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Editorial

ABC Cardiol – Our Home of the Cardiovascular Scientific Research

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ABC Cardiol, the Arquivos Brasileiros de Cardiologia, an official journal of the Brazilian Society of Cardiology has been the premier scientific journal for conveying cardiovascular science publications in Brazil. In 2018 as the new editor-in-chief, I proposed two main approaches to further increase ABC Cardiol relevance in the scientific community. The first one was to increase our journal impact factor, which had been stabilized slightly above 1 and, secondly to increase the internationalization of the journal, which was recommended by Scielo.[1]

Our most recent journal impact factor (2019) is 1.450 and the 5-year impact factor of 1.724, the highest in our history. Additionally, the number of citations in a given year also reached its all-time highest number of 3065 citations in just one year (Figure 1). There has been an upward trend of our journal impact factor, from the previous 1.318 (2017) and highest impact at 1.679 (2018)[2,3] (Figure 2). International collaboration has been increasing significantly. Currently, about 11% of our published articles are from authors of more than one country (multinational, Figure 3), and 22% of articles are originating from countries other than Brazil (Figure 4). Our editorial board has now international associated editors that are the angular stone for increasing international collaboration and publications in the ABC Cardiol. Moreover, collaboration with the international scientific community and societies has been boosted.[4]

We have also increased our requirements for excellent articles and reviews.[5] Guidelines and statements have become an educational source of updating knowledge for medical professionals. ABC Cardiol has implemented a continuous line of scientific publications of high-quality guidelines ranging from prevention, and lifestyle to advanced cardiology. This specific role has an intrinsic link to our social responsibility as a scientific journal that is to bring the benefits of science to our society.

Despite this significant development in the ABC Cardiol, we still struggle to get recognition from one of our national journal rank (QUALIS) provided by our country agency for post-graduation programs, CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).[6] The agency correct attempt to have only one rank score for each scientific journal, independently of its specific area or category stumbled by the use of percentiles of each research area. For example, the highest impact factor and the number of very high impact factor journals vary considerably according to the specific research area. This makes percentile comparisons between journals belonging to different research sub-areas completely inaccurate and unfair. In the cardiac and cardiovascular system category that includes Cardiology, where ABC Cardiol is inserted, the highest impact factor is 23.603 with many journals with extremely high impact factors. This constitutes a clear misuse of Journal impact factor.[7,8] None of the critical factors such as high ethical standards, support of our professional society, publication in English and local language simultaneously, our very intense use of social media, and our scholar and academic network were ever considered by CAPES. This represents a lack of understanding of what is relevant science, which should include the true impact of academic articles, not only a novelty but also methods adequacy, ethical soundness, and relevance to the scientific community locally and globally. The QUALIS from CAPES was captured in many fallacies such as the deductive, inductive, argument from authority, and ad hominem argument.[7] Urgent corrections are needed before severe damage is definitively made to Brazilian Science.

Dealing with cold numbers of Journals rank scores is a tricky business,[9,10] nonetheless, a more civic and patriotic approach, with the ultimate goal of forwarding Brazilian science and scientists through using national scientific journals as the vehicle for communicating their best science is the right way to go.

Finally, despite the unfairness of our national agencies, we will continue to pursue the goal of maintaining ABC Cardiol as a scientific publication of excellence in Cardiology and consolidate science in our society.

Keywords

Bibliometrics; Metrics; Periodicals; Journal Impact Factor; Peer Review, Research.

