board, Port Harcourt, Nigeria.

Results

A total of 2,244 patients were admitted to the children's emergency ward, of whom 92(4.1%) were diagnosed with heart failure. The parents or guardians of all patients gave informed consent prior to registration in the database. Three patients with incomplete data were excluded from the analysis, while the remaining 89 were analyzed (Figure I).

Characteristics of the Study Population

The included children ranged from one month to 16 years of age, with a median age of 11 months (IQR: 5- 38 months). There were 45(51%) males, with a male-to-female ratio of 1.1:1. Most patients 72(81%) lived in urban areas, belonged to the middle class 52(58%), and lived with both of their parents 80(90%). Most presented directly to the hospital 53(60%) without being referred, although 67(75%) had taken medication before presenting to the hospital. Of those who had taken medication prior to admission, 28(42%) took prescription medication while 10(15%) took herbal medications (Table 1).

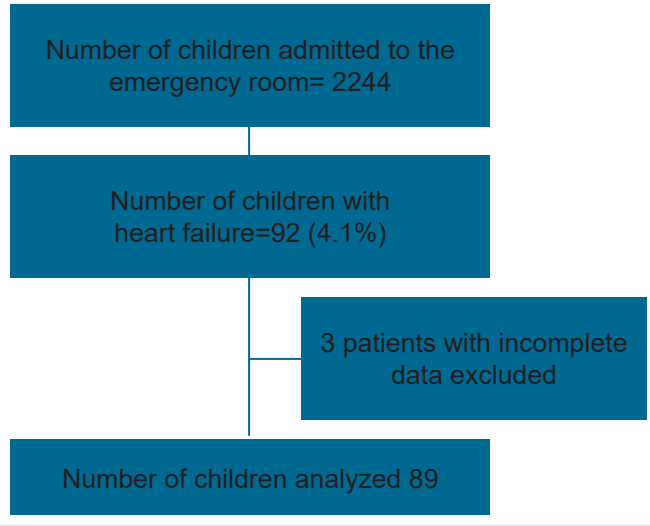


Figure 1 – Study flow chart.

Table 1 - Characteristics of studied patients

Variable	All patients (n=89) (%)
Age months (Median, 25th,75th percentile)	11 (5, 38)
1month to ≥ 5 yrs	72 (81)
>5 to 10 yrs	11(12)
>10 yrs	6 (7)
Gender	
Female	44 (49)
Male	45 (51)
Residence	
Urban	72 (81)
Rural	17 (19)
Who child resides with	
Both parents	80(90)
Single parent	5(6)
other	4(4)
Social class of parents	
Upper class (1 to 1.7)	9(10)
Middle class (1.8 to 3.3)	52(58)
Lower class (3.4 to 5)	28(32)
Prior treatment	
Yes to medications	67(75)
No to medications	22(25)
Prior Medications (N= 67)	
Prescribed	28(42)
Over-the-counter	29(43)
Herbal	10((15)

Data are expressed in (%) unless stated otherwise.

Clinical Features of Children with Heart Failure

Forty-six (52%) of the children were malnourished, of whom 32(36%) were severely malnourished. The median hemoglobin level was 8.6(IQR 6.3, 11) g/dl, and 41(46%) patients were severely anemic (with a hemoglobin level of less than 8g/dl), while 10(11%) had dysmorphic features suggestive of Down syndrome. Sixty-seven (75%) had moderate heart failure according to the modified Ross classification. Non-cardiac disorders contributed to heart failure in 74(83%) cases. The most common causes of heart failure were bronchopneumonia 32(36%), sepsis 21(24%), and congenital heart disease 15(17%). A blood transfusion was given to 41(46%) patients, while 64(72%) received furosemide (Table 2).

Patient Outcomes

Seventy-four (83%) of the patients were discharged home, and the median time for resolving heart failure was 60 hours. Seventy-five percent of the discharged patients were discharged by 108 hrs. Of the 10(11%) who died, the median time of death was 180 hrs (range 2 to 24 days), while the median time for those who left against medical advice was 156 hrs. One patient was referred to another hospital within 2 h of admission due to a health worker strike that interrupted services (Table 3). Of the 10 children who died, 3 had bronchopneumonia and 5 had sepsis; only one had a diagnosed congenital heart defect and one had severe malaria. The median time to resolution of heart failure with a modified Ross score <2 was significantly longer for malnourished children than those with a normal nutritional status (72 Vs 48hrs, log-rank : 0.001; see Figure 2). Although a modified Ross score >7 was associated with a relatively longer recovery time (72 vs, 48 hrs.), the difference was not statistically significant (log-rank: 0.2; see Figure 3). Children with a modified Ross score >7 and those with sepsis were more likely to die, with odds ratios of 8.8 (CI 1.2 to 72.5, p 0.02) and 3.9 (CI 1.01 to 15.2, p 0.04), respectively.

Univariate Analysis of Risk Factors Associated with Poor Outcome

Children less than 2 years of age were more likely to have poor outcomes (OR 3.1, CI 1.2 to 8.5, p = 0.02), which were defined as persistence of heart failure 4 days after admission or death. Residential location and family size did not affect the odds of a poor outcome. Dysmorphic features significantly increased the odds of a poor outcome (OR 7.2 95% CI 1.5 to 36, P = 0.009), while gender, nutritional status, modified Ross score at admission, prior treatment and anemia did not affect the odds of a poor outcome. Heart failure due to congenital heart disease was associated with a higher likelihood of a poor outcome OR 3.6, 95% CI 1.1 to 12, P = 0.02. Each unit increase in Z-score decreased the odds of a poor outcome (OR 0.77, CI 0.63 to 0.95, p = 0.016; see Table 4).

Using the clinical relevance of variables for non-cardiac causes of heart failure and a p-value cut-off of 0.1 to select

Table 2 - Clinical characteristics and treatment of children with heart failure

Variable	All patients (n=89) (%)
Nutritional status Z-score (median, IQR)	-2.1 (-3.7, -0.5)
>2SD (Overweight)	4(4)
2 to -2SD (Normal)	39(44)
<-2 to -3SD (Moderate Malnutrition)	14(16)
<-3SD (Severe Malnutrition)	32(36)
Hemoglobin in g/dl (median, IQR)	8.6 (6.3, 11)
Hb <8g/dl	41(46)
Hb >8g/dl	48(54)
Dysmorphic features	
Yes	10(11)
No	79(89)
Modified Ross score	
3 to <7 (Mild HF)	20(23)
7 to <11 (Mod HF)	67(75)
11 to 12 (severe HF)	2(2)
Cause of Heart Failure	
Bronchopneumonia	32(36)
Sepsis	21(24)
Congenital heart defect	15(17)
Severe Malaria	10(11)
Sickle cell	8(9)
Tuberculosis	3(3)
Treatment received	
Blood transfusion	41(46)
Furosemide	64 (72)
Captopril	15(17)
Spironolactone	15(17)
Digoxin	15(17)

Table 3 - Time until outcome

Outcome	N (%)	Median in hours (1QR)
Heart failure resolved	74(83)	60 (60; 108)
Death	10(11)	180 (60; 348)
Discharged against medical advice	4(5)	156 (48;216)
Referred	1(1)	2 (2)

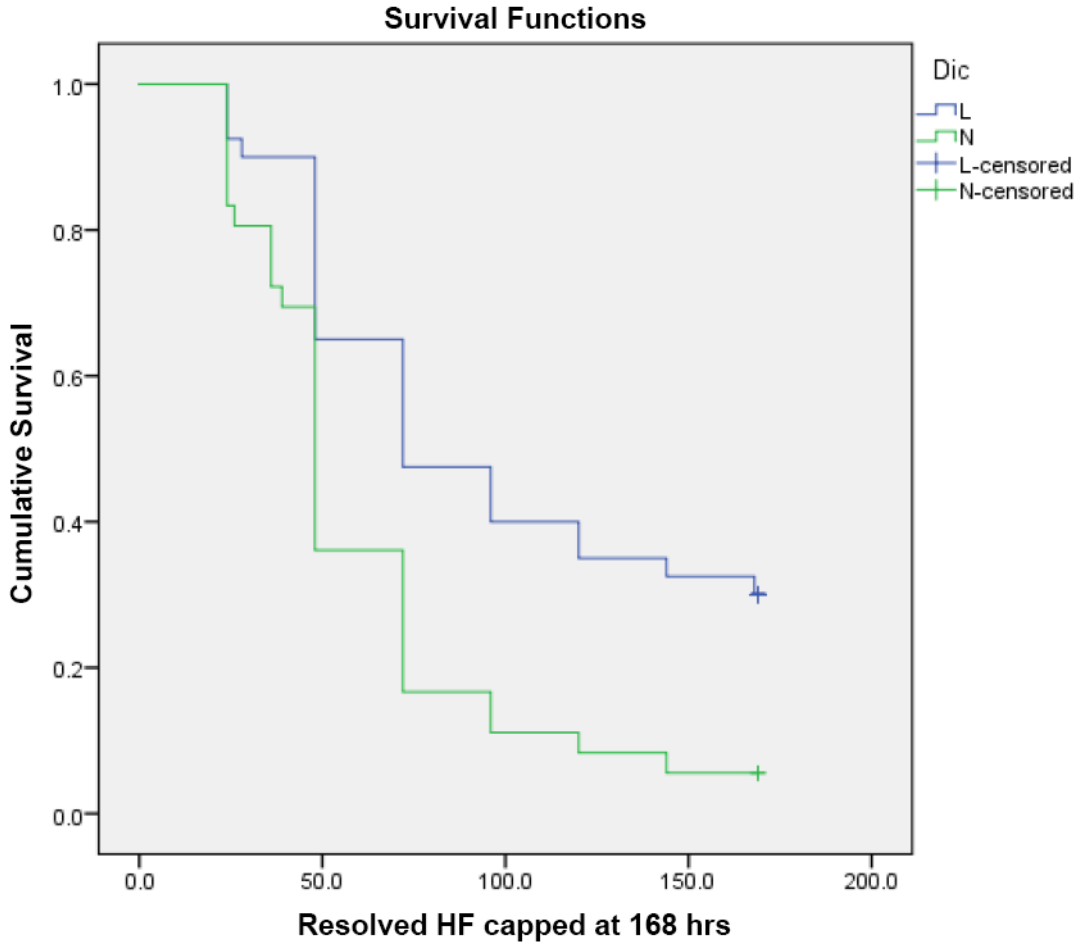
the model of best fit, the following variables were added into multivariable logistic regression model (Table 5): age less than 2 years, weight-for-age score, and modified Ross score >7. This model explained 13.9% (R^2) of the variance in outcome of heart failure and correctly classified 66.3% of the cases. The area under curve for the predictability of poor outcome was 64% (95% CI; 52 to 76%) Figure 4.

Discussion

The 4.1% heart failure prevalence seen in this study is similar to the 5.8% and 2.7% previously reported in Nigerian studies.[8,18] Other African countries, including Kenya and Ethiopia, have reported much lower heart failure rates (1:1000 and 2.9%, respectively).[19,20] However, the children in the Ethiopian study were relatively older than our sample, and the Kenyan study was a retrospective review of clinical notes, which would have limitations identifying all patients with heart failure. Most European studies[21,22] on heart failure prevalence have been performed in patient populations with specific cardiac pathologies, thus their findings cannot be compared with ours.

The fact that we excluded neonates, as well as the fact that fetal diagnosis and corrective cardiac surgery are not performed in our department, could mean that most of the children with congenital heart defects who do not survive beyond early neonatal life were excluded from our population. This could mean that the actual prevalence of children with congenital heart defects who may have developed heart failure remained undetected. It may also be indicative of underreporting in developing countries .

As reported in other African studies, non-cardiac causes were the predominant etiology of heart failure.[7,18,19] Bronchopneumonia has been reported in previous studies as the leading cause of heart failure in children in developing countries.[7,19,20] In Thai and Nigerian studies of hospitalized



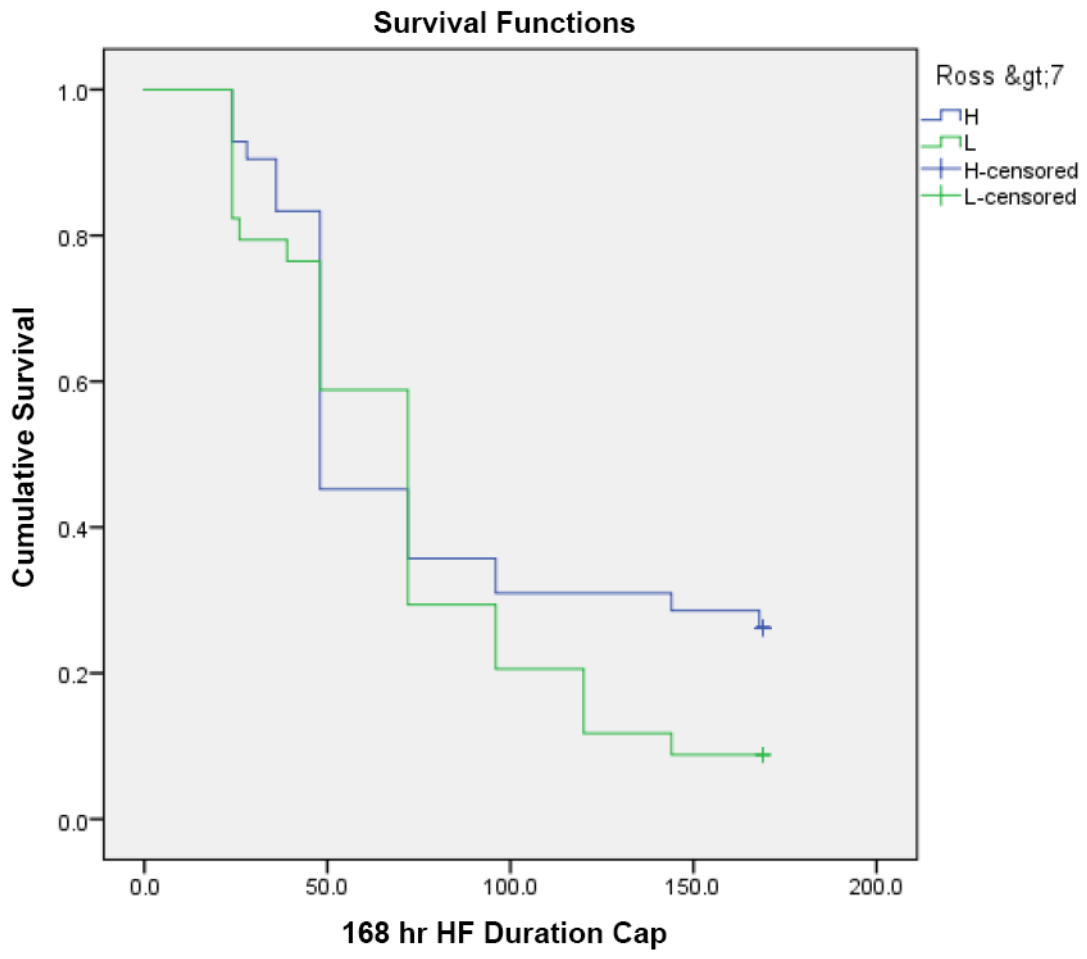
L = Z score < -2 (Malnourished), N = Zscore > -2 (Not malnourished), HF = Heart failure, DIC Zscore = Dichotomized Zscore, Cum Survival = Cumulative survival

Nutritional status	Mean Hrs	Median(Hrs)	95% confidence interval		Log rank
			lower	upper	
L = Malnourished	99	72	42	102	0.001
N = Not malnourished	61	48	44	52	

Figure 2 – Time to resolution of heart failure according to nutritional status.

under children under 5 years of age, congestive heart failure complicated bronchopneumonia in 10% and 39.4% of the patients, respectively.[23,24] In bronchopneumonia, inflammation of the alveoli and inter alveolar septum increases pulmonary arterial vascular pressure, resulting in an increased afterload on the right ventricle, which can cause the right ventricle to fail if it cannot adequately pump against the raised pulmonary vascular resistance .[24]

In a study aimed at assessing the cardiac systolic function of children with severe malaria, 48% had elevated cardiac troponin I compared to healthy controls, which may be suggestive of myocardial injury.[25] Myocardial dysfunction in children with severe malaria has been postulated to be caused by acidosis, which depresses the myocardium and has a negatively inotropic effect on the heart.[26,27]



H = Mod Ross > 7; L=Mod Ross< 7; Ross%gt7 = Modified Ross score cut off at 7

Nutritional status	Mean Hrs	Median(Hrs)	95% confidence interval		Log rank
			lower	upper	
H = Modified Ross score >7	86	48	36	60	0.2
L = Modified Ross score <7	74	72	60	84	

Figure 3 – Time until resolution of heart failure according to modified Ross score at admission.

Malnutrition was associated with a higher likelihood that recovery time from heart failure would be greater than 24 hrs. We found a relatively slower recovery time among malnourished patients than has been reported in previous studies. Malnutrition was associated with prolonged intubation time (12.4 h) and prolonged intensive care unit stay (2.7 days) among children with congenital heart disease undergoing corrective surgery.[28] In addition, malnutrition exacerbates the symptoms of heart failure by worsening fluid retention, inflammatory response and neurohormonal activation .[29]

Our results show that the severity of heart failure (classified by the modified Ross score) helps stratify the risk of mortality in children with acute heart failure. In a study conducted among a group of children with dilated

Table 4 - Factors associated with poor outcomes

Variable	Poor Outcome (n= 36)(%)	Odds ratio	95% confidence interval		P
			Lower	Upper	
Residence					
Urban	32(44)	2.6	0.7	8.8	0.1
Rural	4(24)				
Who child lives with					
Both parents	35(45)	0.1	0.01	1.3	0.06
Others	1(11)				
Age					
<2yrs	29(49)	3.1	1.2	8.5	0.02
>2yrs	7(23)				
Gender					
Female	20(45)	0.6	0.3	1.6	0.34
Male	16(35)				
Referred					
Yes	18(50)	1.9	0.8	4.6	0.13
No	18(34)				
Social class					
Upper	8(38)	1.1	0.4	3.2	0.8
Lower	28(41)				
Family size					
>4 children	7(35)	1.3	0.5	3.7	0.6
<4 children	29(42)				
Nutritional status					
Severe Malnutrition	16(50)	1.9	0.8	4.5	0.17
No severe Malnutrition	20(35)				
Z-score Weight/age	-	0.77	0.63	0.95	0.016
Dysmorphia					
Yes	8(80)	7.2	1.5	36	0.009
No	28(35)				
Modified Ross >7					
Yes	22(61)	1.5	0.6	3.5	0.3
No	141(38)				
Prior treatment					
Yes	7(32)	1.6	0.5	4.5	0.3
No	29(43)				

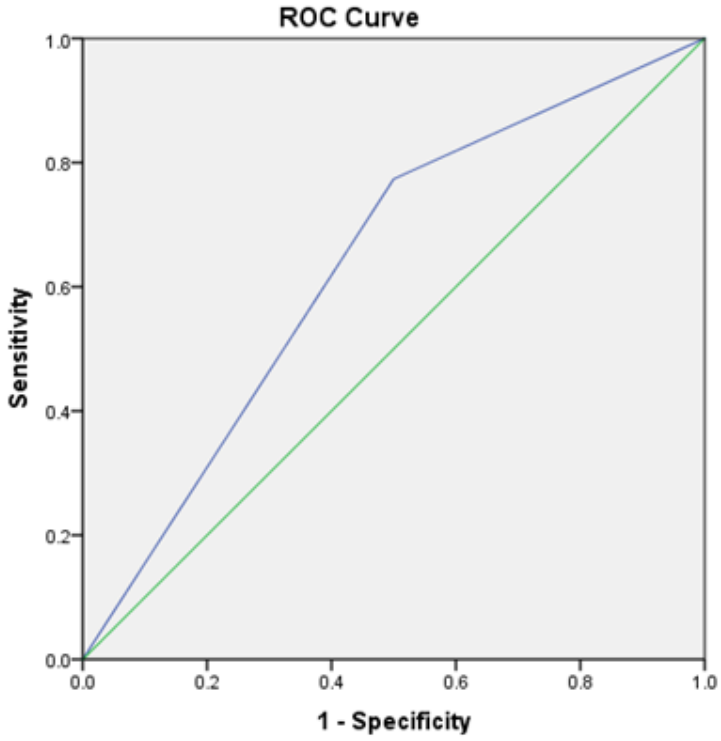
Herbs					
Yes	5(50)	1.5	0.4	5.6	0.3
No	31(39)				
PCV <24					
Yes	14(34)	0.6	0.3	1.4	0.2
No	22(46)				
Sepsis					
Yes	9(42)	1.1	0.4	3.0	0.06
No	27(40)				
Bronchopneumonia					
Yes	10(31)	0.5	0.2	1.3	0.1
No	26(46)				
Coronary heart disease					
Yes	10(67)	3.6	1.1	12	0.02
No	26(35)				
Malaria					
Yes	2(20)	0.3	0.6	1.6	0.1
No	34(43)				
Blood transfusion					
Yes	15(36.5)	0.7	0.3	1.7	0.5
No	21(43)				

Table 5 - multivariate logistic regression for poor outcome

		B	SE	Wald	df	Sigma	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1[a]	Z-scoreWA	-.202	.112	3.261	1	.071	.817	.656	1.017
	<2yr(1)	.837	.535	2.449	1	.118	2.310	.810	6.594
	Rossgt7(1)	.310	.462	.450	1	.502	1.364	.551	3.375
	Constant	-1.585	.525	9.108	1	.003	.205		

Hosmer and Lemeshow Test: Sig: 0.5, Nagelkerke R Square: .139
B: / Exp(B): / Wald: / SE: standard error / df: degrees of freedom / <2yr(1): age less than 2 years / Z-scoreWA: weight-for-age score / Rossgt7(1): modified Ross score >7.

cardiomyopathy, Ross scale scores >11 were significantly associated with death or transplant.[30] Rocha Araújo et al.,[31] used the recently modified 20-point Ross scale to classify their patients. The Ross scale was expanded from its old version (which incorporated only clinical variables) to include laboratory variables in order to improve its sensitivity for predicting outcomes in children with heart failure.[31] The following variables were added to the scale: N-terminal pro b-type natriuretic peptide, ejection fraction, systemic atrioventricular valve insufficiency and percentage of predicted maximal oxygen uptake for children 9 years of age and older.[31] In resource poor settings however, these



Area Under the Curve

Test Result Variable(s): Predicted group

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.637	.061	.029	.517	.757

Figure 4– Predictability value for the model, ROC and test results.

laboratory investigations may not easily be available, making the newer Ross classification system more difficult to apply. Even where the resources are available, using the newer scale is more cumbersome and difficult in daily practice.[30] We used the Laer-modified Ross classification system,[32] which uses simple bedside clinical signs and symptoms to classify the severity of heart failure. However, it is important to point out that there are limitations to using clinical parameters alone to predict outcomes in heart failure patients.[33,34] Since half of the variables in the old version of Laer-modified Ross scoring system were related to the work of breathing, it may undervalue congestive heart failure symptoms. Ross himself acknowledged this problem, which led to the expansion of the system to include specific laboratory parameters for accessing cardiac physiology.[31] Nevertheless, considering that most of the children in our study had heart failure due to non-cardiac disorders and that the newer scale specifically focuses on for heart failures due to cardiac pathology, we considered the older version more appropriate for our study.