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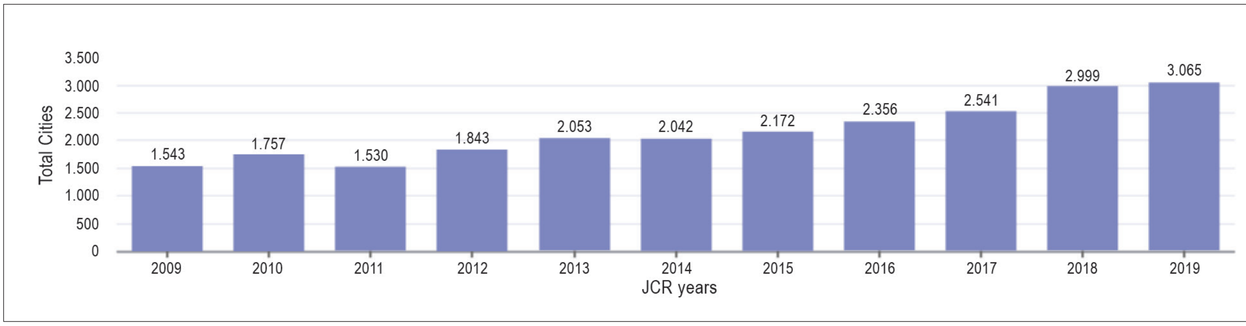
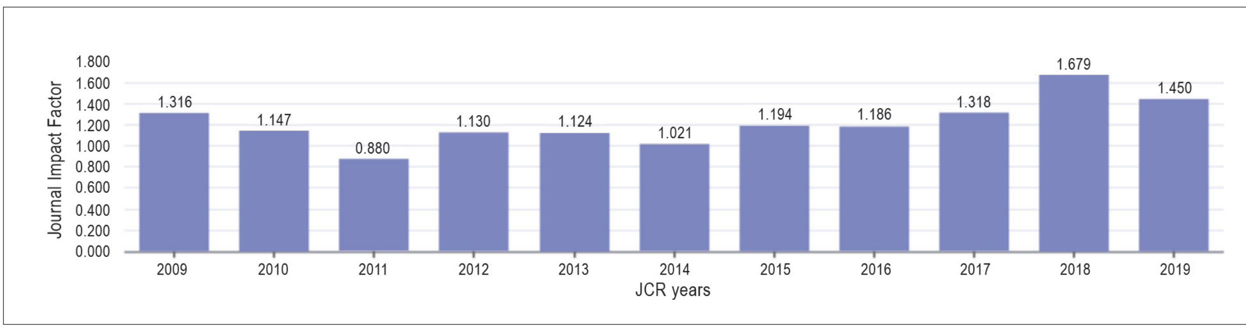


Figure 1 – *ABC Cardiol number of total citations per year (Journal of Citation Reports – JCR – Clarivate).*



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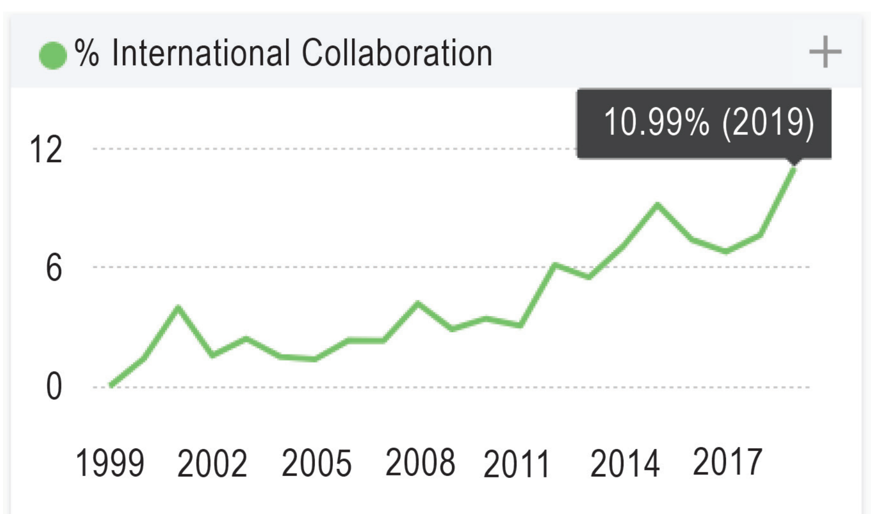

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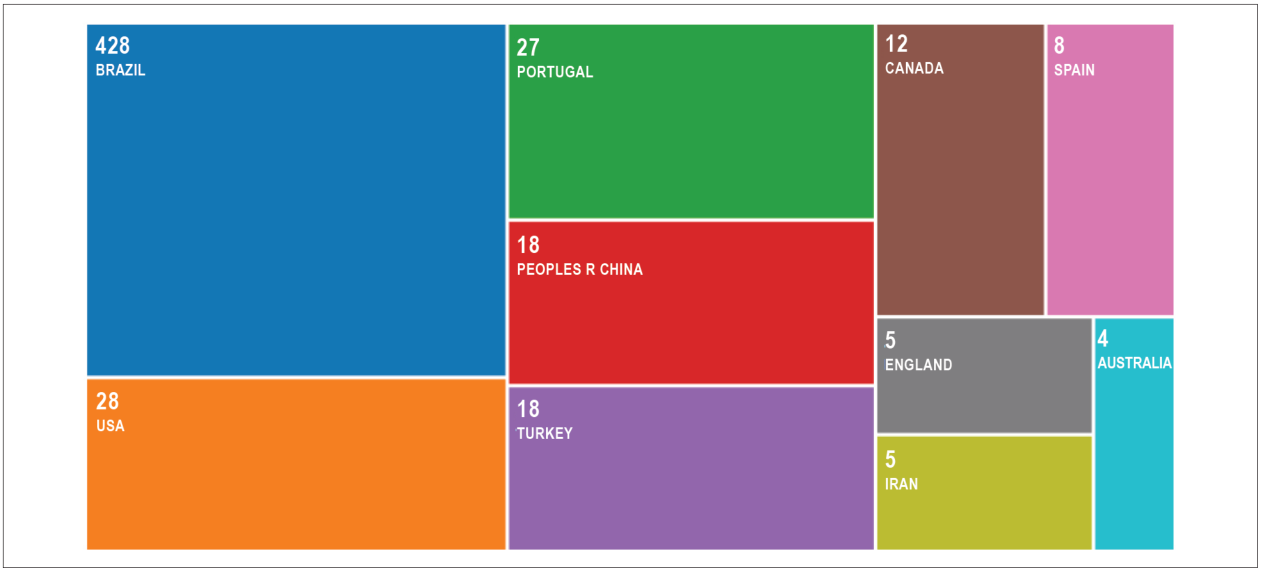

Figure 4 – *ABC Cardiol number of publications by Country in 2018 and 2019 (Web of Science – Clarivate).*

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Editorial

Painting the History of Brazilian Cardiology

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The mural painted by the visual artist Flávio Tavares for the Brazilian Society of Cardiology (SBC), The Heart of the Tropics, is an eloquent witness of his unique talent as a painter (Figure 1). The mural portrays the development of Brazilian cardiology. It comprises three juxtaposed acrylic-on-canvas panels, measuring 6.30m of length and 1.80m of height, with real and imaginary characters illustrating more than one century of the practice of cardiology in the largest nation of the tropics. Similarly to the most famous mural on the history of world cardiology painted by Diego Rivera in 1944 for the *Instituto de Cardiología de México*, the mural by Flávio Tavares is a legacy for the history of Brazilian cardiology.[1]

Medicine, a gift from the Gods to physicians to relieve human suffering, is monumentally represented by figures, among which Aesculapius (Asclepius) and his daughter Hygieia (Salus) make way for the pioneers of Brazilian social medicine. In the background, in a smooth and harmonious transition, the Amazonian landscape is replaced by the *Mourisco* Castle from Fiocruz, a Brazilian underdeveloped rural setting, and then the building of the *Instituto do Coração* of the Hospital das Clínicas of the University of São Paulo (InCor).

With its exuberant biodiversity, the Amazonia symbolizes a huge frontier for the research of possible active principles used in medicine. The medicinal properties of plants have been described for millennia, an example being the foxglove plant (*Digitalis purpurea*), used to treat heart conditions. The British physician William Whittering, who has discovered the medicinal properties of *digitalis* present in the foxglove plant, stands out in the painting. Similarly, Vincent Van Gogh, the Impressionist genius, has immortalized foxglove in "The Portrait of Dr. Gachet" painting *(Musée D'Orsay* – Paris), shaping his relationship with medicine and art. The magic of the painting confirms the vision of the explorers that ours is a fertile land, and a leafy willow tree, the base for the acetylsalicylic acid synthesis by Felix Hoffman, was integrated into the Amazonian landscape.