In our sample, sepsis was associated with a higher likelihood of mortality. This is not surprising, since myocardial dysfunction in septic patients has been found to significantly increase mortality compared to septic patients without myocardial dysfunction.[35]. Sepsis can cause myocardial depression via cytokines and nitric oxide-mediated cardiomyocyte hyporesponsiveness, and it can also cause direct cardiomyocyte injury or death.[36-38]

Younger children were also found to have slower recovery and relatively poorer outcomes than older children in this study. Young age is associated with longer hospitalization and higher mortality in children with heart failure. In a national survey of pediatric heart failure over a 9 year period ,[39] admissions for heart failure were significantly longer in children than adults, with a mean of 16.2 vs. 6.8days, p <0.001. It is important to note that cardiac reserve is relatively lower in older children than adults, so they are less able to accommodate increased demand on the heart.[40]

Children with congenital heart defects and those with dysmorphic features suggestive of Down syndrome were also associated with poor outcomes. Hospitalized children with Down syndrome have a high prevalence of congenital heart disease (up to 62%)[41]

Anemia is another important comorbidity seen in both adult and pediatric heart failure patients.[7,42] It can occur in more than a third of children with heart failure, as seen in our study and other studies,[7,43] and its prevalence is higher in acute decompensated heart failure than in chronic heart failure.[42] The etiology of anemia in heart failure is micronutrient deficiency from inadequate intake (especially vitamin B12, folic acid, and iron) and inadequate absorption. Surprisingly, anemia did not affect outcomes in our study. The fact that the 75% of our study population had a hemoglobin value ≤11g/dl, which is below the -2 standard deviation cut off values for most pediatric age groups,[44] could have made it difficult for us to have a suitable number of controls for comparison.

This study highlights some of the peculiarities of health care in a developing country, one of which is self-medication with both over-the-counter and alternative medicine rather than going to the hospital to seek medical help. Self-medication with both prescription and over-the-counter drugs is a common problem in developing countries, unlike in developed countries, where self-medication usually involves only over-the-counter drugs .[45-49] The incidence of self-medication varies in developing countries, ranging from 12.4 to 91.3%. In our patient population 43% took self-prescribed over-the-counter drugs.[46,48,50] Improper self-medication may delay patients from seeking medical treatment, thereby leading to complications and increased risk of mortality. It could also lead to adverse drug effects, drug interactions, incorrect diagnosis and antibiotic resistance.[51,52]

Our study found a relatively higher likelihood of poor outcomes among those that used herbs, although the finding was not statistically significant. This could be due to our small sample size, which made our confidence interval very wide. Nigerian studies have found that the herbal preparations used by traditional herbalists for treating various ailments grew high doses of various pathogenic bacteria that were resistant to many antibiotics. Large strains of fungi were also isolated from the herbal concoctions.[53,54] This brings to light the potential problems of herbal medicine, i.e., not only is the therapeutic efficacy of these substances in doubt, but their unhygienic preparation leaves the finished product with pathogenic and possibly lethal microbes. If these herbs are taken by an ill child, it would be a case of double jeopardy: doing more harm to an already sick child in a bid to treat an ailment.

Another problem seen in our patients was discharge against medical advice. In pediatrics, this decision is made by parents on behalf of their children. However, requests for discharge against medical advice are encountered worldwide, and the reasons and prevalence vary by region. In developed countries, discharge against medical advice among pediatric patients is uncommon due to efficient child protection systems that protect children from actions that would endanger their well-being.[55] The 5% prevalence of discharge against medical advice in our patient cohort is similar to the overall rates reported in other Nigerian studies (3.1 to 7.5%) .[56-58] The reasons for discharge against medical advice for pediatric patients in Nigerian hospitals include financial constraints (27 to 42%), lack of perceived clinical improvement (10 to 26%), perceived clinical improvement (22 to 27%), the inconvenience that admission causes the parents or caregiver (7 to 8%) and dissatisfaction with the medical care (5 to 8%).[56-58] When health care costs are paid out of pocket, as is the case in Nigeria, it leads to catastrophic expenditures and adverse outcomes, creating barriers to receiving and providing health care. It is not surprising that financial constraint is the major reason parents prematurely remove their children from the hospital; without a system to take over the continued cost of providing for the child's needs, health care workers can only play an advisory role in such cases.

These added risk factors, associated with poor outcomes seen in children with acute heart failure from developing countries, are products of the weak health care systems and social structure in developing economies. These problems require strong political will and government commitment to invest in a sustainable framework that will improve health care and social services.

Although our regression model could predict a poor outcome, it had moderate discriminatory ability, with an AUC of 64%. Since the model has a role in sensitizing clinicians to the common risk factors that can adversely

affect outcomes in children with heart failure, it can be used alongside other clinical parameters to stratify the risk of poor outcome in children with heart failure. Using the newer version of the Ross score to classify our patients might have improved the discriminatory ability of our model.

Limitations of our Study

This study has some limitations. Since the data was collected for registry purposes, it involved the limitations inherent to a retrospective study, including possible confounders that were not measured and problems with missing data.

Conclusions/ Recommendations

In conclusion, the prevalence of heart failure was 4.1%, while the mortality rate was 11%. Non-cardiac disorders were the most common cause of heart failure, contributing to 83% of the causes. Malnutrition was significantly associated with delays in resolution of heart failure. Management of children with heart failure should include prompt treatment of underlying sepsis and malnutrition through standard protocols to improve their clinical outcomes. Further adequately powered prospective studies are needed to identify all the risk factors associated with poor outcomes in children with heart failure.

Author contributions

Conception and design of the research: Onubogu U. Acquisition of data: Onubogu U. Analysis and interpretation of the data: Onubogu U. Statistical analysis: Onubogu U. Writing of the manuscript: Onubogu U. Critical revision of the manuscript for intellectual content: Onubogu U.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the River State Health Research. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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REVIEW ARTICLE

Nuclear Medicine Methods for Assessment of Chronic Chagas Heart Disease

Marcus Vinicius Simões, Denise Mayumi Tanaka, José Antonio Marin-Neto

Universidade de São Paulo, São Paulo, SP – Brazil.

Abstract

Several different imaging methods can be used to evaluate patients with Chagas heart disease (CHD) for diagnostic and prognostic purposes, including plain chest radiography; echocardiography; myocardial perfusion scintigraphy, for detection of ischemia and fibrosis; radionuclide gated-angiography, for evaluation of biventricular function; ^{123}I-MIBG labeling of sympathetic myocardial innervation; MRI, for detection and quantitation of myocardial fibrosis; and coronary angiography. This study aims to review the contributions of these nuclear medicine methods to understanding of the pathophysiology of chronic Chagas cardiomyopathy (CCC). Careful analysis and integration of findings provided by these imaging methods in patients with CCC at different stages has contributed significantly to improving understanding of several peculiarities of the disease. Clinical and experimental studies in animal models show that perfusion abnormalities detected in association with dysfunctional but viable myocardium are a common finding in CCC patients and correspond to areas of cardiac sympathetic denervation, as assessed by ^{123}I-MIBG imaging. Furthermore, recent reports have demonstrated a close relationship between coronary microvascular disturbances and myocardial inflammation. Thus, ongoing research, mainly focused on refinements of ^{18}F-FDF -PET techniques and further exploration of nuclear methods, such as SPECT, have the potential to contribute to detection and monitoring of early subclinical myocardial damage thereby enabling evaluation of therapeutic strategies targeting inflammation and microvascular ischemia that could result in better prognostic stratification of patients with CHD.

Keywords

Chagas Cardiomyopathy; Chagas Disease; Diagnostic, Imaging; Prognosis; Echocardiography; Myocardial Perfusion.

Introduction

Chagas disease (CD) is caused by a protozoan parasite, *Trypanosoma cruzi (T. cruzi)*, which is mainly transmitted among human beings through a triatomine vector, but other transmission routes also exist, including congenital, blood transfusion, oral transmission, laboratory contamination, and organ transplantation.[1] The disease is a serious health problem that is still endemic in many regions of Latin America, where some 8 to 10 million people are estimated to be infected, and it represents an emerging public health issue in nonendemic countries such as the United States and European and Asian countries[2,3] because of globalization and migratory waves from endemic regions.

CD presents two distinct phases. The acute phase is of short duration, lasting from 1 to 3 months, and is usually a benign febrile disease, but can rarely involve serious cardiovascular and neurologic complications caused by intense inflammatory changes secondary to *T. cruzi* parasitism in multiple organs and systems. In most cases, the disease will be asymptomatic in the chronic phase, without clinical evidence of structural organ damage throughout the individual's life, constituting the indeterminate form of Chagas disease (IFCD).[4] However, approximately 30% of chronically infected patients develop symptoms, with progressive cardiac and/or digestive organ complications. The cardiac form is the most relevant clinical manifestation of the disease in the chronic phase and may manifest as dilated cardiomyopathy arising about 2 to 3 decades after the initial infection.[5]

Mailing Address: Marcus Vinicius Simões
Av Bandeirantes, 3900. Postal Code: 14049-900, Ribeirão Preto, São Paulo, SP - Brazil
E-mail: msimoes@fmrp.usp.br

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The mechanisms of injury that lead to such a delayed development of myocardial damage are an intriguing aspect of the pathogenesis of CCC. The main pathologic feature of CCC is a low intensity and incessant chronic focal myocarditis that is initially silent but causes progressive myocardial damage with extensive reparative and reactive interstitial fibrosis that ultimately leads to a severe form of dilated cardiomyopathy.[6] Impairment of left ventricular wall motion that predominates in the inferior, posterior-lateral, and apical regions is a common finding in the early stages of CCC, preceding global cardiac systolic dysfunction. Additionally, the finding of an isolated, thin walled, left ventricular apical aneurysm, with a "finger glove" appearance, is considered a hallmark of the disease.[7]

The earliest clinical manifestations of CCC include cardiac conduction disorders,[8] LV wall motion abnormalities,[9] and diastolic dysfunction.[10] Sudden death due to complex arrhythmias may occur during the entire clinical course. Late manifestations include an important dilatation of cardiac chambers, as well as changes in their function, resembling dilated cardiomyopathy in clinical terms. The most common clinical manifestations in this phase are signs and symptoms of heart failure, systemic thromboembolism episodes, atrioventricular blocks, and severe ventricular arrhythmias.[11, 12]

Several imaging methods can be used to evaluate patients with Chagas heart disease for diagnostic and prognostic purposes.[13] Radionuclide imaging is an important tool employed to investigate and characterize several aspects of cardiac involvement in CCC patients. This primarily includes radionuclide ventriculography for bi-ventricular function evaluation, myocardial perfusion scintigraphy for recognition of coronary microvascular disturbances, ^{123}I-MIBG for imaging of cardiac sympathetic innervation, and, most recently, use of PET imaging has been suggested as a promising tool for detecting myocardial inflammation.

Radionuclide Ventriculography

Planar radionuclide ventriculography was one of the first nuclear imaging techniques employed to explore right and left ventricular function and to assess wall-motion abnormalities in patients with CCC.[14] That study[14] reported that radionuclide ventriculography provided reliable information on global LV function and regional wall motion abnormalities, with good correlation between radiologic contrast ventriculography performed during cardiac catheterization and radionuclide ventriculography results.

A prominent feature in patients with Chagas disease is right ventricular dysfunction that may occur in the absence of any detectable LV disorder.[15] These findings were described by Marin Neto et al[15,16]and confirmed previous studies employing planar rest gated equilibrium radionuclide angiography with ^{99m}Technetium.[15, 16] Both studies showed that reduced right ventricular ejection fraction can be the only functional cardiac disorder detectable in some chronic Chagas patients with the indeterminate or the digestive forms, without any other clinical signs of heart disease.

Application of gated SPECT technique enables tomographic acquisition of blood pool imaging and more detailed assessment of LV dysfunction. Previous studies have used this approach to achieve a more accurate correlation between SPECT myocardial perfusion changes and regional wall motion abnormalities in cohorts of CCC patients with varying myocardial disease severity, demonstrating a close topographic relationship between regional wall motion impairment and reversible or fixed myocardial perfusion defects. [17]

More recently, radionuclide ventriculography image acquisition with the SPECT technique, which produces tomographic images of the ventricular cavity, co-registered with myocardial perfusion gated-SPECT imaging of the ventricular walls, were used to provide complementary information allowing characterization of left ventricle apical aneurysm,[17] the most notable segmental disorder in chronic Chagas' heart disease. That study described severe perfusion defects in the aneurysmal apical region, although relatively smaller when compared to the aneurysm size, identified by radionuclide ventriculography. Notably, the myocardial segments surrounding the aneurysm have preserved segmental wall motion, resulting in an aneurysm with a narrow neck, and the dyskinetic ventricular cavity has a "glove finger" appearance (figure 1). This aspect clearly diverges from what is classically found in apical aneurysms secondary to ischemic heart disease, in which the LV wall segments of the aneurysmal formation show typically dyskinetic movement. It is important to note that early detection of the aneurysm using several diagnostic nuclear imaging methods is clinically relevant because the apical region is somewhat more difficult to assess when standard echocardiographic methods are used. Furthermore, detection enables risk stratification with therapeutic implications, mainly with relation to

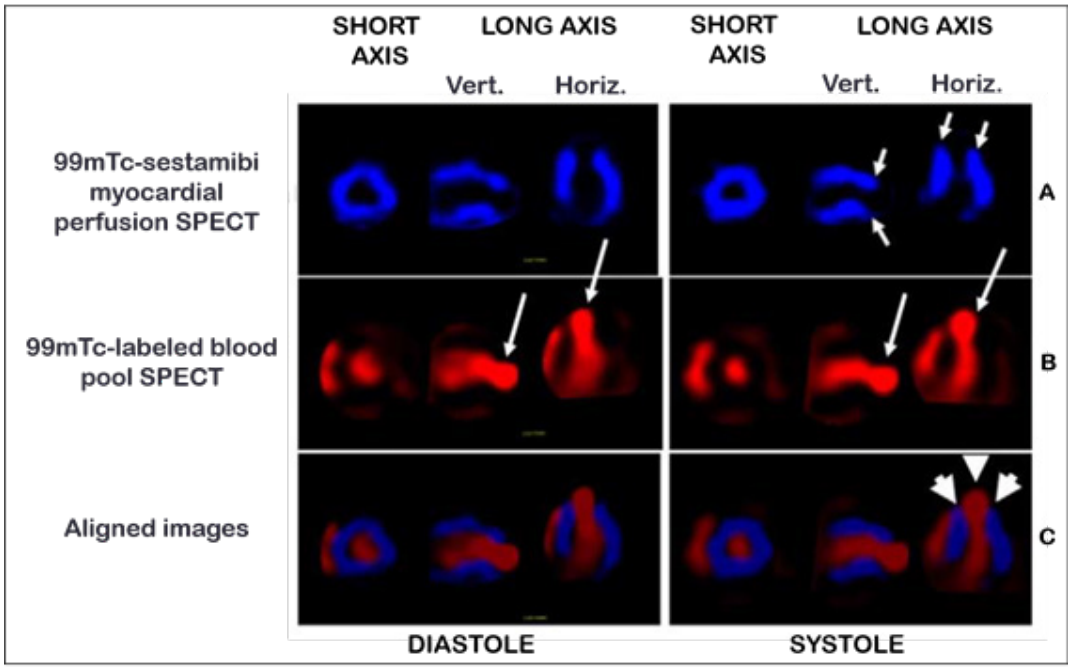

Figure 1 – Tomographic images. The left panels show the diastolic frames, and right panels are the systolic frames. A: Myocardial perfusion SPECT showing a severe perfusion defect involving a moderate portion of the cardiac apex, with preserved motion of the segments surrounding it (short arrows). B: Radionuclide ventriculography revealing an apical aneurysm extending beyond the left ventricular walls (long arrows). C: Co-registered images showing topographic correlation between the aneurysm cavity, the myocardial segments that form its "neck", and the perfusion defects (wide arrows). Adapted with permission from Simoes, et al. [17]

the risk of thromboembolism and potential indication of anticoagulation therapy.[17]

Myocardial Perfusion Scintigraphy

One particular feature of CCC is the clinical and laboratorial presentation masquerading as coronary artery disease.[18] Previous reports called attention to the occurrence of regional LV dyssynergia associated with rest (fixed) myocardial perfusion defects, mainly in the apical and basal portion of the posterior-lateral wall, that could be misinterpreted as regions of scar tissue resulting from previous myocardial infarction and atherosclerotic coronary artery disease.[19] Furthermore, precordial chest pain is a common manifestation and mimics acute or chronic coronary syndromes usually associated with classic coronary artery disease, but with normal epicardial coronary arteries on angiography. [20, 21] In this scenario, several clinical studies using myocardial perfusion scintigraphy reported findings of reversible defects compatible with reversible myocardial ischemia in CCC patients exhibiting normal coronary arteries, indicating the presence of coronary microvascular dysfunction.

There is now sound evidence in the literature suggesting that myocardial perfusion disturbances (MPD) caused by microvascular dysfunction participate in the pathogenesis of the myocardial damage process that ultimately leads to CCC.[6, 22] This hypothesis is also supported by pioneering autopsy studies showing a topographic correlation between coronary microvascular obstruction and ischemic myocardial lesions in CCC patients,[23, 24] Use of scintigraphy myocardial perfusion imaging makes a substantial contribution towards confirming the participation of microvascular disturbances in the pathogenesis of CCC.

Clinical Studies

In clinical settings, the first report of the occurrence of MPD in CCC patients employed assessment of global myocardial flow using ^{86}Rubidium and was published by Kuschnir and colleagues.[25] They observed a reduction in myocardial perfusion at rest and during physical exercise in comparison with healthy individuals. After that, remarkable myocardial perfusion abnormalities in CCC patients with angiographically normal coronary arteries were reported in 30-50% of patients by several

independent investigations and the presence of perfusion disturbances due to coronary microvascular dysfunction was postulated.[21, 26]

Marin-Neto et al. studied 23 patients with CCC and normal coronary arteries using thallium-201 stress-redistribution planar images and observed MPD in all cases.[26] Fixed defects, predicting regional myocardial fibrosis, were mainly found in myocardial regions exhibiting akinesis or dyskinesis, while reversible myocardial ischemia located in LV segments with less severe wall motion impairment was detected in 8 (35%) patients. Corroborating those findings, a further study with thallium–201SPECT investigated 37 patients with various stages of CCC, including 12 patients without any apparent cardiac involvement, 13 patients with regional LV dysfunction, but normal global LV systolic function, and 13 patients with advanced CCC with reduced LVEF.[19] All types of perfusion defects (fixed, paradoxical, and reversible) were again observed in 78% of the patients. Additionally, a significant topographic correlation was observed between perfusion disturbances and wall motion abnormalities in the apical and inferior-posterior-lateral LV segments. Notably, reversible MPD were detected in 42% of 12 CHD patients who otherwise had no evidence of myocardial disease (Figure 2). These reversible ischemic defects were mostly observed in the apical and inferior-posterior LV segments that correspond to regions in which regional contractile dysfunction is more frequently found in later stages of CCC,[26] strongly suggesting that myocardial perfusion disturbance precedes development of regional myocardial damage in CCC. This concept was further supported by another investigation using ^{99m}Tc-sestamibi myocardial perfusion SPECT in patients with the indeterminate form and myocardial reversible perfusion defects affecting LV segments also exhibiting wall motion abnormalities were reported in 25% of patients.[27] Overall, these findings support the concept that MPD occurs in early stages of CCC and may precede regional LV dysfunction.[22]

Hiss et al.[28] provided additional evidence supporting this hypothesis with a longitudinal, retrospective study of 36 patients with CHD who were initially evaluated with stress-rest myocardial perfusion scintigraphy and then had the nuclear scans repeated after a mean period of 5.6 years.[28] At baseline, 20 of the 36 patients (56%) exhibited reversible MPD involving an average of 10.2% of the LV area, as determined by the SPECT technique. Over the course of the follow-up period, the LVEF declined significantly from 55% ± 11% to 50% ± 13% and several of the initially reversible defects became fixed over time. Moreover, there was a correlation between the increase in the perfusion defect area at rest and the reduction in LV ejection fraction. Most notably, presence of ischemia in the initial evaluation exhibited a

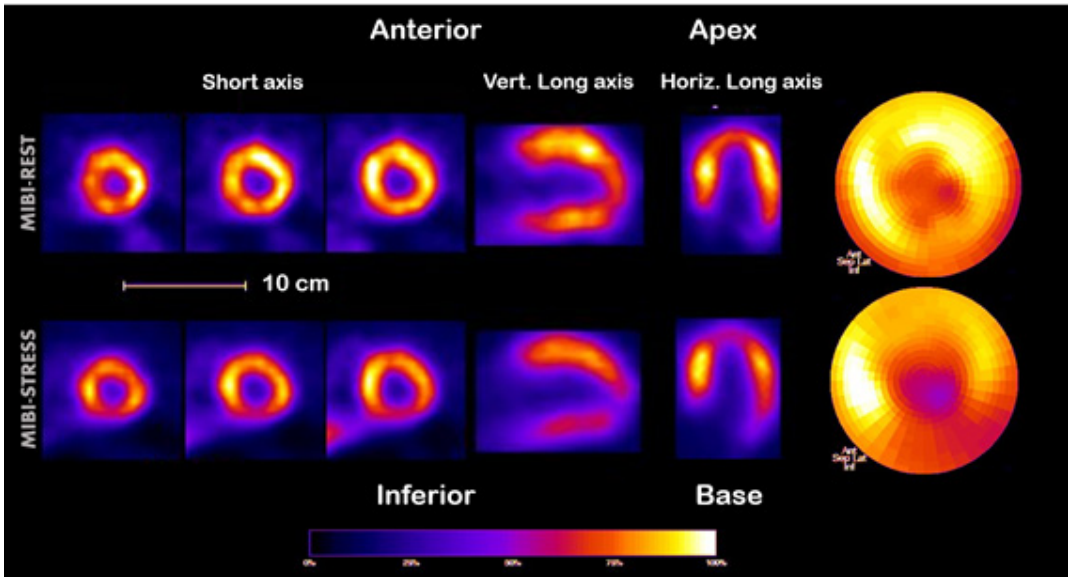

Figure 2 – Representative slices of stress-rest SPECT imaging with 99mTc-sestamibi of a 66-year-old female patient with CCC and normal coronary arteries on angiography, presenting reversible perfusion defects in the segments of the apex and inferior wall, involving 22% of the LV polar map surface area (stress).

topographic association with later development of wall motion abnormality in the same area; of the 47 segments presenting reversible perfusion defects in the initial study, 32 (68%) progressed to perfusion defects at rest, and of the 469 segments not showing reversibility in the initial study, only 41 (8.7%) had the same progression. In summary, in this longitudinal study, deterioration of LV systolic function over time was associated with both the presence of reversible ischemic defects at the initial assessment and with an increase in the extent of rest perfusion defects indicative of regional myocardial fibrosis during follow-up.

There is therefore compelling evidence indicating that coronary microvascular disturbances play a significant role in myocardial damage and progression of CCC, and that SPECT myocardial perfusion imaging is a promising tool for early detection, risk stratification, and monitoring of the progression of CCC.[29]

Experimental Studies

More recently, experimental models of chronic Chagas heart disease in small animals were investigated in vivo employing high-resolution scintigraphy images, enabling histological correlation of the perfusion disturbance and providing relevant information to clarify the participation of perfusion and inflammation derangements in the pathophysiological mechanism of CCC.

A pioneering study by Lemos de Oliveira et al.,[30] reported detection of rest MPD using in vivo high-resolution ^{99m}Tc-sestamibi SPECT myocardial perfusion imaging in an experimental model of CCC in hamsters. In that cross-sectional study, Syrian hamsters were investigated in the chronic phase at time windows of 6 and 10 months after experimental infection with *T. cruzi*. The results showed severe rest MPD occurring at similar rates as have previously been reported in humans at comparable stages of development of CCC (50%), and involving segments of the anterior-lateral and apical walls. The results of the in vivo images were topographically correlated with data from quantitative histopathological analysis, revealing no areas of transmural fibrosis in those segments with MPD, but showing higher intensity of inflammatory infiltrate. [30]

To understand those findings in greater depth, Tanaka et al.,[31] tested the effects of prolonged use of dipyridamole, a coronary microvascular dilating drug, on the rest MPD of CCC hamsters. Six months after experimental *T. cruzi* infection, infected animals (assigned to receive either dipyridamole or placebo) had larger areas of perfusion defect than the non-infected control animal groups and preserved LV systolic function. After treatment, the infected animals that received dipyridamole exhibited a significant reduction of the MPD area (from 17.3 ± 3.7 to 6.8 ± 2.1%, p = 0.001) (Figure 3).[31]

In summary, these findings support the hypothesis that areas with rest MPD correspond to viable but hypoperfused myocardium, similar to the hibernating myocardial phenomenon found in ischemic disease, and that coronary microvascular disturbance is closely linked to inflammation, playing a role in the pathophysiology of myocardial damage in CCC. Future research should target elucidation of the causal relationship between inflammation and microvascular ischemia and seek to discover the contribution made by each disorder to the pathogenesis of CCC.

Myocardial Sympathetic Innervation Imaging with ^{123}I-MIBG

Cardiac autonomic denervation is another remarkable feature of CCC and was first described in human autopsy studies.[32] Although this finding is not specific for CCC, the intensity of the cardiac neuronal depopulation surpasses that seen in any other etiology of heart disease.[33,34] Striking depopulation of the parasympathetic neuronal bodies in the atrial tissue and of the sympathetic paravertebral ganglia has been reported by several independent investigators. As a consequence of these anatomical findings, several methods of investigation have been employed in previous studies and showed functional abnormalities of reflex autonomic control of the heart rate.[6] Myocardial scintigraphy with ^{123}I-MIBG (MIBG) has been used in several stages of CCC to noninvasively assess myocardial sympathetic innervation and provide accurate information about the integrity of sympathetic nerve fibers and the degree of activation of cardiac sympathetic innervation.[19, 35]

Assessment of cardiac sympathetic innervation in patients with CCC using ^{123}I-MIBG scintigraphy was first described by Simões et al.[12] In that study, a series of 37 patients with several degrees of LV dysfunction underwent planar and SPECT ^{123}I-MIBG imaging and the results were correlated with myocardial perfusion scintigraphy and LV function assessments. It was observed that defects of MIBG uptake were seen in the majority of patients: in 33% of the patients without any other evidence of cardiac disease and 77% of the patients

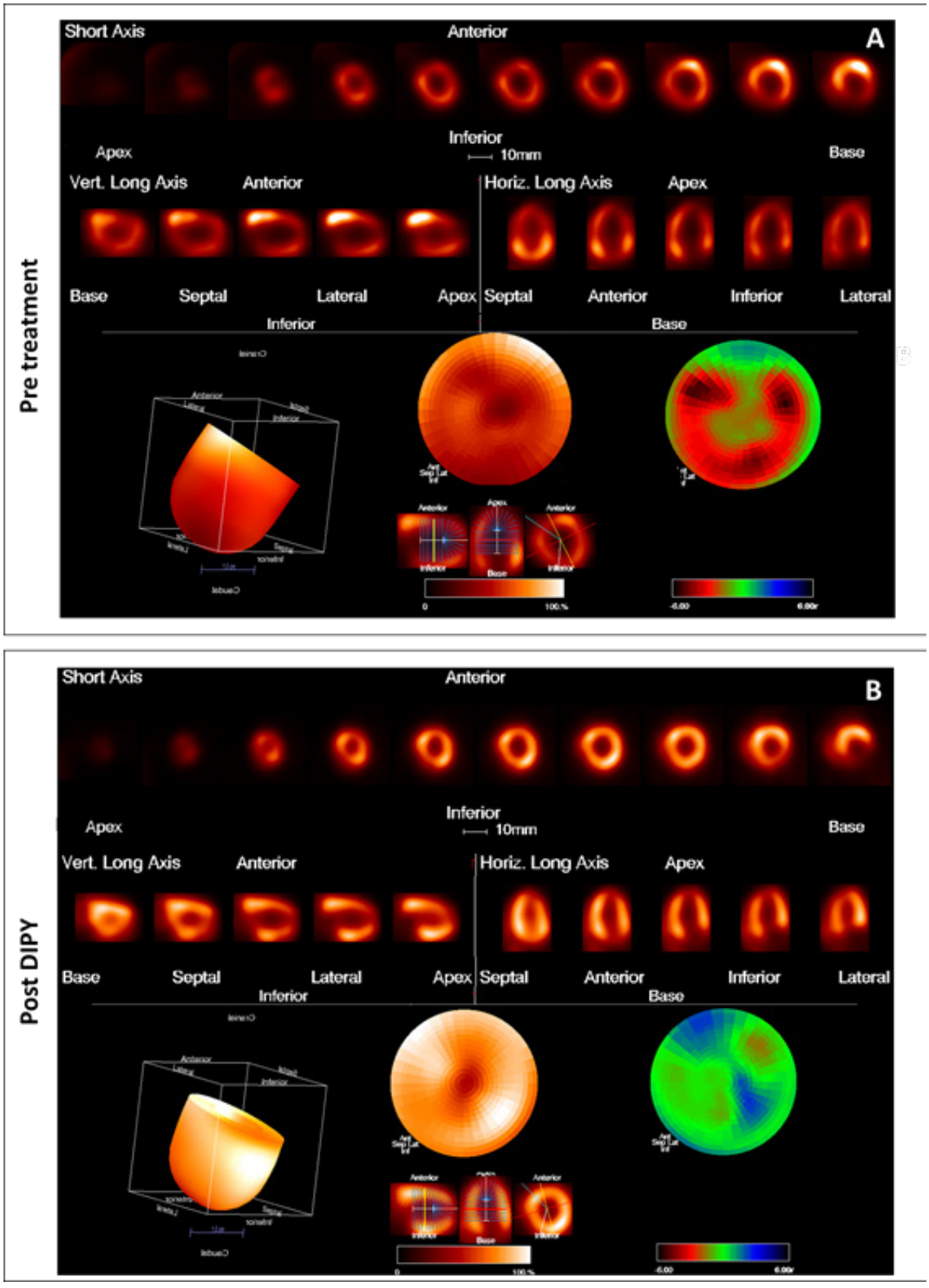

Figure 3 – Illustrative images from a myocardial perfusion study of a T. cruzi infected animal at 6 months post infection at (A) pre-treatment and (B) after 4 weeks of dipyridamole treatment. Representative slices of tomographic images (SPECT) are shown. The images were obtained along short axis and on vertical and horizontal long axes, with the resulting polar map shown in the lower panel of the figure. The dipyridamole-treated animal presented a severe perfusion defect involving the septal, anterior, lateral, and apical wall at baseline evaluation, with a striking reduction of perfusion impairment in the images acquired in the post-treatment evaluation.

with regional LV wall motion disturbance. Furthermore, patients with more severe LV dysfunction had a higher prevalence of MIBG defects (92%). Notably, there was a topographic correlation between areas of myocardial sympathetic denervation and areas exhibiting fixed and reversible myocardial perfusion scintigraphy defects and abnormal segmental LV wall motion predominantly involving the inferior, posterior-lateral, and apical LV walls. These initial results indicated that sympathetic denervation is an early derangement in the pathophysiology of CCC, before development of regional LV contraction disturbance or global dysfunction (Figure 4).[19] This hypothesis was corroborated by the results of an independent study showing abnormal MIBG uptake in most CCC patients with no other signs of cardiac involvement.[36]

A more recent study employed image co-registration in 13 patients with CCC to investigate quantitative and topographic correlations between areas of cardiac sympathetic denervation using ^{123}I-MIBG-SPECT, myocardial hypoperfusion using ^{99m}Tc-sestamibi-SPECT, and myocardial scarring using magnetic resonance imaging (MRI).[37] The results showed strong topographic agreement between areas of denervation and areas of stress-hypoperfused myocardium, corresponding to 60.8% of the denervated area. MRI showed that only 16.1% of the denervated area corresponded to areas of fibrosis.[37]

Miranda et al.,[35] addressed the correlation between presence and extent of myocardial sympathetic denervation and occurrence of severe ventricular arrhythmia in CCC patients with normal or mildly reduced LVEF.[35] In this study, patients with sustained ventricular tachycardia had higher ^{123}I-MIBG summed defect scores than 11 patients without sustained ventricular tachycardia. These findings indicated a relevant role of myocardial sympathetic denervation as a trigger mechanism for malignant ventricular arrhythmia in CCC.[35]

Another recent study was conducted with the objective of investigating the correlation between the extent of cardiac sympathetic denervation and occurrence of ventricular arrhythmia of varying severity in CCC patients. In that study, 15 CCC patients with sustained ventricular tachycardia had larger areas of viable but denervated myocardium, assessed by the summed difference defect scores between MIBG and ^{99m}Tc-sestamibi SPECT images (20.0 ± 8.0), than 17 CCC patients with a less severe form of ventricular arrhythmia, i.e., non-sustained ventricular tachycardia, (11.0 ± 8.0, $p < 0.05$), and also had larger areas than CCC patients without any repetitive ventricular arrhythmia, according to Holter monitoring (2.0 ± 5.0, $p < 0.0001$).[38] It is important to emphasize that severe ventricular arrythmia can lead to sudden death in early phases of the disease, even in patients with preserved global left ventricular function,[39]and so a risk stratifying tool such as that provided by assessment

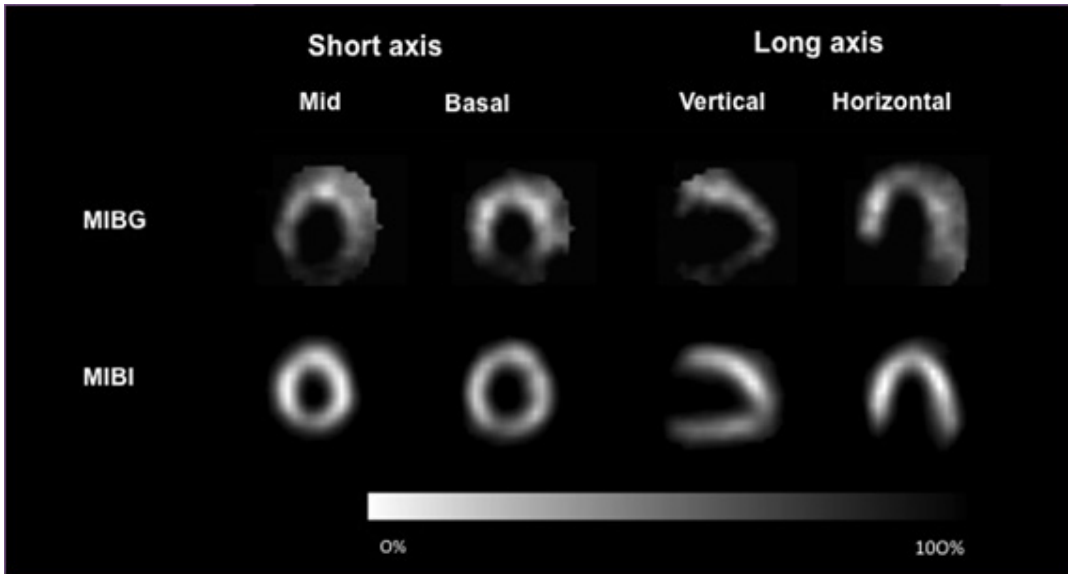

Figure 4 – Representative image of ^{123}I-MIBG (upper panel) and ^{99m}Tc-sestamibi SPECT (lower panel) showing normal Tc99m-Sestamibi uptake and severe ^{123}-I-MIBG uptake defects in the segments of the inferior, inferior-lateral, and septal inferior walls, indicating the presence of viable but denervated myocardium.

of cardiac sympathetic denervation could be useful in this clinical scenario.

In summary, the available data reinforces the notion that the extent of myocardial sympathetic denervation is closely correlated with the incidence of malignant ventricular arrhythmia in CCC patients, and MIBG scintigraphy may be a potential tool for stratification of arrhythmic sudden cardiac death risk.

Imaging Myocardial Viability with FDG-PET

Positron emission tomography (PET) is a useful tool for in vivo investigation of myocardial metabolism.[40] The metabolic state of the myocardium can be evaluated by regional uptake of ^{18}F-FDG, which is an analogue of glucose.[41] Thus, regions with preserved uptake of ^{18}F-FDG correspond to metabolically viable myocardium.

In experimental studies, a variety of strategies can be employed to improve ^{18}F-FDG accumulation by cardiomyocytes, such as use of different anesthetic agents, such as isoflurane, enhancing detection of myocardial metabolic viability.[42] In this scenario, Lemos de Oliveira, et al.[30] studied a model of chronic Chagas cardiomyopathy in hamsters using in vivo imaging methods including resting ^{99m}Tc-sestamibi and ^{18}F-FDG PET under isoflurane anesthesia, observing preserved or only mild reduction of ^{18}F-FDG uptake in regions with severe myocardial prefusion defects at rest, showing the presence of myocardial viability in those regions (Figure 5). Moreover, histopathological analysis of fibrosis reinforced these findings, since no coalescent fibrosis was found.[30]

Imaging Cardiac Inflammation with FDG-PET

To further improve understanding of the relationship between inflammation and progression of CCC in humans, it is essential to employ an imaging method able to detect and quantify myocardial inflammation in vivo. In this scenario, several studies have demonstrated the possibility of imaging myocardial inflammation using ^{18}F-FDG-PET

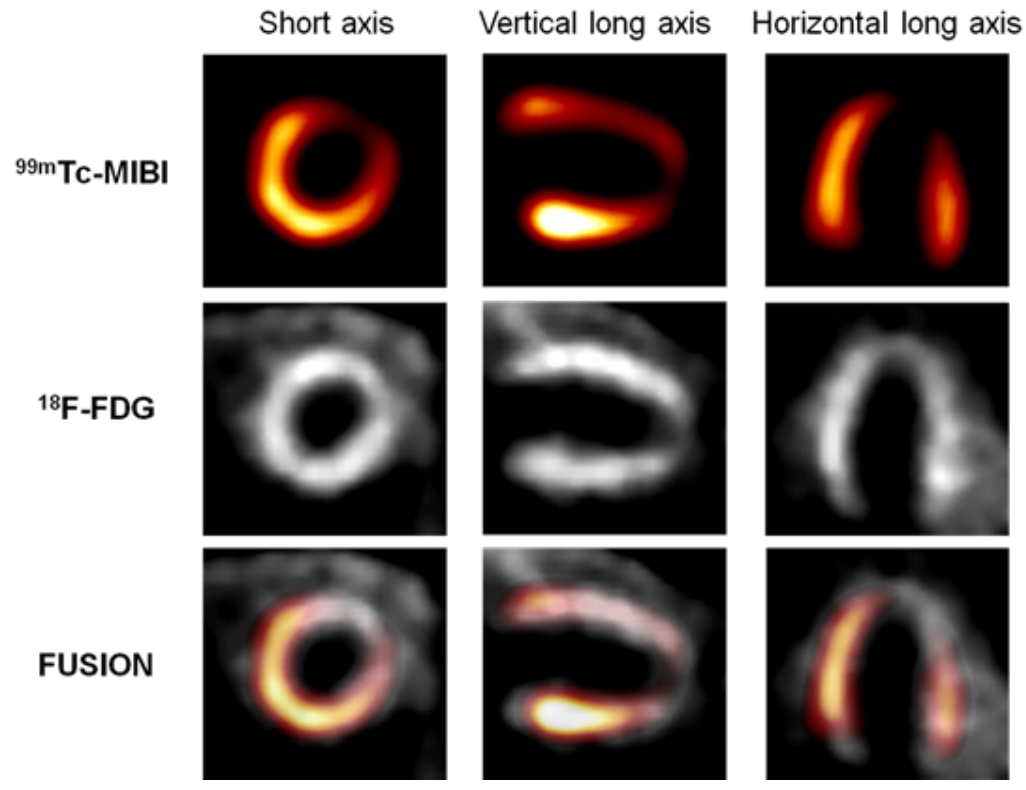

Figure 5 – RTomographic slices from myocardial perfusion imaging of a *T. cruzi*-infected animal with high-resolution ^{99m}Tc-Sestamibi (upper panels), ^{18}F-FDG-PET imaging (middle panels), and fused images of myocardial perfusion (in hot iron) and myocardial viability (in gray), shown in the lower panels. The images show severe perfusion defect involving the anterior, anterior-lateral, and apical segments, topographically associated with normal or mildly reduced radiotracer uptake demonstrating myocardial viability in the hypoperfused areas.

imaging under special metabolic myocardial conditions to suppress cardiomyocyte FDG uptake. Several strategies to suppress cardiomyocyte uptake of ^{18}F-FDG in order to achieve a suitable metabolic state have been reported in clinical and experimental scenarios, including fasting protocols, heparin administration and, in small animals, use of anesthetic combinations such as ketamine and xylazine. Under such conditions, cardiac uptake of FDG is dependent on inflammatory cell infiltrate.[42, 43]

However, clinical use of PET imaging for evaluation of inflammation in CCC patients is still limited to a few case reports. The first report was published by Garg et al.[44] These authors described a CCC patient with dyspnea, acute chest pain, and troponin elevation, but normal coronary angiography. Echocardiography images showed a decrease in LV ejection fraction (35%) and apical and aneurysmal ballooning of the apex and of the basal inferolateral wall. PET imaging with ammonia ($^{13}NH_3$) revealed MPD at the apex, basal inferior-lateral, and lateral walls. Additionally, PET imaging with ^{18}F-FDG showed diffuse uptake throughout the myocardium. Notably, the most intense focal uptake was adjacent to the apical and basal inferior/inferolateral aneurysms that had severe $^{13}NH_3$ defects and prominent myocardial delayed enhancement on MRI.[44] Another clinical case with very similar characteristics was recently reported by Salimy and colleagues.[45]

Shapiro and colleagues reported on two patients with CCC presenting arrhythmic storm with recurrent ventricular tachycardia (VT) and demonstrated higher uptake of ^{18}F-FDG in myocardial regions from which the VT originated, suggesting on-going inflammation contributed to triggering VT.[46] More recently, Moll-Bernardes et al. published a case report of a CCC patient with episodes of sustained ventricular tachycardia and increased uptake of ^{18}F-FDG on PET/CT adjacent to hypoperfused or fibrotic areas.[47]

These initial observations therefore suggest a relationship between myocardial inflammation detected by in vivo FDG-PET imaging and the genesis of severe ventricular arrhythmias in CCC. This is consistent with the structural and functional changes described in myocardial inflammation due to other conditions, i.e., irreversible cell damage with scar formation generating reentrant arrhythmias and exacerbated automaticity within inflamed areas.[48]

Although further studies with larger patient populations are needed, preliminary results suggest that detection of inflammation in vivo using ^{18}F-FDG-PET is a promising tool for monitoring disease progression and even for risk stratification of patients with different degrees of CCC. Future research should therefore consider these potential new clinical applications of PET imaging.

Conclusions

CD is a complex illness with multiple pathophysiological mechanisms responsible for its most common and ominous manifestation, CCC. Myocardial changes are distinct at each stage of the disease and radionuclide imaging offers opportunities for detection of diverse cardiac abnormalities throughout the course of disease progression. In the early stages of chronic disease (indeterminate form), and also in patients with the isolated digestive form, it is common to observe impairment of right ventricle function that can be detected by radionuclide ventriculography. In patients with full-blown CCC, coronary microvascular disturbances detectable on myocardial perfusion scintigraphy and cardiac autonomic denervation observed on myocardial scintigraphy with ^{123}I-mIBG are very prevalent. Thus, an array of nuclear medicine methods constitute useful non-invasive tools for monitoring disease progression and for risk stratification.

Future research should address the efficacy of SPECT and PET images for detecting and monitoring early subclinical myocardial damage in CCC patients as a potential tool for evaluation of therapeutic strategies targeting inflammation and microvascular ischemia.

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Potential Conflict of Interest

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Author Contributions

Conception and design of the research: Tanaka DM. Critical revision of the manuscript for intellectual content: Marin-Neto JA, Simões MV.

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REVIEW ARTICLE

Heart Transplantation for Chagas Cardiomyopathy

Maria da Consolação Moreira, Fabio Morato Castilho, Renato Braulio, Guilherme Ferraz Messina de Pádua Andrade, José Renan da Cunha Melo

Universidade Federal de Minas Gerais (UFMG), Minas Gerais, MG – Brazil.

Abstract

Heart transplantation (HT) is an established treatment for patients with advanced heart failure (HF). Chagas disease (CD), caused by the *Trypanosoma cruzi* (*T.cruzi*) is an important cause of HF in Latin America. Considering CD is a chronic infectious disease, the use of immunosuppressive therapy after HT can reactivate *T. cruzi* infection and compromise outcomes. Early diagnosis and treatment of this complication is extremely important, which requires knowledge, experience, and a high degree of suspicion by transplant physicians. Furthermore, with the international immigration of people, CD is no longer exclusive to Latin America, since a large number of immigrants with *T. cruzi* infection are living in non-endemic countries. This phenomenon represents not only a new global epidemiological problem, but also a challenge for transplant teams. This review aims to discuss the peculiarities of HT in the context of CD, with a focus on reactivation of the infection, clinical manifestations, etiological treatment of *T. cruzi* and differential diagnosis with allograft rejection, among HT recipients.

Introduction

Heart transplantation (HT) is an established treatment for selected patients, with advanced heart failure (HF), with refractory to optimal medical treatment, and without contraindications that would compromise the outcomes. [1,2]

The procedure in these patients has proven to be a treatment that is effective in decreasing mortality rates and improving patients' quality of life.[3] At present, not only are the number of heart transplant candidates increasing, but they are also becoming much more complex. [3,4] The great advances that have occurred in the field of transplants notwithstanding, there are still challenges to be faced:

- older age of both recipients and donors;
- the need for mechanical circulatory support (not available in several Centers);
- the growing use of combined organ transplants;
- high proportion of sensitized candidates;
- shortage of organ donors;
- uncommon etiologies of HF requiring HT;
- Chagas disease (CD) as a worldwide challenge and the complexity of *T. cruzi* infection reactivation.[5-7]

In the past, CD was considered a contraindication for heart transplantation due to the possibility of reactivation of *T. cruzi* infection as a consequence of immunosuppressive therapy to prevent allograft rejection.[5,8] The first heart transplant due to CD was performed in Brazil in June 1985, by Dr Euryclides de Jesus Zerbini, in the city of São Paulo.[8] Since then, CD has emerged as a complex indication for heart transplant, and even today it remains a challenge for transplant teams in endemic countries. As a result, CD has added more challenges to the field of transplantation.