Keywords

Cardiology/history; Cardiology/trends; Cardiologists; Medicine in the Arts/history; Paintings.

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Biodiversity and its use for science are an innovative theme, although it has always been present in medicine. According to Paracelsus, medicine is based on nature, and nature is medicine, which should only be pursued by men in nature; nature is the master of the physician, because nature is older than the physician and exists inside and outside men. This is supported by the research by Sergio Henrique Ferreira, who led the synthesis of the bioactive peptide found in the Bothrops jararaca venom. This venom is the base to produce captopril, a drug that has changed the natural history of illnesses, such as arterial hypertension and heart failure.

The researchers William Harvey, Daniel Hale Williams and Willem Einthoven represent the dawn of cardiology as a science, beyond the classical Greek symbols. Sir William Harvey, considered the father of cardiology, has unveiled the mysteries of blood circulation, challenging all the concepts of his time, including religious beliefs. Harvey has written the book *De Motu Cordis*, the oldest scientific paradigm of medicine, whose 400 years of publication is celebrated by world cardiology.[2] In 1893, Daniel Hale Williams, an avant-garde Afro-American surgeon, performed the first successful open-chest surgery to repair a pericardial wound.

Willem Einthoven, bestowed with the Nobel Prize of Medicine 1924, has played a unique role in cardiology, having mandatory presence in the history of that specialty. Rubens Maciel states that Einthoven, when receiving the Nobel Prize of Medicine on December, 8th, 1925, in a memorable conference about the string galvanometer and measurement of the cardiac action potential, has highlighted: "A new chapter has been opened in the study of heart diseases, not by the work of a single investigator, but by that of many talented men, who have not been influenced in their work by political boundaries and, distributed over the whole surface of the Earth, have devoted their powers to an ideal purpose, the advance of knowledge by which, finally, mankind suffering is helped".[3]

The beginning of Brazilian cardiology has been influenced by the physician Pedro Francisco da Costa Alvarenga, from the Brazilian state of Piauí, who, at the end of the 19th century, wrote about congenital heart disease and became a celebrity of French cardiology, returning later to Brazil.[4] Medicine practiced from the 19th century to the mid-20th century is well portrayed in the mural. At that time, little could be done to change the natural course of diseases, leaving only humanism and faith as a relief for the sick.

The patient-doctor interaction, essential for the practice of medicine, is highlighted in the mural. The semiotic assumptions of the cardiovascular system examination – pulse

Figure 1 – *Painting the History of Brazilian Cardiology.*

and blood pressure measurement and cardiac auscultation – are represented. The Frenchman René Leannec, by inventing the stethoscope, enabled cardiologists to differentiate from other physicians by interpreting the "voice of the heart". The ability to distinguish heart sounds, clicks, and murmurs, and to correlate them with heart diseases became a desired gift and a requirement for understanding the true symphony of the heart. Cardiac auscultation is originally portrayed in the mural, inspired by the Oswald de Andrade's anthropophagic movement: a cardiologist is portrayed auscultating a South American Indian in her native household. The aboriginal symbolism of the image reassures the need for the harmonious coexistence of people from different cultures with the environment.

The vocation of women for caring has long been recognized. However, in the beginning, their presence in cardiology was limited. Thus, the pioneering effort of the female physicians Rita Lobato Velho Lopes and Anna Turan Machado Falcão is a way to register the incomparable ability of women for the practice of medicine. Rita Lobato, from the Brazilian state of Rio Grande do Sul, was the first Brazilian female physician. She started medical school in Rio de Janeiro and concluded it in Bahia. The other pioneer, the female physician from the state of Pará, Anna Turan Machado Falcão, also had her remarkable life trajectory portrayed. She graduated in April 1887 in New York with only nine other women in her class. When receiving her diploma, she was awarded the golden medal of Honor to Merit. Although they were not cardiologists, they are portrayed in the mural because they are an inspiration to all Brazilian female physicians.