Brazilian physicians were pioneers in performing HT in chagasic patients, gaining experience in this new area of transplants. From 1985 on, HT has become a well-established alternative for patients with end-stage Chagas heart disease.[5,9,10] Despite the complexity of the reactivation of *T. cruzi* infection, which occurs frequently in HT recipients, its proper diagnosis allows for an adequate treatment and ensures a good prognosis.[5(

Keywords

Trypanosoma cruzi; Chagas disease; Cardiomyopathy; Heart failure; Heart transplantation.

Mailing Adddress: Maria da Consolação Moreira
Av. Alfredo Balena, 190. Postal Code: 30130-110, Belo Horizonte, MG – Brazil.
E-mail: mariacvmoreira@gmail.com

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Peculiarities of Chagas Disease in the Context of Heart Transplant

Since 1990, several intergovernmental initiatives coordinated by both the Pan American Health Organization (PAHO) and the World Health Organization (WHO) have been implemented in an attempt to eliminate domestic triatomines and to prevent transmission via blood transfusions in Latin America.[11] As a consequence, the number of new cases of infection was significantly reduced. However, an estimated 7,968,094 *T. cruzi* infected individuals worldwide, mostly in Latin America, have been reported. [12]

The increased flow of individuals from rural areas to large cities and the international migration of people has led to a globalization of the disease that is no longer exclusive to Latin America. A large number of immigrants with chronic *T. cruzi* infection are living in non-endemic countries, such as those in North America and the European Union, as well as in Australia and Japan. This fact causes concern for transplant teams and a challenging epidemiological problem.[6,7]

Chagas disease is characterized by an acute phase after an initial infection followed by a chronic form. The acute phase, usually asymptomatic or accompanied by mild symptoms, progresses with high levels of *T.cruzi* in the blood, proliferation of amastigote forms in various tissues, and resolution in 4 to 8 weeks. The patients then evolve to the chronic form, with low parasitemia levels. The chronic form is also divided into indeterminate, an asymptomatic form that can persist for life, and a clinically symptomatic form occurring in 20% to 30% of all cases. The cardiac, digestive, or cardio-digestive clinical manifestations may appear even decades after the initial infection. [13] The chronic cardiac form includes arrhythmias, conduction defects, HF, and sudden cardiac death. Heart failure due to Chagas etiology has a worse prognosis and a higher mortality rate when compared to other etiologies. [14]

Chagas disease is the third leading cause of HT in endemic countries, corresponding to 35% of all patients undergoing the procedure[5,9,10]

The reactivation of chronic infection by *T. cruzi* may occur in conditions of immunosuppression, such as AIDS, cancer undergoing chemotherapy, or after the use of immunosuppressive drugs, such as in the context of organ transplants. [13]

Transplant professionals from endemic and non-endemic countries need to be aware of the risk of *T. cruzi* transmission from infected donors to recipients as well as to the risk of reactivation of chronic infection in organ transplant recipients, receiving immunosuppressive therapy to avoid allograft rejection.[5,13]

Recipient Selection and Listing Criteria

The indications and contraindications for HT in the setting of CD follow the classic HT guideline criteria for other HF etiologies. [1-2,5] A patient with severe terminal HF refractory to optimal medical treatment and without formal contraindications, might benefit from the procedure and should be included on the waiting list for a heart transplant. [1,2,5.] Clinical treatment needs to be optimized for symptom relief and to improve survival, necessarily including the following drugs: an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor added to a beta blocker (in maximum tolerated doses) and a mineralocorticoid antagonist if possible.[15-17]

Some peculiarities in the selection of HT potential donors and recipients in the context of CD should be observed.[2,5]

Chagas patients usually have lower values of pulmonary arterial pressure, which can reduce right ventricular dysfunction, a frequent complication in the postoperative period of HT. Thus, cardiac manometry by right cardiac catheterization may not be always necessary before HT.[2,5] Most of these patients come from poor rural areas. Social inequalities may influence results and survival rates after HT, but these issues are still not well understood. However, it seems that the patient's socioeconomic condition has no impact on outcomes after HT. [18] The megaesophagus and megacolon may occur in CD as a cardio-digestive form and should be evaluated. Depending on the severity of digestive manifestation, these may constitute contraindications to the procedure.[5]

Chagas cardiomyopathy is a highly arrhythmogenic disease, and sudden cardiac death corresponds to 55%-65% of all deaths, frequently caused by malignant arrhythmias, such as tachycardia and ventricular fibrillation.[18] Patients with malignant ventricular arrhythmias usually receive an implantable cardioverter-defibrillator (ICD). They may require multiple ICD therapies, more than 4 shocks per day, featuring an electrical storm. This group of patients might also benefit from a heart transplant.[19]

In Brazil, according to governmental regulation, serology for *T. cruzi* infection in all potential donors and recipients is mandatory, and a positive donor for heart

recipients is not accepted.[13] Potential organ donors and recipients should always be screened for Chagas disease, in both endemic and non-endemic countries whose potential donor/recipient has a positive epidemiology.[6,13]

Mechanical circulatory support has a potential benefit as a bridge for HT in chagasic patients. However, due to the high costs, this device is not available in the Public Health System (SUS in Portuguese) in Brazil, which funds more than 90% of heart transplants in the country.[5]

Immunosuppression Strategies

Induction therapy for HT, regardless of the etiology of HF, consists of intense immunosuppressive therapy during the transplant procedures or in its immediate postoperative period. It is recommended in high-risk patients in an attempt to reduce the risk of hyperacute rejection or delay the use of higher doses of calcineurin inhibitors, thus minimizing kidney damage.[19,20] The most widely used inducing agents are polyclonal anti-thymocyte immunoglobulins (polyclonal antibody - thymoglobulin) and interleukin 2 receptor inhibitors, which have low immunogenicity, such as daclizumab and basiliximab[21]

Basic immunosuppressive therapy for the maintenance of heart transplant patients generally includes a calcineurin inhibitor agent (Cyclosporin A or tacrolimus). These agents must be associated with mycophenolate mofetil, mycophenolic acid, azathioprine, rapamycin, or everolimus. Prednisone is associated with this standard regimen and, in most patients, can be suspended six months after the transplant, in the absence of rejection.[21] In the context of Chagas disease, induction and/or maintenance immunosuppressive therapy can reactivate *T. cruzi* infection.[2,5,13]

There are no randomized control clinical studies comparing the various immunosuppressive regimens in HT chagasic patients. However, a greater number of reactivations have been described in recipients using mycophenolate mofetil.[(22)] Therefore, it is recommended that Chagas patients receive the lightest immunosuppressive therapy, as long as there is no rejection.[5]

Diagnosis and Treatment of Rejection

Graft rejection is an important cause of morbidity and mortality after heart transplant in general, although the incidence of treated rejection continued to decline. In the last decade, only 12.6% of HT recipients were treated for rejection between hospital discharge and one year after transplant.[3]

Rejection is classified into hyperacute, antibody-mediated, and acute cellular rejection (ACR), the last representing the most prevalent form of rejection in an HT setting. Histologically, it is defined by inflammatory infiltrates, which are typically lymphocyte predominant, and associated myocyte injury. The International Society for Heart and Lung Transplantation (ISHLT) has revised (R) categories of ACR as follows: 0R (no rejection), 1R (mild), 2R (moderate), or 3R (severe).[23]

Hyperacute rejection is mediated by preformed antibodies to the allograft in the recipients and manifests as a severe graft failure within minutes or a few hours after the HT procedure. It is now uncommon due to the advent of prospective cross-matching and more potent immunosuppressive therapy.[23]

Antibody-mediated rejection is poorly defined and challenging, especially in HT performed for Chagas cardiomyopathy.[5,23] The frequency of hyperacute rejection and antibody-mediated rejection after HT due to CD have not been reported.[5]

Although rejection is a major cause of death amongst chagasic recipients, occurring in 10%–14% of all patients, no difference in the incidence of rejection episodes (grade 2R or 3R) between HT recipients with or without Chagas disease has been reported in Brazil.[3,9,10,20,24]

To date, there are no laboratory markers for rejection. Most patients are asymptomatic, and symptoms, when present, are vague and nonspecific. Thus, early detection of cardiac rejection relies on histological diagnosis through endomyocardial biopsy (EMB), the gold standard method for the diagnosis, and the monitoring of allograft rejection. Despite its invasiveness, EMB is associated with a very low morbidity and mortality when performed by experienced operators.[25] In most transplant centers, it is used for routine rejection surveillance, varying the frequency of biopsies in Center protocols.

A myocarditis secondary to reactivation of the *T cruzi* infection in the transplanted heart can often occur, which makes the differential diagnosis between allograft rejection and reactivation of Chagas' disease a great challenge.[5]

Endomyocardial biopsy is considered the best method for the differential diagnosis between inflammation caused by immunological rejection and *T. cruzi* infection reactivation. The definition of one of these two conditions is still a challenge if parasites are not found at the biopsy fragments. Under routine histopathology staining techniques, if parasites are not seen, the inflammatory histopathological features found in either rejection (grade 2R or 3R) or reactivation are quite similar. Thus, the detection of an inflammatory mononuclear

infiltrate in the EMB slides is not enough to rule out the diagnosis of Chagas disease reactivation and poses a medical dilemma as the aggressive immunosuppressive treatment to abort rejection may facilitate Chagas disease reactivation.[5]

The findings of *T.cruzi* amastigote nests with inflammatory mononuclear infiltrates in the EMB fragments do not exclude concomitant allograft rejection, as the two conditions may occur concomitantly.

The therapy of rejection in transplant recipients with and without Chagas disease is similar. In general, a mild grade of rejection (ISHLT 1R), in the absence of clinical or hemodynamic compromise, generally do not require additional intervention. However, higher grades (≥ 2R) require an aggressive supplemental immunosuppression. The majority of cases with ACR respond properly to pulse corticosteroid therapy, although rescue therapy may be required for certain patients.[5,21]

Rejection constitutes a risk factor for Chagas reactivation, as over 85% of all patients have at least one rejection episode before reactivation occurs.[5]

Moreover, up to 43% of all patients with findings of inflammatory infiltrate compatible with the diagnosis of 2R or 3R rejection, at EMB fragments, do not respond to immunosuppressive therapy, but they do show a good response to anti-trypanosomal drug treatment.[5]

Post Heart Transplant *T. Cruzi* Infection Reactivation

Clinical presentation

The instituted immunosuppressive therapy increases the risk of *T. cruzi* infection reactivation. The incidence after HT varies from 19.6% to 90% in Brazil.[9,20,24] A recent publication from a United States case series shows a rate of CD reactivation of 61%, which is within the broad range reported here.[26]

The Latin America Guideline for the Diagnosis and Treatment of Chagas Heart Disease has established several risk factors for reactivation, as follows:[25,26]

- number of rejection episodes;
- intensity of Immunosuppression;
- use of mycophenolate mofetil;
- presence of malignancy;
- HIV infection and other immunosuppression status.[5]

Considering the potential morbidity and mortality, the diagnosis and appropriate management of Chagas disease reactivation in the context of organ transplants is extremely important. Therefore, this procedure must be performed within a structured clinical and laboratory protocol to monitor the reactivation of the infection and its subsequent treatment.[5,9,13] The diagnosis of reactivation is based on clinical signs and symptoms and/or the presence of parasites in blood, cerebrospinal fluid and other fluids, bone marrow, or tissues.[5,9] After HT, the patient must be closely and regularly monitored. Clinical monitoring aims to identify the first signs of reactivation and promptly establish anti-*T. cruzi* treatment. Clinical reactivation has cardiac and extra-cardiac manifestations including: myocarditis, ventricular dysfunction, arrhythmias, new atrioventricular/intraventricular blocks on the ECG, new skin lesions (subcutaneous nodules, panniculitis), fever, bone marrow involvement or neurological manifestations. The central nervous system involvement is a rare and severe clinical manifestation. It manifests through meningoencephalitis, chagoma, brain abscess, or stroke, as well as through spacing-occupying lesions in the white matter of the brain.[5,9,27] Figure 1 is an example of post-heart transplant Chagas reactivation.

The myocarditis of the reactivation can be mistakenly diagnosed as a graft rejection, receiving intensified immunosuppressive treatment, which will aggravate the reactivation of the infection.[28] The differential diagnosis between rejection and reactivation myocarditis is still a major challenge. In the presence of inflammatory infiltrate, amastigote nests and/or positive PCR for *T. cruzi* in the myocardium, it can be said that there is a reactivation, but it is impossible to safely exclude associated allograft rejection. Despite this complexity, the survival rates of chagasic patients undergoing HT do not differ from other etiologies.[9,20]

Parasitological diagnosis of reactivation

The purpose of laboratory monitoring is to identify any subclinical signs of reactivation before cardiac and extra-cardiac symptoms, as well as allograft dysfunction.[5,13] Serological tests are useful only in potential donors, in the diagnosis of chagasic cardiomyopathy in potential recipients, and in seronegative recipients who receive organs from seropositive donors.[5,13] These tests play no role in the diagnosis of reactivation. Traditionally, laboratory monitoring has used parasitological methods (direct blood search of *T. cruzi* and blood cultures) and serial histological examinations of EMB, in search of *T. cruzi* amastigotes, in tests with low sensitivity.[5,13] In recent years, several studies have demonstrated the value of the PCR test in peripheral blood and EMB fragments

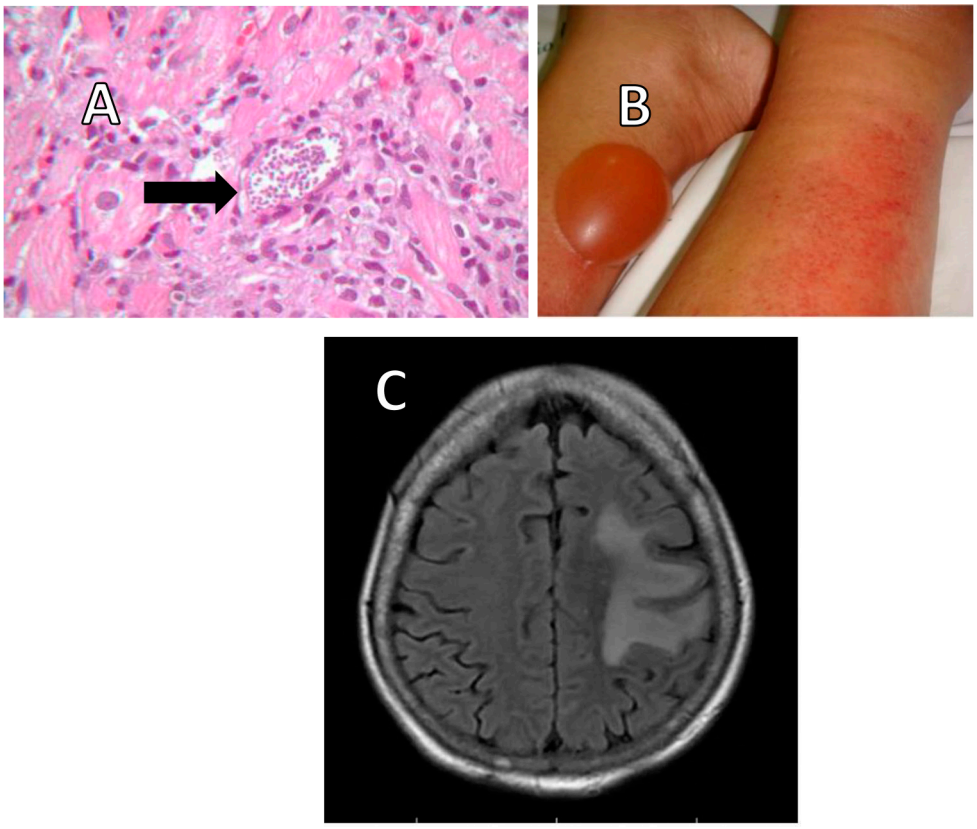

Figure 1 – Illustration of Chagas disease reactivation in the heart (A), skin (B), and brain (C) in chagasic patients submitted to HT.
A: Endomyocardial biopsy fragment showing myocarditis and a nest of amastigotes in the transplanted heart (hematoxylin-eosin staining). B: Bullous skin lesions and dermatitis in the legs. The bubble fluid analysis showed trypomastigote forms. C: Expansive lesion in the brain as shown by magnetic resonance imaging. A stereotaxic brain biopsy demonstrated nests of amastigotes upon hematoxylin-eosin staining and immunohistochemistry for T. cruzi and confirmed the diagnosis (not shown) (Authors file).

in detecting early reactivation, before the appearance of symptoms and/or cardiac allograft dysfunction.[29-32] Several studies have shown that PCR analysis is able to detect *T.cruzi* either in the blood or in EMB before clinical manifestations of reactivation by two or more months. Currently, PCR diagnosis is a precious tool to help physicians decide whether patients should begin treatment with anti-parasite drugs or changes in the immunosuppression protocol.[29-32]

It is very important to monitor HT recipients for early detection of *T.cruzi* reactivation, allowing etiological treatment before clinical manifestations appear. However, no specific definition about when and how the monitoring protocol should be applied is available. Some centers agree that Chagas recipients should be routinely monitored for *T.cruzi* reactivation as they are monitored for rejection and any time when clinical suspicion occurs. Variations in the protocol can occur depending on the transplant team's policy.[5,17,26,33]

Thus, concerning the frequency of clinical visits, laboratory monitoring, and EMB, there is still no consensus in the literature. Table 1 is our suggestion for a clinical, laboratory, and histological monitoring protocol for chagasic patients undergoing HT and the etiological treatment, which is in line with main available guidelines.[5,17,26,33] In countries where Chagas disease is not endemic, failure to identify patients with Chagas disease reactivation constitutes a major medical problem, as severe or fatal outcomes may supervene the incapacity to establish a proper diagnosis.[33,34]

Etiological treatment of reactivation

Benznidazole and nifurtimox are the anti-trypanosomal drugs of choice and have proven to be effective when administered to patients in the acute phase of Chagas disease and in those showing *T.cruzi* infection reactivation.[5,13] However, their efficacy upon the chronic phase has been a subject of debate.

Table 1 – Clinical and laboratory monitoring of *T.cruzi* infection reactivation after heart transplantation in Chagas disease and etiological treatment

Procedure
Before transplantation
- Serological tests for Chagas disease for the donor
- Serological tests for Chagas disease for the potential recipient with some possibility of Chagas cardiomyopathy
After transplantation
- Periodic clinic visits with attention to signs/symptoms of reactivation, including ECG and Echocardiogram
- Routine blood *T.cruzi* test (smear, blood culture) for diagnosis of infection reactivation
- Routine blood test for *T.cruzi* by PCR if available
- Routine periodic endomyocardial biopsies, with *T.cruzi* search (histology, immunohistochemistry, and PCR analysis, when available)
- Search of *T.cruzi* in tissues (skin, bone marrow, among others) in a suspicion of *T.cruzi* infection
Frequency of procedures after transplantation
- First month: weekly
- Second month: every two weeks
- Third to sixth month: monthly
- Seventh to 12th month: every 3 months
- After 12 months: every six months
Etiological treatment of reactivation
- Benznidazole 5mg/Kg/day for 60 days

Adapted from references [2,5], and [26].

Thus, etiological treatment for Chagas disease is recommended for patients with acute infection, congenital infection, women of childbearing age for the prevention of vertical transmission, and reactivated infection in immunosuppressed patients. Other chronically infected people in the early chronic phase (especially children less than 15 years of age) may also benefit from treatment.[13]

Antiparasitic treatment is not recommended for patients in the chronic phase with advanced cardiomyopathy, as is the case of the heart transplant candidates, since there is no evidence of benefit. There is no evidence to support the prophylactic anti-*T.cruzi* treatment strategy for reactivation.[13]

In the heart transplant scenario, the presence of clinical manifestations of *T.cruzi* infection reactivation or identification of the parasite in the blood, cerebrospinal fluid, EMB fragments, or in other tissues constitute sufficient evidence to begin etiological treatment without delay. Benznidazole, a nitroimidazole derivative, is the first-line treatment drug of choice.[5,13] Each tablet contains 100mg of the active substance. It is absorbed by the gastrointestinal tract and predominantly excreted by the kidneys, with a half-life of 12 hours. The recommended dose is 5mg/kg/day, for 60 days, with the daily dose being divided into two or three times.[5,13] Its most important side effect is urticarial dermatitis, which occurs in about 30% to 60% of all patients, commonly occurring early at the end of the first week of treatment, presenting a good therapeutic response with the use of antihistamines or small doses of corticosteroids. In a few cases, fever and adenomegaly may appear, in which case the medication should be discontinued. Other adverse effects include polyneuropathy, with pain and/or tingling in the lower limbs. Anorexia, significant leukopenia, and agranulocytosis are rare, and when present, the interruption of treatment is mandatory.[(13)] Nifurtimox is not available in Brazil. These trypanosomicidal medications are contraindicated in pregnant women and in patients with either renal or hepatic impairment.[13] A patient may have more than one reactivation episode after treatment. Therefore, it is necessary to maintain the monitoring of reactivation after anti-*T.cruzi* treatment.[5,13]

Post Heart Transplant Complications and Survival

The clinical outcomes, morbidity, and mortality in HT recipients with and without Chagas disease are similar.[9-10,20] In both classes of patients, the major complications reported after transplant are almost the same: allograft dysfunction (20%); rejection (2R or 3R, 10%-14%); bleeding (10%); non *T.cruzi* infection (20%-30%); acute kidney failure

(up to 70%); cardiac allograft vasculopathy, which seems to be less frequent in chagasic recipients. Moreover, a reported higher incidence of malignancy has not been confirmed in all series.[8-10, 20, 35]

In Brazil, the survival rate of Chagas patients undergoing HT is 76%, 71%, and 46% at six months, 5 and 10 years respectively, which is better when compared to the cohort of patients undergoing HT due to other etiologies.[9] It has been postulated that the reason for the detected differences may well be due to particular chagasic patient characteristics, such as their young age, less comorbidities, and less previous cardiac surgery.[8-10,20]

However, it should be emphasized that the only national registry compiling the results of HT in Brazil was carried out in 1999, more than 20 years ago[5,9,10]

Conclusions

Heart transplantation is an established treatment for end-stage Chagas cardiomyopathy. The reactivation of *T.cruzi* infection occurs frequently in HT recipients, but a proper diagnosis allows for an adequate treatment and ensures a good prognosis. The survival rate of Chagas patients undergoing HT is better when compared to patients undergoing HT due to other etiologies.

Despite many advances in this complex field, there are still many unanswered questions and challenges. Chagas disease (American trypanosomiasis) is no longer exclusive of Latin American. The globalization of Chagas disease also requires attention and knowledge from transplant teams in non-endemic countries. Failure to diagnose Chagas disease in potential organ donors and recipients from endemic areas, as well as reactivation after transplant can evolve to fatal consequences.

With the incorporation of PCR techniques, the reactivation concept should be revised. The differential diagnosis between rejection and reactivation remains a challenge and warrants further study. Multicenter studies comparing different immunosuppression protocols are desirable, as are a national registry to assess candidate selection, the management of immunosuppression to prevent and treat rejection episodes, the treatment of eventual *T. cruzi* reactivation, patient surveillance, and the evaluation of long-term results from the procedure.

Author Contributions

Conception and design of the research: Moreira MCV. Acquisition of data: Moreira MCV, Andrade GFMP. Analysis and interpretation of the data: Moreira MCV, Castilho FM, Cunha-Melo JR. Writing of the manuscript: Moreira MCV, Castilho FM, Andrade GFMP, Cunha-Melo JR. Critical revision of the manuscript for intellectual content: Moreira MCV, Cunha-Melo JR.

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

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REVIEW ARTICLE

Cardiac Magnetic Resonance in the Assessment of Chagas Disease and its Complications

Ariane Binoti Pacheco[1,2], Rodrigo de Jesus Louzeiro Melo[2], Carlos Eduardo Rochitte[2]

Multiscan Inteligência Diagnóstica[1], Vitória, ES - Brazil
Universidade de São Paulo[2], São Paulo, SP - Brazil

Abstract

The well-known occurrence of Chagas disease in endemic areas has become a worldwide problem, and cardiac magnetic resonance allows the early detection of cardiac involvement and complications of this disease. Cardiac magnetic resonance is a useful tool in all phases of Chagas disease, and new promising techniques using T1 mapping and extracellular volume measurements are able to detect cardiac involvement even earlier than conventional techniques.

Introduction

The protozoan *Trypanosoma cruzi* is the causal agent of Chagas disease (CD), considered a significant global health problem. It affects the young productive population and is responsible for losses of around 752 000 working days in endemic countries.[1] The migratory flux between endemic and non-endemic countries has spread CD worldwide and turned it into a global health problem, especially in countries with little knowledge on CD and its transmission.[2–4]

The natural progression of CD is divided in acute and chronic phases. The chronic phase is subdivided into indeterminate and determinate forms. The pathogenesis of CD involves an inflammatory response, as well as cellular damage and fibrosis that can be identified by cardiac magnetic resonance (CMR) imaging sequences.

Keywords

Chagas Diseases/complications; Chagas Cardiomyopathy/complications; Fibrosis; Heart Failure; Magnetic Resonance Imaging/methods; Gadolinium /radiation effects; Extracellular Volume; T1 Mapping; Endemic Diseases.

CMR has been applied to evaluate several cardiomyopathy etiologies; it is considered efficient in the diagnosis of the different stages of CD and for determining prognosis, in addition to being a non-invasive method that does not expose the patient to ionizing radiation[5].

Different CMR sequences are available to confirm early or late cardiac involvement in patients with CD and to investigate heart failure of unknown causes where typical findings of CD could provide additional diagnostic information.

The diagnostic role of CMR in acute CD

Most patients with acute CD are oligosymptomatic and hardly ever seen in non-endemic areas; it is estimated that only 1–2% of the cases are diagnosed.[5] In this phase, mortality is high and some patients develop severe myocarditis, meningoencephalitis, or both. Accurate diagnosis in the acute phase is particularly important because of the high probability of cure reached through the use of antiparasitic drugs.[6]

The consequences of heart muscle inflammation resulting from cardiac cell injury caused by *T. cruzi* and its related immune reactions can be identified by CMR using T2-weighted and late gadolinium enhancement (LGE) sequences for detecting myocarditis.

The T2-weighed sequence is able to identify areas of signal hyperintensity corresponding to myocardial edema using inversion pulses to suppress blood contrast and fat signals. On the other hand, the LGE sequence reveals regions of myocardial necrosis/fibrosis due to myocardial injury. This sequence is performed 10–20 min after the injection of a gadolinium-based contrast agent that reaches the myocardium and is distributed within the extracellular space; areas containing dead heart muscle cells retain the gadolinium and generate white images (Figure 1).

Mailing Address: Carlos Eduardo Rochitte
Departamento de Imagem Cardiovascular, Universidade de São Paulo, Instituto do Coração do HCFMUSP
Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code: 05403-900, Cerqueira César, São Paulo, SP - Brazil.

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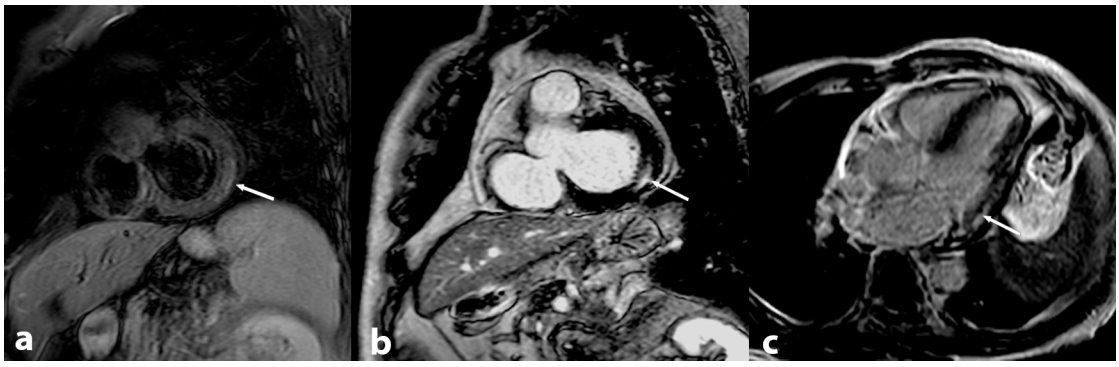

Figure 1 – Example of acute Chagas disease. In a, T2-weighted edema imaging demonstrating area of signal hyperintensity in the LV basal inferoseptal segment (short axis view) corresponding myocardial edema (arrow). In b and c, LGE imaging revels area of myocardial necrosis/fibrosis in the same region (arrow).

Fortunately, antiparasitic drugs cure 50-80% of patients with acute CD and are able to prevent progression to the chronic phase.[7] However, since most patients are unaware of the disease and the diagnosis is hardly performed during the acute phase, it usually resolves spontaneously.

The diagnostic role of CMR in chronic CD

Approximately 30% of non-treated patients develop chronic CD after the acute phase.[8] Most of them remain in the indeterminate form, with neither clinically apparent disease nor radiologic or electrocardiographically evident abnormalities for a long period or even a lifetime. In the chronic phase, CD can only be diagnosed by positive serology and/or xenodiagnosis tests.

CMR allowed the observation of myocardial fibrosis (MF) and edema in some patients in the chronic phase of CD; this contradicted the classical definition of this phase and revealed a less benign scenario than previously believed.[9] Rochitte et al.,[10] used LGE in patients at various stages of CD and have demonstrated MF in 20% of patients in the indeterminate form.[10] Moreover, Torreão et al.,[11] revealed evidences of myocardial inflammation even long after the acute phase using T2-weighted and early gadolinium enhancement sequences, which corroborated histopathological findings *in vivo*.[11,12]

Approximately 30% to 40% of patients with CD will develop a determinate form of the disease 10–30 years after infection, with cardiac and/or digestive involvement; 5% to 10% will develop it directly after the acute phase7

Chronic Chagas cardiomyopathy is the most important complication of CD and its pathogenesis is related to parasite-induced and immune-mediated myocardial injury, cardiac dysautonomia, and ischemia.[13] It can present itself as heart failure, cardiac arrhythmia, and pulmonary or systemic thromboembolism.

The small and progressive damage secondary to chronic myocarditis and myocardial perfusion abnormalities results in regional cardiac dysfunction. Extensive regional damage leads to cardiac enlargement, myocardial dysfunction, and heart failure, which is responsible for mortality rates of around 50% in 4 years. Cardiac involvement is usually biventricular, with a more pronounced failure of the right ventricle (RV).[14] Some patients may develop isolated RV dysfunction that can be detected early by CMR (Figure 2).[1,5]

The assessment of cardiac volumes and function can be performed using cine CMR. This technique presents advantages over echocardiography mainly in RV measurement, which can be performed directly by the Simpson method instead of being calculated by geometric approximation.[16] Cine CMR provides an excellent myocardium-to-cavity contrast ratio, allowing the accurate delineation of endocardial borders; this is especially important in patients with significant changes in ventricular geometry such as ventricular apical aneurysm, a typical finding of chronic CD (Figure 3). Owing to these advantages, it is considered a gold standard technique for assessing volume and cardiac function.

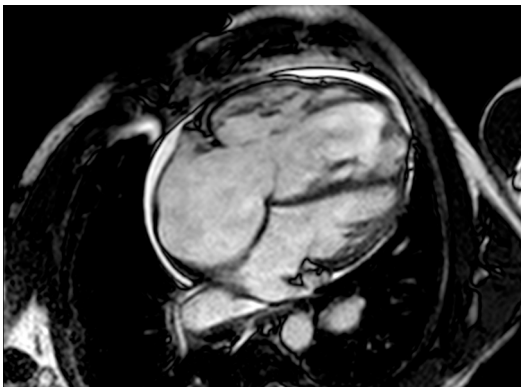

Figure 2 – A 50-year-old man present isolated RV involvement secondary to chronic Chagas disease easily detected by cine-CMR sequence.

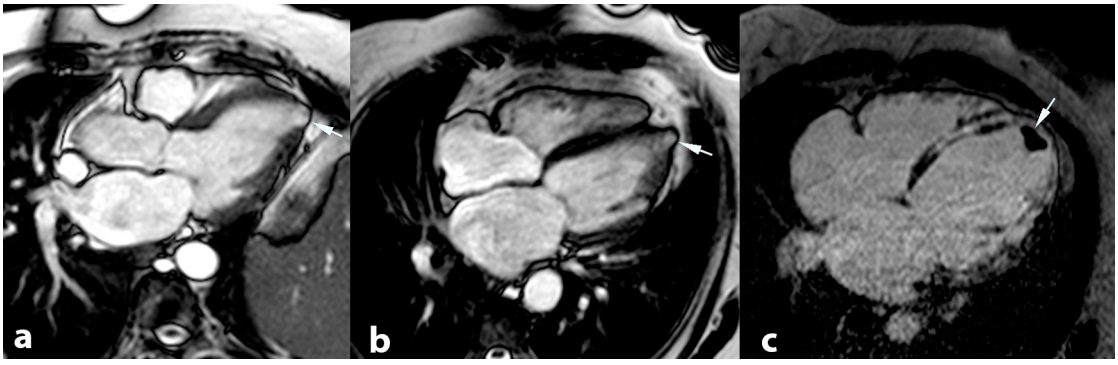

Figure 3 – Examples of complications of chronic Chagas disease in two representative patients. First patient: (a-b) cine-CMR reveals typical ventricular apical aneurysm (vorticilar) (arrows). Second patient: (c) LGE-CMR reveals apical thrombus (arrow) and LV myocardial fibrosis.

Adding myocardial tagging in cine CMR improves the detection of regional dysfunction through the visualization of myocardial deformation, which is an early abnormality of CD. The assessment of myocardial deformation has recently advanced through speckle-tracking echocardiography and feature tracking by CMR. These techniques provide the assessment of ventricular dynamics, including the performance of quantitative segmental analyses of ventricular function, while global systolic function is still preserved[17] Although the role of feature tracking by CMR in CD still needs to be assessed and standardized, speckle-tracking echocardiography has been extensively studied in patients with this disease.

Due to the very low sensitivity of echocardiography in detecting RV systolic dysfunction in patients with CD, speckle-tracking echocardiography has been used in the detection of RV impairment[18,19] and the early involvement of the left ventricle (LV) even in patients with preserved LV ejection fractions.[20–22]

An analysis performed in patients in early stages of CD observed, through CMR, a decrease in global longitudinal and circumferential LV strain only in patients with MF.[23]

The emergence of a perfusion CMR sequence allowed physicians to identify myocardial perfusion abnormalities associated with microvascular damage in patients with normal coronary arteries and ischemic-like symptoms.[24]

The progressive myocardial destruction with consequent replacement fibrosis has been described by pathological studies[12] and can also be observed by CMR. MF was first quantified on LGE–CMR by Rochitte et al.,[10] who demonstrated its presence in

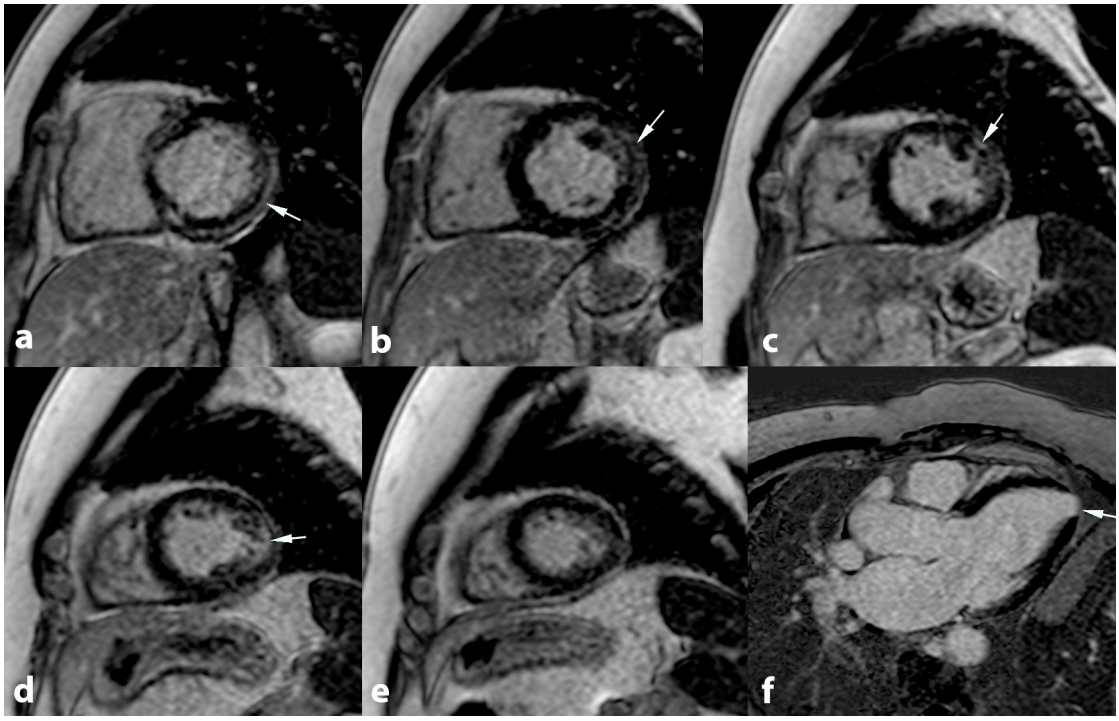

Figure 4 – LGE-CMR showing classic cardiac involvement in chronic Chagas disease (arrows). In a-e, midwall and subepicardial myocardial fibrosis in the LV inferolateral regions (short axis view). In f, myocardial fibrosis in the LV apex (three-chamber view).

68.6% of patients in all cardiac phases of CD. The amount of MF progressively increased from the indeterminate to determinate forms of the disease. The more MF, the worse the ventricular dysfunction and clinical condition of the patient. Researchers also found that the most affected regions were the apex and inferolateral regions of the LV, with a predominance of midwall and subepicardial layers (Figure 4). An atypical pattern was found in 46.9% of the analyzed LV segments, including subendocardial and transmural patterns that were indistinguishable from the fibrosis secondary to coronary disease (Figure 5).[10]

Another study evaluated sex differences by CMR. Investigators found significantly more fibrosis and ventricular dysfunction in male patients with CD than in female patients. The distribution of MF was also different between both sexes, where men displayed more transmural fibrosis than women.[25]

Finally, considering that an apical ventricular aneurysm increases the risk of intracardiac thrombosis and thromboembolic phenomena, ventricular thrombus can be easily recognized by using LGE–CMR.[26]

CMR as a risk stratification tool

Sudden cardiac death is responsible for 55% to 65% of all deaths in CD.[27] The close relationship of MF, ventricular arrhythmias, and sudden cardiac death has been described by several studies on ischemic and nonischemic cardiomyopathies.[28–32]

Distinguishing different patterns of MF and determining its extent by LGE–CMR provides important information that allows physicians to distinguish the etiology of cardiomyopathies and improve prognosis scores. White et al.,[33] demonstrated that the etiology of aborted sudden cardiac death or sustained monomorphic ventricular tachycardia was changed in 50% of the cases where patients were evaluated by CMR in comparison to conventional diagnostic investigation with transthoracic echocardiography and coronary angiography.[33]

The use of MF in the prediction of adverse events in patients with CD was assessed by Uellendahl et al.,[34] the authors correlated MF with prognostic data using the validated Rassi score, which identifies patients at risk (low, intermediate, or high) of dying prematurely. This correlation

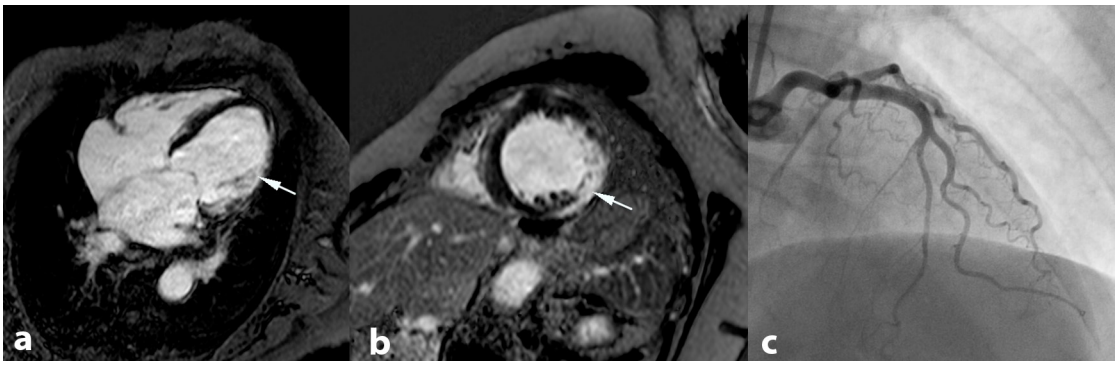

Figure 5 – An 83-year-old woman with positive serological tests for Chagas disease and atypical LGE that simulates transmural infarction. In a and b, myocardial fibrosis in the circumflex artery territory (lateral wall - arrows). In c, coronary angiography showing absence of coronary artery disease.

evidenced a progressive increase in MF from low- to high-risk Rassi score groups and also confirmed a strong association among MF, cardiac dysfunction, and arrhythmia.[34]

Recently, Senra et al.,[35] identified MF in 76.1% of patients with chronic Chagas cardiomyopathy and defined a cutoff value for the myocardial fibrosis mass of 12.3 g for predicting the combined endpoint (all-cause mortality, heart transplantation, antitachycardia pacing or appropriate shock from an implantable cardioverter-defibrillator [ICD], and aborted sudden cardiac death). The study had an average follow-up of 5 years with an area under the curve of 0.79 (95% confidence interval [CI] 0.72–0.87). The MF observed on CMR was an independent predictor of the combined endpoint.[35]

LGE imaging represents a powerful tool to identify patients at higher risk of cardiovascular events and who would benefit from an ICD.[36,37] Furthermore, the presence of MF in patients with heart failure who underwent device implantation revealed a high likelihood of appropriate ICD therapy, while its absence predicted a low risk of appropriate therapy.[38]

Future perspectives

T1 mapping and extracellular volume measurements represent potentially powerful emerging techniques that have allowed the assessment of myocardial affection at early stages of CD, where LGE images still cannot be obtained. By employing these techniques, it is possible to assess the replacement and permeation of myocardial tissue in several cardiomyopathy etiologies.[39–46] Extracellular volume estimation uses hematocrit and T1 values (pre- and post-contrast)[47] and has a strong correlation with extracellular matrix.[48–50] Similarly to LV ejection fraction, the extracellular volume is an important prognostic tool in the evaluation of cardiomyopathies.[51,52] In CD, native T1 and extracellular volume increase along with disease severity; abnormal values may be seen even in the indeterminate form of the disease and in regions without MF. This prompts these parameters as tools for identifying and monitoring early myocardial damage, in addition to performing risk stratification (Figure 6). [53]

Conclusions

Despite the difficulties of using CMR in clinical settings, especially in endemic areas of CD with budget limitations, the early detection of cardiac involvement by CMR has an important impact on the clinical approach and disease prognostics.

Although CD was discovered more than 100 years ago, recent technological advances have allowed a better understanding of this disease and the early detection of cardiac involvement. CMR has the potential to detect not only biventricular systolic dysfunction in the chronic cardiac phase, but also myocardial inflammation (by T2-weighted and early gadolinium enhancement imaging) and MF (by LGE imaging) in the acute and indeterminate phases, even when no other tests show abnormalities.

CMR is also valuable for predicting adverse events. T1 mapping and extracellular volume sequences are promising techniques for assessing Chagas cardiomyopathy before MF becomes apparent.

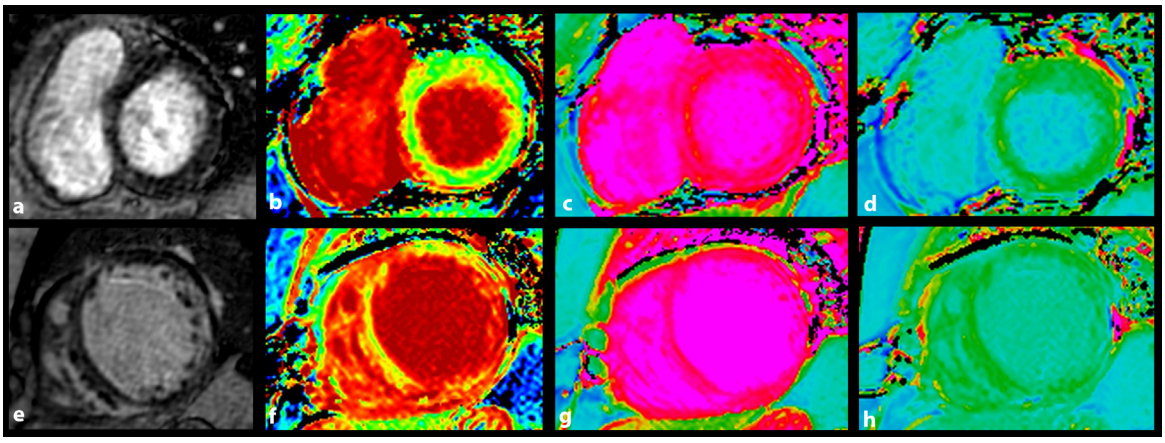

Figure 6 – Examples of LGE, extracellular volume, native and post-contrast T1 mid-cavity short axis images in patients with indeterminate form (a, b, c, and d, respectively) and with reduced LV ejection fraction (e, f, g, and h, respectively). In the indeterminate form, we note homogeneous myocardial signal in all sequences, showing no interstitial enlargement. In the Chronic Chagas cardiomyopathy, we see LGE in inferolateral wall, interventricular septum and myocardial junctions; in T1 mapping and extracellular volume sequences, those alterations are more pronounced, showing interstitial fibrosis in LGE-negative areas, as anterolateral and inferior walls.

Author contributions

Conception and design of the research: Pacheco AB. Rochitte CE. Acquisition of data: Pacheco AB, Melo, RJL. Analysis and interpretation of the data: Pacheco AB, Rochitte, CE. Writing of the manuscript: Pacheco AB, Melo, RJL. Critical revision of the manuscript for intellectual content: Rochitte CE.

Potential Conflict of Interest

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

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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.

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VIEWPOINT

Dysautonomic Arrhythmogenesis: A Working Hypothesis in Chronic Chagas Cardiomyopathy

Roberto Coury Pedrosa

Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ – Brazil.

Abstract

Sudden cardiac arrest (SCA) represents the most dramatic course of chronic Chagas cardiomyopathy (CCC) and is closely related to the presence of ventricular arrhythmias and heart disease. Although several aspects of ventricular arrhythmias in CCC have been elucidated in the last decades, such as the role of impaired cardiac autonomic modulation reported in pre-clinical studies, important questions remain unresolved regarding these cardiac problems and SCA. The aim of this article is to discuss recent developments in the understanding of the role played by the autonomic nervous system on arrhythmic events in CCC. We draw attention to the neurogenic theory of CCC ("catecholamine-induced cardiomyopathy") and its autoimmune regulation. Finally, we contextualize treatment strategies for Chagas disease considering the prevention of malignant ventricular arrhythmias. The most clinically relevant message from this article may be the high negative predictive value of dysautonomia for SCA in CCC. Nevertheless, there is a long journey from the identification of a potential marker for SCA to its actual use, which will require a common effort by the entire Chagas community.

Introduction

Chagas disease (Chd), caused by *Trypanosoma cruzi*, is a life-threatening and persistent illness.[1] The World Health Organization (WHO) estimates that over one million people suffer from chronic Chagas cardiomyopathy (CCC) in non-endemic countries,[2] where its prevalence is currently rising. The number of deaths from CCC complications is expected to double with the increase in immigration observed in the last few decades in Europe and the United States.[3]

In Brazil, human Chd is still a major public health problem.[4] In 2010 (data reviewed in 2015), the WHO estimated 1 156 821 infected people and 231 364 people with CCC,[5] leading to 6000 fatal cases per year; these numbers represent around 48% of all deaths caused by human Chd in Latin America.[4] Given the chronic nature of human Chd and the increased life expectancy in Brazil, it can be assumed that mortality due to this disease will remain high in the next decades. In addition, the treatment of the infection has shown no benefits once CCC is established, [6]

Chd has a variable clinical presentation (further discussed in. 7) The *T. cruzi* infection is followed by a short acute phase, which is usually self-limited and is asymptomatic in 95% of the patients; most acute infections are never clinically detected. In less than 1% of infections, the acute phase is severe and life-threatening due to meningoencephalitis or myocarditis.[7] Rather surprisingly, there is still no known proven cure.[8] Acute cases of greater severity resulting from a higher parasitic burden tend to evolve into forms of CCC that are also more severe.[9] The CCC is identified from an electrocardiographic alteration compatible with Chd, as discussed in. [6] In most cases, the disease enters its long-lasting chronic phase starting with the indeterminate form: a long and latent stage of the infection. While most patients infected with *T. cruzi* will remain in the indeterminate form for a lifetime, illustrating that organ/tissue aggression remains controlled in many patients, according to early studies (contemporary natural history

Keywords

Chagas Cardiomyopathy; Chagas Disease; Primary Dysautonomia; Arrhythmias, Cardiac; Sudden Cardiac Arrest.

Mailing Address: Roberto Coury Pedrosa
Rua Prof. Rodolpho Paulo Rocco, 255. Postal Code: 21941-913, Cidade Universitária, Rio de Janeiro, RJ – Brazil.
E-mail: coury@hucff.ufrj.br

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information is scarce,[10] around 20–30% will develop clinically manifest lesions 10 to 30 years after the infection, mainly in the heart [3] and usually with a mild presentation [9] During this long disease progression period, recent literature revealed that the annual incidence of the cardiac form is relatively low, at 1.85%. [10]

CCC is highly arrhythmogenic, more than other cardiomyopathies.[6] It is characterized by severe ventricular arrhythmia beyond the typical conduction system defects, especially with a right bundle branch block and/or left anterior fascicular block [11-13] in the various stages of Chagas disease (often called the "silent killer"). One of the main modes of death is sudden cardiac death ([SCD] 55%-65%), of which 90% of cases are due to sustained ventricular tachycardia (SVT)/ventricular fibrillation (VF) clinically manifest as SCD or sudden cardiac arrest (SCA)/resuscitated SCD.[14-17] In this regard, according to Laranja *et al.*,[18] the potential risk of sudden death should be considered in Chagas patients with evidence of cardiac involvement. Indeed, SCA in Chd is closely related to heart disease,[14] but not all patients with complex ventricular arrhythmias will develop SCA. Although there is no absolute proof that pathogen-induced cardiac remodeling[19] is synonym to arrhythmic death in patients, ie, that halting cardiac remodeling could prevent SCA, there is a consensus that cardiac autonomic dysfunction is required for SCA to occur.[20] Gadioli *et al.*, in a study that analyzed the electrophysiological substrate of complex ventricular arrhythmias in CCC, suggested that factors other than the severity of the left ventricular dysfunction and the presence of regional myocardial fibrosis are likely to contribute to the genesis of these complex ventricular arrhythmias and ultimately SCA. [21]

Thus, the present article aims to highlight recent developments in our understanding of the role played by the autonomic nervous system on arrhythmic events in CCC. We also discuss the neurogenic theory of chronic Chd ("catecholamine-induced cardiomyopathy") and its autoimmune regulation. Finally, we present current treatment strategies for the prevention of malignant ventricular arrhythmias.

The Role of Autonomic Imbalance on Sudden Cardiac Arrhythmic Death

The detection of cardiac dysautonomia is a source of information when resolving the clinical enigma of sudden and unexpected death, particularly in CCC [20]. The type and sequence of dysautonomic events that explain cardiac arrest (detailed in Table 1) are a matter of discussion. CCC is a unique condition because of the association between autonomic nervous system impairment and an increasing number of complex ventricular arrhythmias. [20-24]

1. Evidence from Histopathology Studies

It seems likely that most or all patients with Chagas disease undergo major pathological changes in the intertruncal plexus; these changes are among the least recognized but exceptionally important aspects of CCC. Alterations such as ganglionitis, periganglionitis, neuritis, and perineuritis are present during Chagas infection, with neural depopulation and a marked reduction in ganglionic density in both humans and experimental animal models.[25] These changes predominantly occur during the acute phase of the Chagas infection by a combination of 3 factors: direct parasitism of neurons, degeneration caused by periganglionic inflammation, and an antineuronal autoimmune reaction. [26]

The pathological changes in the intertruncal plexus in human Chd are so remarkable that some researchers consider them the main mechanism leading to SCD. Reviews of studies on cardiac autonomic dysfunction explain the presence of ventricular arrhythmias in the non-remodeled ventricle as a result of a prolonged autonomic imbalance. This imbalance is in turn caused by an intense and early parasympathetic neuronal depopulation, which would eventually lead to a "catecholamine-induced cardiomyopathy". [27]

Studies using animal models showed that neuronal cell death occurs mainly or exclusively during the acute phase [28,29] Nevertheless, the autonomic neurons have a high capability for axonal regrowth or sprouting.[30] and sympathetic reinnervation was reported in humans during the chronic phase of Chd after procedures such as heart transplantation and stem cell therapy.[31,32] However, the re-establishment of functional neuro-effector junctions due to axonal regeneration during the chronic phase is disorganized, random, and not complete. The parasympathetic innervation presents an analogous behavior: a marked destruction of nervous fibers and a decrease in heart acetylcholine (ACh) levels during the acute phase, followed by functional re-establishment in a disorganized, random, and incomplete manner during the chronic phase.[28] It is still unclear why parasympathetic denervation appears more intense than sympathetic denervation, leading to

the "catecholamine-induced cardiomyopathy" present in the realm of the neurogenic theory for Chd; it is possible that the localization of post-ganglionic neurons of the parasympathetic system in the heart may lead to greater damage and a slower reinnervation rate, since neuronal damage seems to be restricted to the nerve terminals [28]. In fact, this residual cardiac sympathetic activation was demonstrated in studies with iodine-123 metaiodobenzylguanidine (123I-MIBG) scintigraphy, where myocardial sympathetic innervation was indicated by an increased 123I-MIBG washout rate. This could be the result of relatively increased cardiac sympathetic activity at the early stage of CCC, supporting the neurogenic theory stated above. [23,33,34] More importantly, the vagal-cholinergic pathway plays a direct role in preventing the initiation of complex ventricular arrhythmias, including non-sustained ventricular tachycardia (NSVT) and ventricular fibrillation. [35,36]

Corroborating previous reports, a recent study used myocardial scintigraphy with 123I-MIBG to measure sympathetic innervation and rest myocardial perfusion using 99mTc-Sestamibi (MIBI) in Chagas patients with normal or mildly reduced left ventricular systolic function. The results indicated that the occurrence of ventricular arrhythmias of different degrees of severity correlated quantitatively with the extent of ventricular sympathetic denervation, but not of fibrosis, suggesting that myocardial sympathetic denervation played a major role in triggering these arrhythmias. [21] Moreover, the presence of different degrees of myocardial sympathetic denervation in patients with similar resting myocardial perfusion imaging summed scores but different MIBG summed scores suggested that the mechanism of sympathetic neuronal damage may not be related to the microcirculation abnormalities responsible for perfusion defects. The reason why some patients with similar levels of fibrosis and perfusion defects have different amounts of denervated myocardium is still unknown, and the future understanding of the causes of neuronal damage in CCC should contribute to the design of effective treatments.

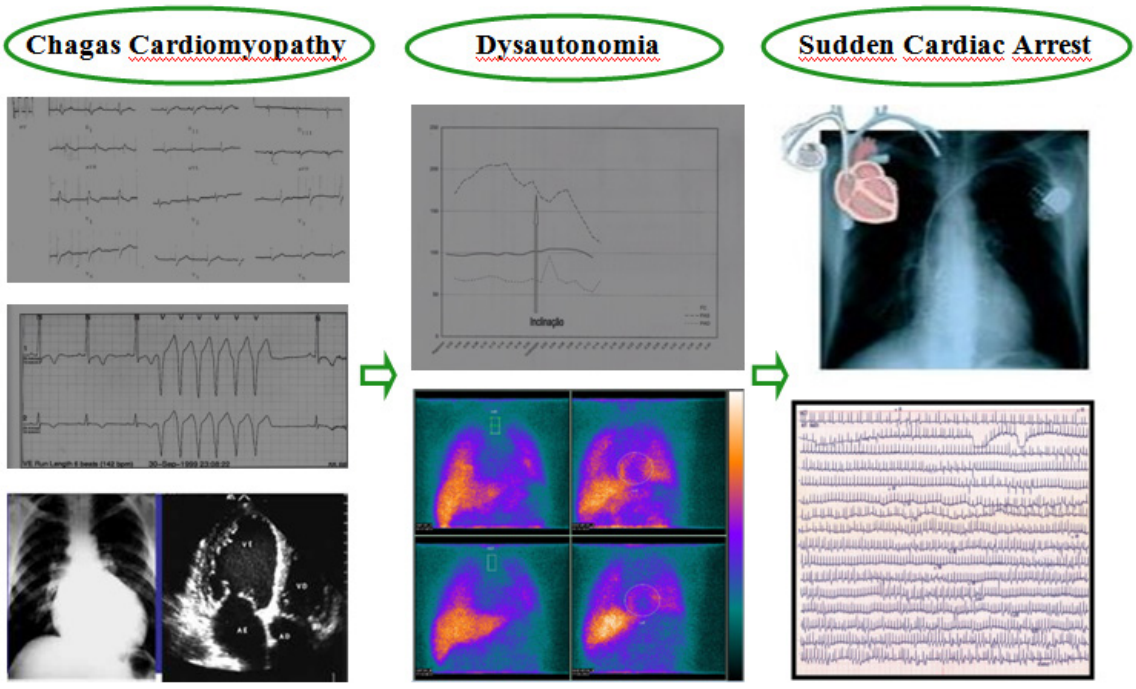
The coexistence of denervated and innervated areas [37], the presence of regional myocardial fibrosis,[37,38] and the potential influence of these structures in inotropic, chronotropic, and dromotropic activities in the diseased myocardium is clear. Their effects on the recovery of excitability result in an increase of the dispersion of action potential duration to a critical level [39] during residual sympathetic activation and increase the propensity to ventricular arrhythmias. [33-35,40] Although it is difficult to determine the independent effects of impaired cardiac autonomic modulation, it certainly influences the recovery of excitability , as recently suggested by myocardial scintigraphy studies. [21] This is certainly an area of research that merits further investigation. Differences in the response to residual sympathetic activation can be due to heterogeneous sympathetic innervation or ion channel distribution, in addition to myocardial remodeling and the resultant ventricular electrophysiological effects. [41]

2. The Mechanism of Autonomic Dysfunction

Although the mechanism of autonomic dysfunction in CCC has yet to be clarified, studies reported the presence of circulating antibodies with the capacity of binding to cholinergic (Ac-M) as well as adrenergic (Ac-β) receptors.[42-46] These findings could conciliate neurogenic alterations [20] and an immunological aggression [47] as interacting and relevant pathophysiological factors (particularly, the electrophysiological role of antibodies).

A research group at the Federal University of Rio de Janeiro, Brazil, first reported in 1994 that a humoral component could be involved in the genesis of ventricular arrhythmia in CCC. Their results indicated that sera from rabbits infected with *T. cruzi* generated atrioventricular conduction disturbances in isolated rabbit hearts.[48] Three years later, we confirmed this hypothesis by showing that antibodies originated from chronic chagasic patients presenting complex ventricular arrhythmias decreased heart rates and caused atrioventricular blocking in isolated rabbit hearts.[49] In line with these studies, a research group characterized 58 serum samples of patients with CCC and described that some of them had a β-adrenergic effect and induced ventricular arrhythmias through communicating junctions in a culture of newborn rat cardiomyocytes. This result suggested another mechanism through which these antibodies could contribute to the occurrence of arrhythmias.[50]

Until 2007, studies associated the role of antibodies to conduction disorders, focusing mainly on the atrioventricular conduction disturbance. However, they did not consider that these proteins could mediate the ventricular repolarization involvement and thus be related to the induction of ventricular arrhythmias, which are among the main causes of death in patients with CCC.[51] Indeed, our group was able to show, for the first time, that patients with CCC who had antibodies with muscarinic activity presented higher QT interval



Chagas patient, male, 30 years old; ECG showed right bundle branch block + left anterior hemiblock + unsustainable monomorphic ventricular tachycardia ; echo / chest radiography revealed dilated cardiomyopathy; TILT test showed dysautonomy; myocardial scintigraphy with MIBG showed sympathetic ventricular denervation (dysautonomia); 24h-Holter highlighted several episodes of unsustainable monomorphic ventricular tachycardia. High-risk patient for sudden death, implanted ICD
ECG: electrocardiography; ICD: implantable cardioverter-defibrillator.

dispersion when compared to chronic chagasic patients that did not have this type of antibody in their sera. It is worth mentioning that antibodies with a muscarinic effect, when perfused in isolated rabbit hearts under controlled heart rates, increased QT intervals.[52] More recently, our group showed that autoantibodies with beta-adrenergic activity from CCC patients induced ventricular arrhythmias and early afterdepolarization in drug-induced LQT2 rabbit hearts.[53]

3. The Electrophysiological Proposal

In CCC, the prolongation of the QT interval is associated with functional re-entry, ventricular arrhythmia (especially torsade de pointes), and sudden death. Studies showed that increases in catecholamine residual levels prolong the QT interval in Chagas disease ,[52,53] and robust data link the presence of cardiac repolarization abnormalities and the risk of arrhythmic death in CCC. Cohort studies reported, after Cox regression adjustment for cardiovascular disease, that an abnormal QT interval or increased QT dispersion,[54] as well as T-wave axis deviation [55] or primary T-wave abnormalities in a 12-lead ECG [56] were associated with an increased risk of death. Other methods of evaluating repolarization variability, such as T-wave amplitude variability [56] and T-wave spatial heterogeneity,[57] were independently associated with higher risk in a relatively small cohort. Finally, microvolt T-wave alternans, evaluated by a commercial method and useful in other conditions, is abnormal in CCC,[58]

Nevertheless, a consensus emerges from these studies that successful risk assessment of patients with CCC needs to involve a combination of different indices that reflect not only the pathological substrate but also the autonomic regulation of cardiac electrophysiology. It is important to state that pre-existing electrophysiological heterogeneity is a *sine qua non* for ventricular arrhythmias to occur. In fact, some studies aimed at addressing this requirement used the dynamic beat-to-beat method as a measure of repolarization heterogeneity.[41,59] It is nonlinear, highly dynamic, occurs independently from underlying heart rate variability, and varies with normal and abnormal physiological conditions, including autonomic state. It is also important to note that there

is no correlation between QT dispersion, a conceptually flawed measure of repolarization heterogeneity, and the dynamic beat-to-beat method.[60]

Recent studies analyzed the electrical restitution heterogeneity in another disease [61,62] and suggested autonomic modulation as a factor that contributed to the break-up of the electrical wave front, increasing the propensity to ventricular arrhythmias.

Some researchers suggest dynamic beat-to-beat analysis as a promising novel biomarker of SCD risk in ischemic cardiomyopathy. [36,41,59,61-66] Ongoing clinical studies, including a multicenter British study, are being conducted to consolidate the evidence base for periodic repolarization dynamics and develop a successful clinical tool for the assessment of SCD risk.[62] In Brazil, our group has explored the potential role of dynamic beat-to-beat analysis in SCA risk stratification in CCC. **MobileECG**, a ubiquitous platform that explores beat-to-beat dynamics over collaborative databases, is currently being developed for its application in the Brazilian Unified Health System in patients with CCC. [67]

Therapeutic Perspectives

After more than three decades dedicated to vector control and blood safety programs with successful results, the approach to Chagas disease by the scientific community and global health policy makers is entering a new phase. Today, the main priorities of international funders are treatment models that may produce clinical effects in the patients. The future will rely on the search for new therapeutic strategies that are efficient and well tolerated, reflecting in the clinical improvement of patients with this neglected tropical disease.

As previously mentioned, ventricular arrhythmias are very common in patients with CCC,[6] and sustained rapid ventricular tachycardia is recognized as the most important cause of sudden cardiac death in Chagas heart disease. [68] It has been identified in patients with segmental diseases, with or without important ventricular dysfunction, and ICD implants are recommended to prevent sudden cardiac death. [68,69] However, the use of ICDs is hampered by the lack of controlled data to establish precise indications and efficacy.[70-72] In fact, the evidence on the use of amiodarone, β-blockers, enzyme inhibitors, aldosterone blockers,[73] and devices such as the ICD is not yet conclusive to support or reject their use,[71,72] which is recommended based on limited observational data and the extrapolation of results from other patient populations.

Official statistics record about 12,500 deaths due to Chd each year, with 60% (or 7,500 deaths) occurring suddenly. The annual rate of sudden death can be estimated at 0.17 to 0.19%,[14] since there are 6-7 million infected individuals in Latin America. Thus, in order to prevent two cases of sudden death in the general chagasic patient population, any intervention should be applied to another 998 chagasic individuals who will not present any events. Particularly, the implantation of ICDs represents a high-cost intervention and requires multiple implants to save a life, since studies show that only one in every eighteen ICD implants is actually effective. This is another aspect that demonstrates the uniqueness of Chagas disease and evidences the need for identifying subgroups of sudden death risk patients that would be potential candidates for a more intensive prevention strategy.

Over the years, clinical studies showed that the vagal-cholinergic pathway could play a direct role in preventing the initiation of complex ventricular arrhythmias. Unfortunately, the effects of chronic vagal stimulation (VNS) on the occurrence of arrhythmia were investigated in humans and produced unfavorable results.[74-76] Similar outcomes were obtained with studies on sympathetic denervation through the use of pharmacological agents. [77]

At the moment, all efforts are focused on strategies to eliminate circulating antibodies with the capacity of binding to cholinergic (Ac-M) as well as adrenergic (Ac-β) receptors in patients with CCC.

A relevant and often ignored facet of CCC is the presence in nearly all cardiac chagasic patients of agonistic autoantibodies against G-protein coupled receptors, such as those against muscarinic and beta-adrenergic receptors. Studies by our and other groups have extensively characterized these antibodies and showed that they can modulate electrogenesis and impulse conduction in isolated hearts. [46-53] Both classes of antibodies are regarded as "drivers" of cardiac arrhythmia in CCC. Consequently, to counteract the arrhythmogenic potency of agonistic antibodies against G-protein coupled receptors, treatment strategies that focus on the removal of these antibodies by whole immunoglobulin G apheresis or *in vivo* antibody neutralization [78-80] have been developed; these could possibly have a beneficial effect in Chagas patients with complex ventricular arrhythmias that are refractory to conventional treatments. It is also necessary to explore specific and appropriate suppression times or dose-dependent effects that could contribute to the control of

complex ventricular arrhythmia and consequent SCA in CCC. In fact, this has not yet been tested in prospectively controlled, randomized human studies.

Another therapeutic option could be the use of stem cells for tissue repair. This new strategy is being intensely investigated in clinical assays [81].

Concluding Remarks

Although several aspects of ventricular arrhythmias in CCC have been elucidated in the last decades, important questions regarding the mechanisms of sudden arrhythmic death remain unresolved. While pre-clinical studies have documented the role of impaired cardiac autonomic modulation in ventricular arrhythmias, the translational aspects of this modulation have not yet been fully defined. Thus, understanding the function of autonomic modulation in the clinical severity of ventricular arrhythmias in CCC is an important focus point for future studies. It is also reasonable to believe that a set of autonomic modulation markers, rather than a single "magic bullet", might be needed to ensure adequate correlation with sudden arrhythmic death. The use of retrospective cohorts could be envisaged, but a large prospective study (clinical trial with long follow-up of patients) might be required to verify if autonomic modulation markers are surrogates for sudden arrhythmic death. In either case, this is an endeavor that requires a unified effort from the entire Chagas community, and perhaps the most clinically relevant message from this article may be the high negative predictive value of dysautonomia regarding SCA in CCC.

Author Contributions

Conception and design of the research: Pedrosa RC. Acquisition of data: Pedrosa RC. Analysis and interpretation of the data: Pedrosa RC. Writing of the manuscript: Pedrosa RC. Critical revision of the manuscript for intellectual content: Pedrosa RC.

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

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LETTER TO THE EDITOR

Effectiveness of Rapid Response Teams and the Importance of Preprints

Hermano Alexandre Lima Rocha,[1,2] Sabrina Gabriele Maia Oliveira Rocha,[2] Antônia Célia de Castro Alcântara[3]

Harvard University T H Chan School of Public Health,[1] Massachusetts - USA
Universidade Federal do Ceará, Fortaleza,[2] CE - Brazil
Unimed Fortaleza, Fortaleza,[3] CE - Brazil

To the Editor of the International Journal of Cardiovascular Sciences,

We have read with interest the Point of View:[1] "Performance of the Rapid Response Systems in Health Care Improvement: Benefits and Perspectives" by Viviane Cordeiro Veiga and Salomón Soriano Ordinola Rojas, published ahead of print in the International Journal of Cardiovascular Sciences on April 15, 2019. Rapid response teams to treat trauma patients in Australia 30 years ago, in 1989. From the outset, the aim was to early recognize signs of deterioration and provide a quick response, hence the name of the methodology.[2] The discussion about the activation criteria is relevant and up to date and was treated in a solid manner by the authors in the introduction of the point of view. Indeed, it is known that this is the cause of part of the heterogeneity of results found in studies on the subject.

However, the results section fails to present references that support the claims. New and old papers were cited, leading to a contrast between a point in time of knowledge in which there was still no consensus on the effects of the technology in question and the current knowledge. Especially worrying, it is stated that studies that evaluate the effectiveness of rapid response teams in reducing mortality still present conflicting data, citing Chan's meta-analysis from 2010,[3] which analyzed studies published up to 2008, that is, more than a decade ago. This study and the systematic review of the Cochrane Collaboration from 2007 are undoubtedly studies of extreme importance to the area, but many others have followed. Another meta-analysis, conducted in 2015, evaluated studies published until 2013 and reported a statistically significant reduction in mortality (13%) and in cardiac arrest (35%).[4] Subsequently, further studies were published, and a meta-analysis held in 2018 with increased volume of evidence confirmed this conclusion, with a 15% reduction in mortality.[5]

Obviously, the authors may have reviewed this evidence to form an opinion on the subject, however it is likely that the last decade has produced evidence of sufficient quality to merit at least a discussion from the point of view presented. In this context, it is extremely salutary that the International Journal of Cardiovascular Sciences has encouraged the publication of preprints. The speed of publication has increased and getting reviewers experts in increasingly complex topics has become more and more difficult. With this in mind, other areas of knowledge have stimulated the use of preprints, which allow other peers in that area to have contact with the manuscript prior to publication and to even contribute to the quality of the manuscript. It is believed that this is one of the alternatives to guarantee the quality of the published items, considering the number of retractions and corrections that we have seen in Medicine in the last years.[6]

In conclusion, considering the rapid response team as a consolidated strategy to increment the quality of hospital care, supported by current American Heart Association's recommendations for advanced life support (as reported by the authors), we consider the viewpoint of the authors distant from current literature, which already presents robust evidence for the effectiveness of the technology. Medical and managerial decisions taken at the hospital level affect thousands of individuals, and medical journals should always bring the most complete and reliable information possible.

Keywords

Hospital Rapid Response Team; Patient Safety; Patient Care Team; Hospital Mortality.

Mailing Address: Hermano Rocha
677 Huntington Ave. Postal Code: 02115, Boston, Massachusetts - United States
E-mail: hrocha@hsph.harvard.edu, hermano@ufc.br

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CASE REPORT

Coxiella Burnetti Infective Endocarditis – Detection and Cure

Manuel Martins Barbosa, Carla Dias, Elsa Araújo, Raquel Costa

Unidade Local de Saúde do Alto Minho EPE, Viana do Castelo – Portugal

Introduction

Infective endocarditis (IE) is one of the first diagnostic hypotheses for patients admitted for acute heart failure and evidence of infection. Blood samples are collected for culture, and empiric, broad-spectrum antimicrobial therapy is initiated. Emergent cardiac surgery may be required depending on the severity of the case.

These procedures reduce bacteremia and improve clinical condition, which, in turn, may lead to discontinuation of diagnostic investigation in the presence of blood culture-negative endocarditis. Some of these patients, however, will have another episode of endocarditis.

This is typically seen in the infection by *Coxiella burnetii* (*C.burnetii*), a rare cause of blood culture-negative endocarditis, characterized by recurrent IE and valve dysfunction until the correct diagnosis is established. The condition is recognized by the combined analysis of epidemiological, clinical, serological, and imaging data, with emphasis to echocardiography. The infection is effectively treated only with a long treatment period with hydroxychloroquine and doxycycline.

We present two cases of IE which underwent multiple surgeries before the diagnosis was established and a literature review to understand the difficulty in diagnosing and treating in time these patients.

Case 1

Male patient aged 67 years, with type 2 diabetes mellitus, arterial hypertension, obesity and severe aortic stenosis. At the age of 64, the patient underwent elective surgery for placement of Trifecta® bioprosthetic valve. Less than ten months after the surgery, the patient required reintervention for acute severe aortic insufficiency caused by IE and was started on empiric treatment with gentamicin and vancomycin. The patient took metformin, ramipril and bisoprolol. From the epidemiological point of view, the patient had contact with goats during adolescence.

The patient sought emergency care for dyspnea on exertion with progressive worsening and night sweating for one week. At physical examination, the patient had warm skin, sweating, regular tachycardia of 110 beats per minute (bpm), blood pressure (BP) of 135/73mmHg and axillary temperature of 38.2ºC. No other relevant findings were detected, such as embolic phenomena or splenomegaly. The patient reported no recent dental or endoscopic procedures.

The patient presented hemolytic anemia, increased inflammatory markers and acute renal injury (Table 1). Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed, showing new acute severe aortic insufficiency with partial dehiscence of the prosthetic valve (Figure 1). Blood culture was performed and empiric therapy with gentamicin and vancomycin was initiated.

The patient was screened for blood culture-negative endocarditis, including serology for the detection of *C. burnetii*. The serology was positive for acute infection, with phase I IgM antibody 1:512 and phase I IgG antibody 1:512, and phase II IgM antibody < 1:32 and phase II IgG antibody 1:512 (Table 1).

The definite diagnosis of IE was established based on modified Duke criteria, with one major criterion (new valve dehiscence) and three minor criteria (fever >38ºC, predisposing valvular abnormality, serological levels of *C. Burnetii* that do not meet the major criteria).

Keywords

Endocarditis; Coxiella burnetii; Q Fever; Heart Valve Diseases; Echocardiography/methods; Valvular Prosthesis; Antibiotics/therapeutic use.

Mailing Address: Manuel Martins Barbosa
Unidade Local de Saúde do Alto Minho EPE - Medicina 2
Rua Conde de Bertiandos, S/N. Postal Code: 4990-041, Ponte de Lima – Portugal
E-mail: martinsbarbosa.manuel@gmail.com

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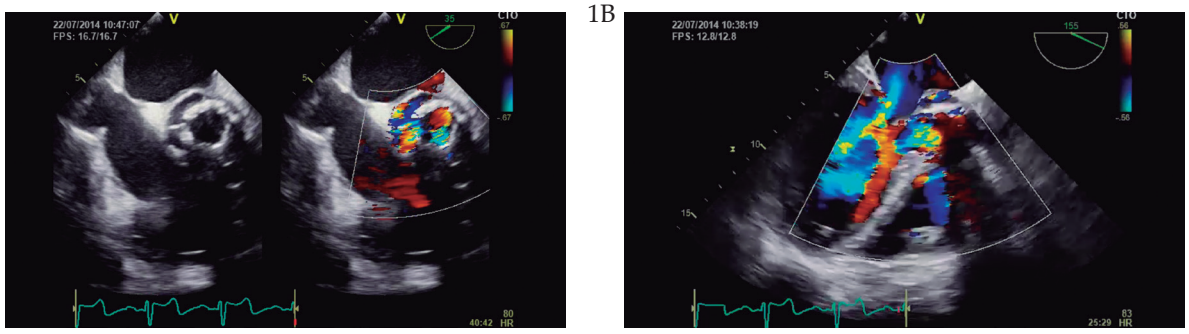

Figure 1 – Mid-esophageal view of transesophageal echocardiography showing aortic biological prosthesis in a short axis with partial displacement of the prosthetic ring (figure 1A). Aortic biological prosthesis in a long axis view with severe paravalvular leak (figure 1B). ***To view the video click on the link: http://publicacoes.cardiol.br/portal/ijcs/ingles/videos/2019-0138/2019-0138.asp*).**

Table 1 - Laboratory results of case 1 and case 2

	Reference value	Case 1	Case 2
Hemoglobin (g/dL)	13.2-17.2	9.1	11.4
Mean globular volume (fL)	80.1-96.1	86.1	87.2
Mean globular hemoglobin (pg)	26.7-30.7	28.8	27.6
Leukocytes x10^9/L (%neutrophils; % lymphocytes)	4.0 - 10.0	17.780 (N: 60%; L: 24.1%)	7.86 (N: 43.8%; L:44.1%)
Platelets x10^9/L	150-400	292	208
Peripheral blood smear		Presence of schistocytes; platelet anisocytosis	Platelet anisocytosis
Reticulocytes (%)	0.5-1.5	6.44%	1.94%
Creatinine (mg/dL)	0.8-1.3	1.10	1.51
Total/ Direct bilirubin (mg/dL)	0.3-1.2 / <0.3	2.79 / 0.58	0.82/0.36
Alanine transaminase ALT (UI/L)	8-35	16	25
Aspartate aminotransferase AST (UI/L)	10-45	14	17
Lactate dehydrogenase LDH (UI/L)	125-225	282	317
High sensitivity troponin i (pg/mL)	<34.2	323.5	57.4
C-reactive protein (mg/dL)	<0.5	2.96	2.32
Sedimentation rate	2-8	39	45
Haptoglobin (g/dL)	16-20	< 8.0	ND
Serology for *C.burnetti* Phase I IgG; phase II IgG	Positive >= 128 Or Positive > 1:256	16.000; 32.000	1:512; 1:512
Serology for *C.burnetti* Phase I IgM; phase II IgM	Positive >=64 Or Positive > 1:256	256; 512	1:512; 1:32
Serology for *Brucella spp.*		Negative	Negative
Blood cultures (3 sets)		No growth	No growth
Imunoglobulin A,G,M	60-400; 300-1500; 40-230	Not available	497.9; 1684.0; 345.0

The patient was referred for cardiothoracic surgery for replacement of the bioprosthesis with the 21mm St. Jude Medical Regent prosthetic valve. The patient was treated with hydroxychloroquine and doxycycline for 24 months; normalization of immunofluorescence antibody titers against *C. burnetiid* was achieved, and the infection was cured.

Case 2

Male patient aged 54 years, hepatitis C virus carrier, with history of recurrent tonsilitis in childhood and hypertension. At the age of 43 years, the patient was diagnosed with severe mitral stenosis and underwent replacement of valve with Medtronic Hall® mechanical prosthesis. Less than one year after the surgery, the patient was empirically treated for IE with gentamicin and vancomycin, without identification of the causative agent. After the treatment period, a perivalvular leak and moderate tricuspid insufficiency were detected by TTE, which led to an elective intervention for closure of the leak and De Vega annuloplasty. Eighteen months later, due to another valve dysfunction, implantation of a double-disc mechanical prosthesis and tricuspid annuloplasty with partial ring were performed.

The patient was under therapy with carvedilol, ramipril, furosemide and warfarin. He had had contact with goats and cattle until the age of 30 years.

After eight years of clinical stability since the last valve intervention, the patient was admitted to the emergency department with dyspnea on exertion with progressive worsening even during mild exertion, non-productive cough, myalgia and fever (>38.5ºC) during the previous two weeks. The patient reported no weight loss, alcohol consumption, or recent dental or endoscopic procedures.

At physical examination on admission, the patient was sweating, and had tachypnea (25 breaths per minute), crepitations on lung auscultation, prosthetic sounds and grade 3-6 holosystolic murmur on cardiac auscultation. Abdominal palpation revealed hepatomegaly 3cm below costal margin and spleen was not palpable. BP of 112/54mmHg and mean heart rate of 144 bpm.

Electrocardiography showed atrial fibrillation and non-specific changes in intraventricular conduction. Analytical study showed anemia and increased inflammatory parameters (Table 1). A TTE was performed and revealed moderate periprosthetic leak, which was later confirmed by TEE, with no evidence of vegetations or abscesses.

An study was conducted for blood culture-negative endocarditis, including immunofluorescence serology for *C. burnetii*. Empiric therapy with gentamicin and vancomycin was initiated and the patient was hospitalized at the Division of Internal Medicine for continuation of follow-up and treatment.

The infection by *C. burnetii* was confirmed by titers of phase II IgG antibody of 1:16.384 and phase II IgM antibody of 1:256, and phase I IgG and IgM antibodies of 1:32768 and 1:512, respectively. The definite diagnosis of IE was established based on two major Duke criteria (phase I IgG antibody >1:800 and new valvular dysfunction on echocardiogram).

The patient was seen by the cardiothoracic surgery group, confirming the need for another replacement of mitral valve prosthesis, which was performed without complications. Detection of *C. burnetii* DNA from resected valvular material was confirmed by polymerase chain reaction (PCR).

Antibiotic therapy was changed, and the patient completed 24 months of treatment with hydroxychloroquine and doxycycline, with normalization of immunofluorescence antibody titers against *C. burnetii*, and completion of treatment of hepatitis C infection. On folow up, the patient presented New York Heart Association (NYHA) class II congestive heart failure, normal functioning of the mitral mechanical prosthesis and moderate depression of left ventricular systolic function of TTE (Figure 2).

Discussion

blood culture-negative endocarditis accounts for up to 70% of all cases, according to some series.[1] Negative blood cultures may be caused by variables associated with the method (inadequate collection of the sample, administration of antibiotics, local protocols) types of agents involved (fastidious, intracellular), and local epidemiological features.[2]

A French prospective study by Fournier et al.,[3] developed a multimodal strategy for diagnosis of blood culture-negative endocarditis. The methodology included the classical serology and PCR of blood samples, and culture and PCR assay of valvular biopsies whenever possible, as well as blood PCR for the most common causative agents in the population.

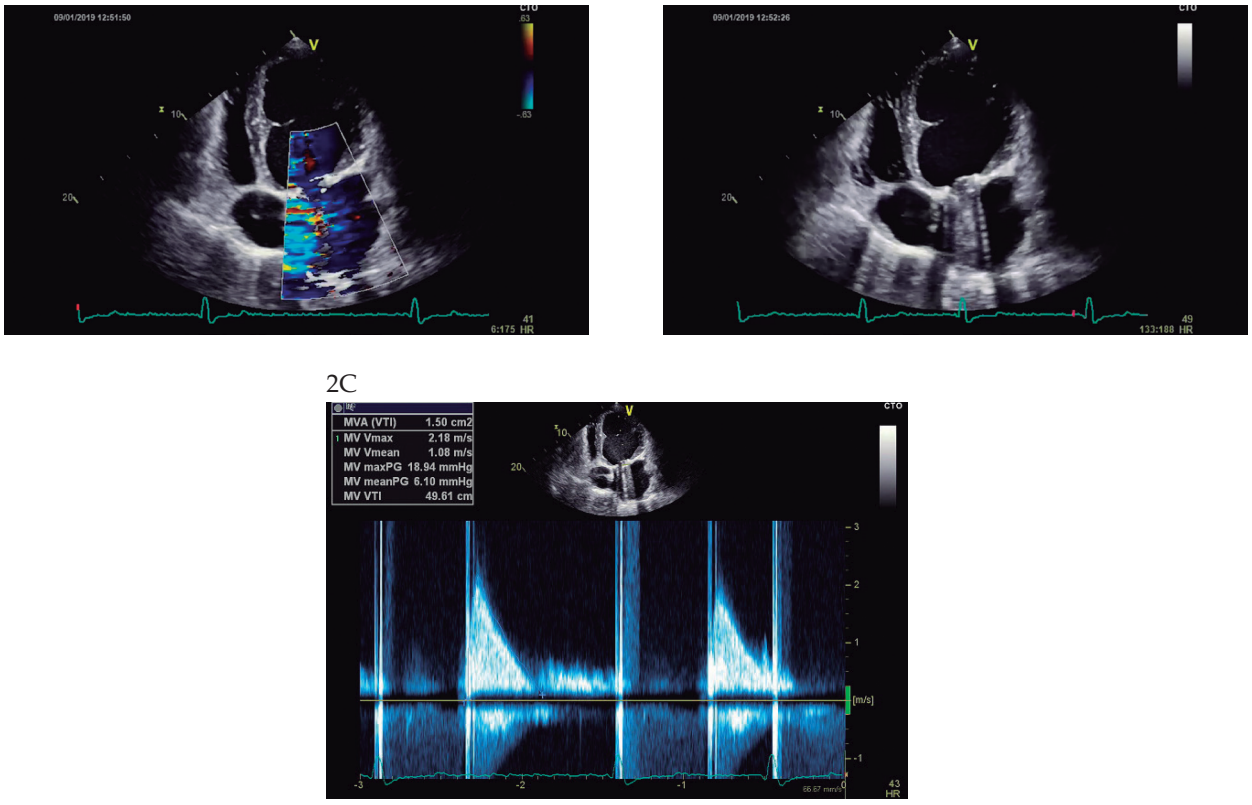

Figure 2 – Transthoracic echocardiography in an apical four-chamber view showing dilatation of right cardiac chamber, mitral mechanical prosthesis with preserved disc motion and moderate depression of left ventricular systolic function (figure 2A). Color Doppler with no evidence of abnormal regurgitation (figure 2B) and continuous Doppler showing transprosthetic gradients and functional area compatible with a normally functioning prosthetic valve (figure 2C). ***To view the video click on the link: http://publicacoes.cardiol.br/portal/ijcs/ingles/videos/2019-0138/2019-0138.asp***

The method allowed an increment in diagnostic efficiency by 24.3%, and the authors suggested that these tests should be used as standard in studies of In a population of 283 cases of blood culture-negative endocarditis, C.burnetii was responsible for 27 cases (9,5%) in this study.[3]

Although *C.burnetii* IE is considered a rare condition, it is more common compared with other causative agents including *Bartonella spp.*, *Brucella spp.*, *Tropheryma whipplei*, *Mycoplasma spp.* and *Legionella spp.*, accounting for 5% of all infective endocarditis diagnoses. According to some series, *C.burnettii* represents up to 48% of all diagnosed cases of IE with negative blood culture.[4]

C. burnetii is an obligate intracellular bacterium, and its common reservoirs are cattle, sheep and goats. The pathogen is transmitted by inhalation of aerosolized particles of biological products that can travel many kilometers, without direct contact in many cases.[5]

The most common disease caused by *C. burnetii* infection is acute Q fever, characterized by pneumonia and hepatitis. In some countries, outbreaks of more than 3,000 simultaneous cases of Q fever have been reported, constituting a public health problem (French in 2007 and Holland in 2010).[6] Most outbreaks, however, are episodic, and in most cases, the illness spontaneously resolves. Therefore, many cases are not properly diagnosed or registered, thereby increasing the number of chronic asymptomatic carriers of *C. burnetii*.[5]

Parreira [7] assessed the prevalence of *C. burnetii* in a group of 150 healthy blood donors in Portugal and found a seropositivity rate of 28.7%. The results suggest that *C. burnetii* infection is endemic in the country, in both urban and rural areas, which is similar to other countries in Europe.[7]

Chronic Q fever is rarer than the acute form, corresponding to 1-5% of the infections by *C. burnetii*.[1]

In 70% of the cases, the chronic disease presents as IE. The latency period between the first contact with the agent and clinical manifestations may vary from one year to more than a decade.[8]

Risk factors associated with *C. burnetii* IE are male sex (75%), age between 40 and 70 years, heart valve disease (91%) particularly in the presence of prosthetic valve (between 30 and 55%, depending on the series) and immunocompromised patients (32%). History of previous exposure to animals was reported in 70% of the cases. Associated comorbidities include alcohol consumption, diabetes, renal failure and hepatitis C virus infection.[9]

Presentation of *C. burnetii* IE is non-specific, which hinders a timely diagnosis. Almost 50% of patients have symptoms of acute heart failure, and most patients have fever (70%), weight loss, fatigue and anorexia (50%). Other manifestations include purpuric rash on extremities and mucosa, digital clubbing, splenomegaly, renal injury caused by immunocomplex deposits and embolic events.[10]

The diagnosis of IE is made using the modified Duke criteria.[11] Serological diagnosis by indirect immunofluorescence is considered a major criterion for *C. burnetii* IE, corroborating its importance. The diagnosis of chronic infection is made by phase I IgG antibody titers >1:800, with specificity of 99.6%, and values lower than that are classified as minor criteria.[1,12]

Endocardial involvement shown by imaging test is another Duke major criterion, which determines the crucial role of echocardiography in detecting vegetations, new heart valve insufficiency or worsening of a pre-existing valvular insufficiency. However, the available literature shows that both TTE and TEE have low sensitivity (12% and 33%, respectively) in detecting changes in heart valve structure, which reinforces the difficulty in obtaining elements for the diagnosis of *C. burnetii* IE.[13]

The diagnosis of *C. burnetii* infection can also be made by DNA sequence analysis or anatomopathological findings of *C. burnetii* in the fragments of valvular vegetation. However, these methods have low cost-effectiveness due to several histological changes these fragments may have.[12]

The risk factors for mortality include delay in treatment, male sex, older age, acute coronary syndrome, prosthetic valve endocarditis, and elevated IgG titers after one year.[14]

Early mortality decreased in the last four decades (from 60% to 5%) in populations diagnosed within six months since introduction of the combined therapy of hydroxychloroquine (200 mg three times per day) and doxycycline (200 mg twice per day). Duration of treatment is 18 months for native valve endocarditis and 24 months for prosthetic valves.[15]

The recommended follow-up period is five years, and the cure is achieved when the IgG phase I titer is reduced by four times from the diagnostic value and the IgM phase II titer is undetectable.

In addition, literature shows a progressive decrease in the need for valve surgery, from 60% in the 70's to 46% today, which is in line with the establishment of early diagnosis, increasing the chances of cure by pharmacological intervention alone. In case of elective surgeries, it is recommended antibiotic therapy for three weeks before the surgery. Emergent surgery is indicated for patients with high hemodynamic instability and advanced valve dysfunction.[16]

Conclusions

There are important messages that can be drawn from these case reports and literature review. The prevalence of Q fever is high in its acute form, but the disease is underdiagnosed and underreported. This increases the number of asymptomatic carriers that may develop chronic Q fever in the presence of risk factors such as heart valve disease, male sex, age between 40 and 70 years, and comorbidities such as hepatitis C, diabetes and hypertension. *C. burnetii* IE has an indolent nature, characterized by non-specific presentation and a long period of destruction of perivalvular tissue.

In the first stages of the disease, bacteremia may respond to empiric antibiotic therapy for IE, which, together with surgical excision of the infected material, may lead to a favorable but temporary condition. Due to its intracellular nature, the chronic infection by *C. burnetii* is not effectively treated and the patient will most likely develop another valvular dysfunction with time.

This seems to be the case of these two of these two reports, who came from a small population of approximately 250,000 inhabitants, and were observed within a short time interval. Although *C. burnetti* is considered a rare causative agent of IE, it is important to highlight that is recognized as the most common cause of blood culture-negative IE. Also, the epidemiological context should be carefully considered.

Therefore, it is worth reinforcing that the hypothesis of *C. burnetii* IE should be considered for the first differential diagnoses, particularly in the presence of blood culture-negative IE and unexplained valvular dysfunction that requires repeat surgeries. The cure of the infection is achieved only with hydroxychloroquine and doxycycline for 18 months for native valve endocarditis and 24 months for prosthetic valve.

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.

Author contributions

Conception and design of the research: Barbosa MM, Dias C, Araújo E. Acquisition of data: Barbosa MM, Dias C. Analysis and interpretation of the data: Barbosa MM, Dias C. Writing of the manuscript: Barbosa MM, Dias C. Critical revision of the manuscript for intellectual content: Barbosa MM, Dias C, Araújo E, Costa R.

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CASE REPORT

Iatrogenic Complications During the Diagnostic Work-Up of an Inflammatory Cardiomyopathy

Hugo Antunes, Júlio Gil, Bruno Marmelo, Maria Luísa Gonçalves, Maria Inês Pires, João Miguel Santos, Miguel Correia, José Costa Cabral

Centro Hospitalar Tondela-Viseu, Viseu - Portugal

Abstract

A 72-year-old woman was admitted for acute heart failure. The echocardiography revealed moderate depression of the left ventricular ejection fraction. Coronary disease was excluded by coronarography. Cardiac magnetic resonance showed predominantly left ventricular septal hypertrophy and severe depression of the left ventricular systolic function. There was also a bright, multifocal and patchy late gadolinium enhancement with subendocardial, mesocardial and subepicardial involvement, suggestive of sarcoidosis. Biochemical study, thoracic computed tomography and positron emission tomography were inconclusive for extra-cardiac sarcoidosis. Therefore, an endomyocardial biopsy was performed. The procedure was complicated by the development of complete atrioventricular block, requiring implantation of a cardiac resynchronization pacing device. A few days after device implantation, the patient developed fever. The echocardiography revealed extensive vegetations, and thus the diagnosis of a device-associated infective endocarditis was made. Even though antibiotic therapy was promptly started, the patient ended up dying. Biopsy results revealed lymphocytic myocarditis.

This case is paradigmatic because it shows how the etiologic diagnosis of dilated cardiomyopathy can be challenging. Non-invasive diagnostic exams may not provide a definite diagnosis, requiring an endomyocardial biopsy. However, the benefits versus risks of such procedure must always be carefully weighted.

Keywords

Iatrogenic Disease / complications; Cardiomyopathies; Diabetes Mellitus; Hypertension; Endocardites; Cardiomyopathy, Dilated; Spectroscopy, Magnetic Resonance / methods.

Introduction

The authors describe an intriguing case of dilated cardiomyopathy with left ventricular systolic dysfunction of recent onset. It is a paradigmatic case of how challenging the etiologic diagnosis of dilated cardiomyopathy can be. Sometimes, non-invasive imaging tests don't provide a definite answer. This paper also discusses the prognosis of cardiac device-related infective endocarditis and the importance of an early surgical intervention in gram-negative infections.

Case Report

A 72-year-old woman with a past medical history of diabetes mellitus and arterial hypertension was admitted for sudden-onset dyspnea. She had been complaining of fatigue and lower exercise tolerance over the previous four weeks. Physical examination showed hemodynamic stability, low peripheral oxygen saturation and signs of respiratory exhaustion. Lung auscultation revealed crackles in the lower two-thirds of both hemithoraces. The patient became clinically stable after non-invasive ventilatory support, along with diuretic and vasodilator therapy.

The electrocardiogram (ECG) showed sinus rhythm and complete left bundle branch block (LBBB). The transthoracic echocardiogram (TTE) revealed left ventricular dilation with a moderately depressed ejection fraction (left ventricular ejection fraction of 35%) and preserved right ventricular systolic function.

Mailing Address: Hugo Antunes
Cardiology Department, Tondela-Viseu Hospital Centre - Av. Rei D. Duarte. Postal Code: 3504-509. Viseu - Portugal.
E-mail: hugo.ads.antunes@gmail.com

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There was no significant valve dysfunction or signs of pulmonary hypertension. Coronary disease was excluded by coronarography.

At discharge she presented with New York Heart Association (NYHA) class II heart failure. During outpatient follow-up, a cardiac magnetic resonance (CMR) was performed, confirming a moderate dilation of the left ventricle, asymmetric septal hypertrophy and severe depression of the systolic function, with akinesia of the mid and basal segments of the antero-septal wall. There were bright areas of late gadolinium enhancement (LGE) in multiple locations, affecting approximately 12% of the myocardial mass, including areas of non-hypertrophied myocardium (Figures 1 A-F). There was a predominantly subendocardial and mesocardial (though almost transmural) LGE area in the mid-segment of the anteroseptal wall; multiple confluent foci in the mid-segment of the septal wall; subendocardial foci in the mid-segment of the inferior wall; and sub epicardial foci in the mid-segment of the infero-lateral wall.

The CMR findings were suggestive of non-ischemic cardiomyopathy, raising the suspicion of cardiac sarcoidosis. Corticosteroid therapy was initiated. Blood work revealed normal levels of alkaline phosphatase, angiotensin converting enzyme and inflammatory markers. Blood and urine calcium levels were also normal. A thoraco-abdomino-pelvic computed tomography did not reveal any lesions suggestive of sarcoidosis.

A ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) revealed diffuse myocardial uptake, with focal areas of hypercaptation, with no unequivocal relationship with the LGE areas. The study was not conclusive because of the patient's inability to do a 12-hour fasting due to a history of diabetes.

The patient presented with a dilated cardiomyopathy (DCM) with severe depression of left ventricular systolic function of recent onset and with no known cause, probably of an inflammatory nature. Considering a possible diagnosis of isolated cardiac sarcoidosis, which is a potentially treatable cause of DCM, an

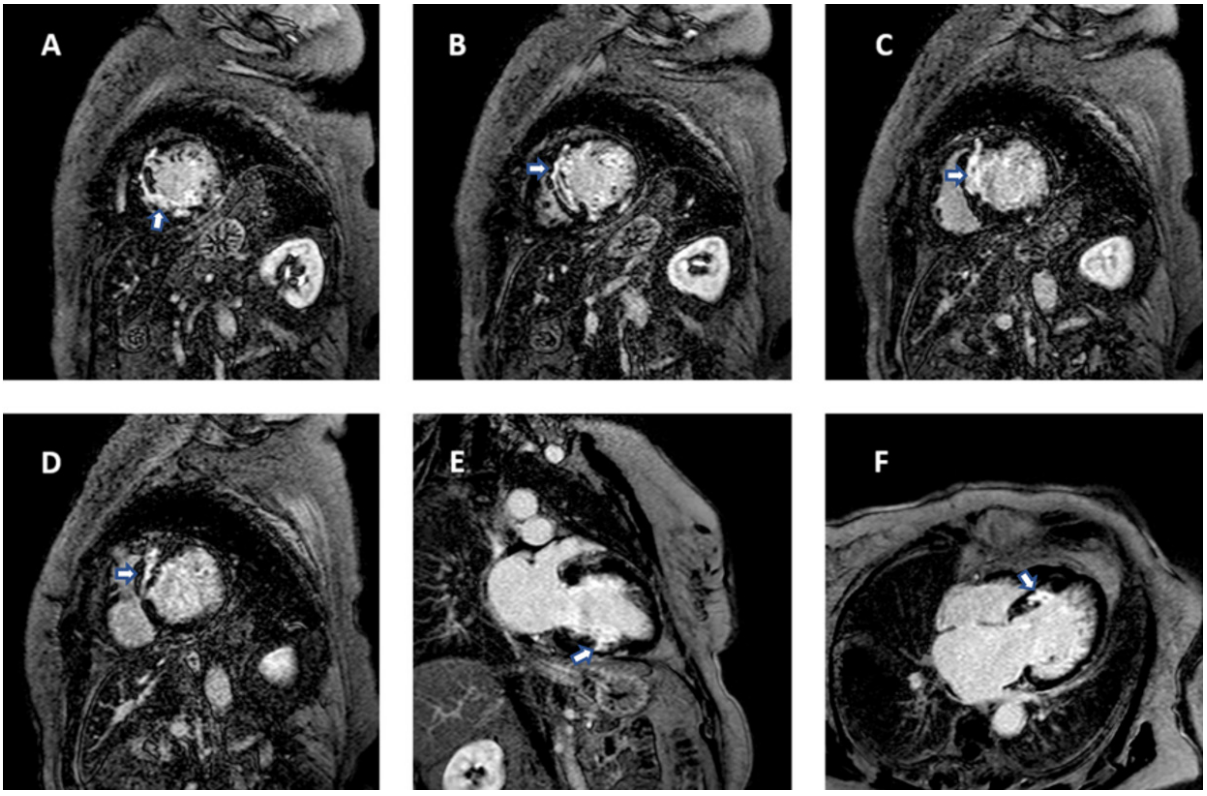

Figure 1 - Cardiac magnetic resonance revealing multifocal areas of late gadolinium enhancement (arrows), suggestive of non-ischemic cardiomyopathy.
A-D: Short axis views, E: 2-chamber view and F: 4-chamber view.

endomyocardial biopsy (EMB) was performed. Three myocardial fragments were successfully collected from the right ventricle.

The EMB procedure was complicated by a third-degree atrioventricular block (AV block), requiring temporary pacing. Four days after the biopsy, the AV block did not disappear. Considering the presence of severe left ventricular systolic dysfunction and LBBB, a cardiac resynchronization therapy pacemaker (CRT-P) was implanted.

Four days after discharge, the patient was readmitted complaining of malaise and fever. Physical examination showed hemodynamic and electrical stability, without signs of localized infection or heart failure (HF). Blood cultures were collected and a course of empirical antibiotic therapy with ceftriaxone was initiated. At day 3 of hospitalization, vancomycin was added to the regimen, and ceftriaxone was substituted with gentamycin due to persistency of fever. Blood cultures revealed *Escherichia coli* (*E. coli*) and methicillin-resistant *Staphylococcus aureus* (MRSA) growth. A transesophageal echocardiography (TEE) revealed significant masses, suggestive of vegetations, the biggest measuring 32 mm, attached to the pacemaker lead, tricuspid and mitral valve (Figure 2), causing severe tricuspid regurgitation and confirming the diagnosis of device-related infective endocarditis (IE).

An extensive endocarditis, with large vegetations, associated with valvular dysfunction was found, in addition to isolation of Gram-negative bacteria. Therefore, cardiac surgery was indicated. While awaiting surgical correction, the patient developed clinical deterioration, with progressive multiorgan failure. She ended up dying at day 21 of hospitalization.

After the patient's death, histopathological results of the EMB revealed morphological damage of cardiac myocytes with cytoplasmic heterogeneity. There was evidence of inflammatory cell infiltrate, including

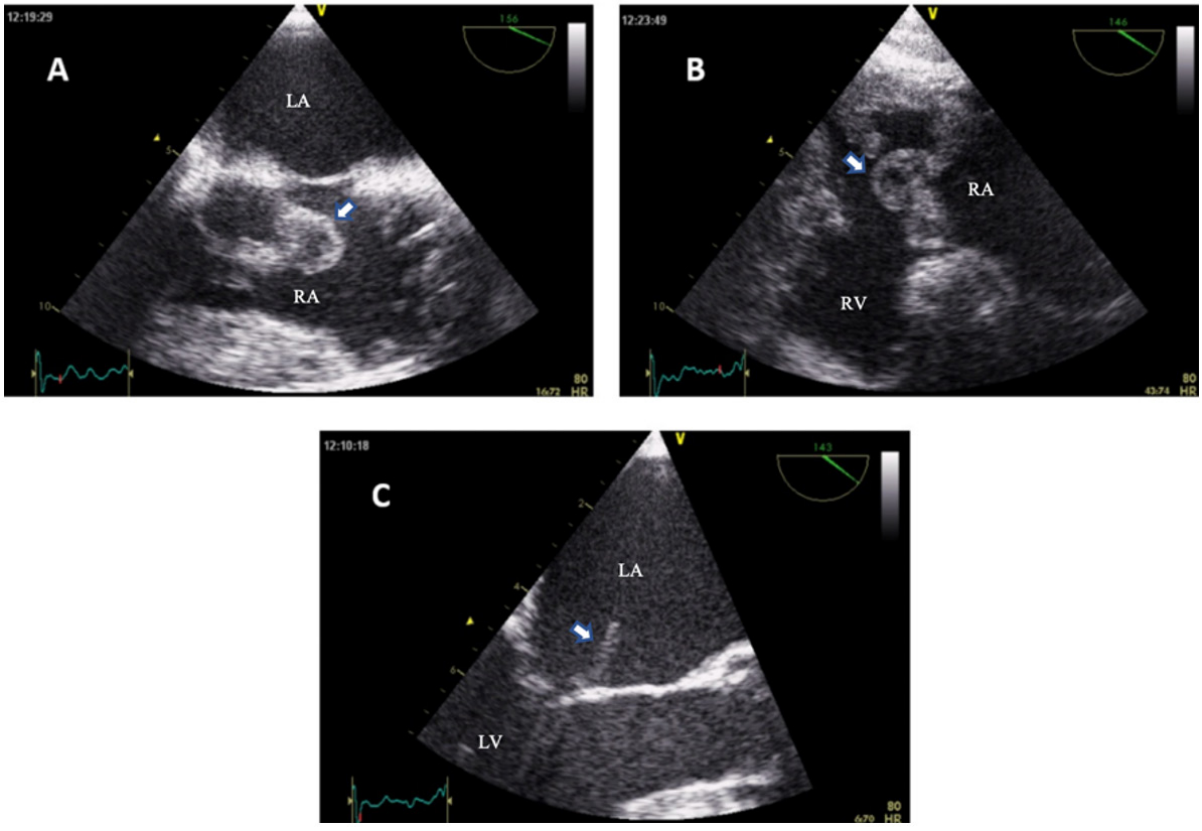

Figure 2 - Transesophageal echocardiography showing large vegetations (arrows).
LA: left atrium; RA: right atrium; LV: left ventricle.

lymphocytes and some neutrophils. PAS (periodic acid Schiff) and haematoxylin staining confirmed myocarditis of a probable infectious nature.

Discussion

The authors describe a case of a woman admitted for acute decompensation of HF. TTE showed left ventricular dilation and depression of systolic function. The patient was started on prognosis-modifying drugs, as tolerable. The CMR confirmed left ventricular dilation and systolic dysfunction, and significant areas of LGE in subendocardial, mesocardial and subepicardial regions. Corticosteroid therapy was initiated due to high suspicion of cardiac sarcoidosis, which was not confirmed by any of the test performed during diagnostic work-up. An EMB was then performed, but the procedure caused a series of events which culminated in patient's death. A complete AV block occurred, requiring temporary pacing and subsequent permanent pacing with CRT-P. Later, the patient developed fever, and had a diagnosis of IE.

This clinical case report demonstrates how non-invasive diagnostic exams may not provide a definite diagnosis. While cine-CMR showed segmental wall motion abnormalities, the main finding of MR was the LGE pattern. There was a multifocal and patchy pattern of LGE, with subendocardial, mesocardial and subepicardial involvement. There is no specific pattern of LGE on CMR for cardiac sarcoidosis.[1-4] LGE is usually multifocal and patchy and is most commonly seen in mid-basal segments of the septum and lateral wall, with mid-myocardical and epicardial involvement, although it can be seen with transmural involvement also.[1,2] The presence of LGE in cardiac sarcoidosis is known to be associated with a worse prognosis, with a higher risk of death, aborted sudden cardiac death and ventricular arrhythmia.[3,5-7] Therefore, LGE pattern was compatible with cardiac sarcoidosis.

A ^{18}F-FDG-PET was performed in attempt to confirm the diagnosis, since, among the non-invasive imaging methods, this technique has the highest sensitivity and negative predictive value for the diagnosis of cardiac sarcoidosis.[3] The PET revealed diffuse myocardial uptake, with areas of hypercaptation, but with no confirmed association with the LGE areas. The diagnosis of cardiac sarcoidosis depends on the presence of a positive EMB or on a confirmed diagnosis of extra-cardiac sarcoidosis, which was excluded in this patient.[8] EMB has a low sensitivity in cardiac sarcoidosis, with reported rates of 20-40%. This is probably due to the patchy nature of the disease, and hence, the fragments may not include the noncaseating granulomas necessary for the diagnosis.[2,8] A posthumous diagnosis of presumable lymphocytic myocarditis was made according to the EMB.

According to the European Society of Cardiology, EMB may be considered in the setting of unexplained, new-onset HF of 2 weeks to 3 months' duration, associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks.[9] The authors decided to proceed with EMB since we were in the presence of a DCM with recent onset HF and unknown cause, not responsive to usual treatment and with hemodynamic deterioration. In addition, the main diagnostic hypothesis was isolated cardiac sarcoidosis, which requires EMB for a definitive diagnosis. The pathological finding of lymphocytic myocarditis ranges from 0% to 63% in patients with new-onset HF of 2 weeks to 3 months' duration, associated with a dilated left ventricle.[9] The reported complication rate of EMB is < 1%.[9] Acute complications include pericardial tamponade, ventricular or supraventricular arrhythmias, heart block, pneumothorax, and damage to the tricuspid valve.[9] Patients with LBBB have a higher risk of heart block.[9]

Unfortunately, the patient developed an extensive IE, probably worsened by the concurrent immunosuppressive therapy. Treatment of this condition requires prolonged antibiotic therapy and complete hardware removal and is associated with a high mortality rate.[10] Transvenous lead extraction is usually the recommended approach since this procedure is associated with lower risks than surgery.[10] However, to this patient, cardiac surgery was indicated due to the following reasons: (1) presence of tricuspid dysfunction requiring repair; (2) large vegetations (> 20 mm); (3) blood cultures indicating MRSA and E. coli; the latter is a gram-negative bacterium, to which the recommended therapy is early surgery.[10] Unfortunately, the patient was not able to survive long enough, corroborating the high mortality associated with cardiac device-related IE.

This case is interesting since it is representative of the challenge it is to establish a definite diagnosis in the study of DCM. The investigation of the etiology is crucial when inflammatory disease is strongly suspected, and there is potential for recovery. It is also important not to overlook a rare diagnosis, such as isolated cardiac

sarcoidosis. EMB may be the only procedure that can provide definite answers in some cases, but it is not devoid of serious complications. Similarly, cardiac device-related IE is a severe disease associated with high mortality which requires prolonged antimicrobial regimens and device removal. Patients with isolation of gram-negative specimens in blood cultures in the context of IE may benefit from early surgical intervention.

Author contributions

Conception and design of the research: Antunes H. Analysis and interpretation of the data: Antunes H. Writing of the manuscript: Antunes H. Critical revision of the manuscript for intellectual content: Antunes H, Gil J, Marmelo B, Gonçalves ML, Pires MI, Santos JM, Correia M, Cabral JC.

Potential Conflict of Interest

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

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ERRATUM

In the September / October (2020) issue vol. 33(5):589-590

In the article "Declaring Physical Activity as 'Essential' During the COVID-19 Pandemic May not be a Good Measure", with DOI number: https://doi.org/10.36660/ijcs.20200165, published in the International Journal of Cardiovascular Sciences, 33 (5): 589-590, on pages 589-590, in the first paragraph the text was included: "Pandemic?",[1]"

Where it read:

"We congratulate the authors on the viewpoint entitled "Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?", and we are thankful for the opportunity to provide some contributions on this current and relevant topic."

References:

1. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Grupo de síntese da Rede CoVida. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. Cien Saude Colet. 2020;25(Suppl.1):2423-46.

2. Jang S, Han SH, Rhee J-Y. Cluster of Coronavirus disease associated with fitness dance classes, South Korea. [Editorial]. Emerg Infect Dis. 2020;26(8). Available online at: https://wwwnc.cdc.gov/eid/ article/26/8/20-0633_article.

3. COVID-19 in Brazil: "So what?"[Editorial]. Lancet. 2020; 395(10235):1461.4.

4. Fundação Oswaldo Cruz. (Fiocruz). Monitora Covid-19 in Brazil. [Cited in 2020 May 05] Available at: https:// bigdata-covid19.icict.fiocruz.br/.

Read:

"We congratulate the authors on the viewpoint entitled "Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?",[1] and we are thankful for the opportunity to provide some contributions on this current and relevant topic."

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1. Pitanga FJG, Beck CC, Pitanga CPS. Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?. Int. J. Cardiovasc. Sci. [Internet]. 2020 July [cited 2020 Sep 09] ; 33(4): 401-403. Available from: http:// www.scielo.br/scielo.php?script=sci_ arttext&pid=S2359-56472020000400401&lng=en. Epub June 05, 2020. https:// doi.org/10.36660/ijcs.20200072.

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Correlation between Surgical Risk Scales with Respiratory Muscle Strength and Functional Independence in Patients Submitted to Coronary Artery Bypass Grafting

André Luiz Lisboa Cordeiro, Átila Darlan Queiroz de Brito, Graziele Freitas Almeida, Leilane Souza Jesus, Flávia de Araújo Oliveira, Janinne Lima da Silva, André Raimundo França Guimarães, Roberto Moreno Barros

Risk Stratification in Chest Pain: Impact on the Diagnosis of Acute Coronary Syndrome

Ana Paula Paz Reis, Karen Brasil Ruschel, Maria Antonieta P. de Moraes, Karlyse Belli, Marco Lumertz Saffi, Jaqueline Eilert Fagundes

Lipoprotein(a) levels in children and adolescents: Ouro Preto Study

Ana Paula C Cândido, Alekson Mendonça-Mendes, Débora RC Cândido, Roney LC Nicolato, George LL Machado-Coelho

Carotid Intima and Media Thickness Correlation with Central Blood Pressure Measurements by Tonometric and Oscillometric Methods: A Proof of Concept

Weimar Kunz Sebba Barroso, Milena de Andrade Melo, Priscila Valverde Vitorino, Claudia Gonçalves, João Alexandre Berigó, Ana Carolina Arantes, Jeeziane Rezende, Thiago Veiga Jardim, Ana Luiza Lima Souza, Paulo César Veiga Jardim

Effects of Inspiratory Muscle Training Using an Electronic Device on Patients Undergoing Cardiac Surgery: A Randomized Controlled Trial

João Vyctor Silva Fortes, Mayara Gabrielle Barbosa Borges, Maria Jhany da Silva Marques, Rafaella Lima Oliveira, Liana Rodrigues da Rocha, Érica Miranda de Castro, Mateus Souza Esquivel, Daniel Lago Borges

Door-to-balloon Time in Cardiovascular Emergency Care in a Hospital of Northern Brazil

Tárcio Sadraque Gomes Amoras, Taymara Barbosa Rodrigues, Cláudia Ribeiro Menezes, Christielaine Venzel Zaninotto, Roseneide dos Santos Tavares

The Role of Cardiovascular Risk Factors and Risk Scoring Systems in Predicting Coronary Atherosclerosis

Suat Gormel, Uygar Cagdas Yuksel, Murat Celik, Salim Yasar, Erkan Yildirim, Baris Bugan, Yalcin Gokoglan, Hasan Kutsi Kabul, Salim Yasar, Mustafa Köklü, Cem Barçın

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