Carlos Chagas, considered the first modern cardiologist and the translational science pioneer because of his leadership in Brazilian public health in the 1919 pandemic, is the central character in the mural.[5] In the painting, he and his mentors Oswaldo Cruz and Miguel Couto are portrayed having a conversation with Brazilian cardiology pioneers. The endeavor to describe American trypanosomiasis, or Chagas disease, as well as the thorough identification of the environment where the endemic spreads are portrayed in detail. Chagas and Oswaldo Cruz symbolize the urgency of investing in social medicine, directed at primary attention and health promotion. The study of Chagas heart disease brought international attention to Brazilian cardiology, and Anis Rassi represents a model of medical leadership that has contributed to the knowledge of the prognostic factors of that important Latin American endemic.[6]

In the beginning of the 1940s, a period of strong cultural and social effervescence, the SBC was founded. In the mural, the figures of Dante Pazzanese (the first president of the SBC), Jairo Ramos and Genival Londres, founders of the SBC and symbols of a golden era of cardiovascular medicine, emerge. Dante Pazzanese was the catalyst of an extraordinary group of physicians from several Brazilian regions who already stood out in the study of heart diseases, and the creation of the SBC was a natural consequence of those actions. By that time, Dante Pazzanese and Genival Londres had already founded the São Paulo and Rio de Janeiro State Institutes of Cardiology, respectively. Genival Londres published the first book about arterial hypertension in Brazil and, by way of illustration, he reported there was no effective treatment for the condition, as highlighted by Rafael Leite Luna. [7]

In the mural, Jairo Ramos is the symbol of perennial commitment to the advance and publication of research in Brazil. He was the first editor of the cardiology journal *Arquivos Brasileiros de Cardiologia* (ABC) and president of the SBC. Currently, the ABC is the journal with the highest impact factor in the Portuguese language, constituting the live registry of the evolution of Brazilian cardiology and the outreach channel for the Brazilian scientific production.[8]

The cardiology of the first half of the 20th century was built on clinical acuity supported by electrocardiography, chest radiography and phonomechanocardiography. At that time, the French, English, and later Mexican masters were the great references for the formation of our cardiologists. The brilliant professor Ignácio Chaves, by founding the *Instituto de Cardiología de México*, has created a unique environment of teaching, researching and healthcare, forming and influencing generations of Brazilians.

The Santa Casa philanthropic hospitals were initially the place to treat poor people with heart disease, but little by little they were turned into cardiovascular research and teaching centers. Professor Nelson Botelho Reis has introduced the clinical-hemodynamic reasoning at bedside on the 6th Ward of the Santa Casa from Rio de Janeiro. On the 29th Ward of the Santa Casa from Porto Alegre, the great educator and leader Rubens Maciel has promoted a new vision of healthcare and created the medical postgraduation program.

The cardiology of the mid-20th century was still very impacted by rheumatic disease affecting children and young adults, which was associated with the then precarious sanitary conditions of Brazil. The book by Luiz Venere Décourt about rheumatic disease, issued in 1965, represents a landmark of the medical publications in our country. Luiz Venere Décourt has been an icon of cardiology, synthesizing the science and humanism necessary to the practice of medicine. He opened the doors for Brazilian modern cardiology. His unique trajectory has been immortalized with the creation of InCor, which inaugurated a new perspective for Brazilian cardiology. Décourt and Zerbini were the authors of InCor, a public hospital directed at healthcare provision, teaching and research, which, under the leadership of Fulvio Pileggi and Adib Jatene, has definitely consolidated the insertion of Brazilian cardiology among the most respected ones worldwide.

Since cardiovascular surgery has been essential for the development of Brazilian cardiology, its remarkable advance is portrayed in the mural. Euryclides de Jesus Zerbini and Adib Jatene, two icons and personalities who have crossed the frontiers of cardiology, were the leading figures. Zerbini, an emblematic person who praised hard-working, performed the first heart transplantation in Latin America, right after Christiaan Barnard, inaugurating a golden era in Brazilian cardiac surgery. His effort payed off. Currently Brazil has the largest public program of heart transplantation in the world. Adib Jatene, considered the most prominent physician of his generation, has been Brazil Minister of Health twice and is portrayed in the mural according to his most human quality: returning joy to mothers of children with congenital heart diseases. The challenge of performing the anatomical correction of the transposition of the great arteries has been overcome by Jatene's technical skill, a great leap for pediatric cardiovascular surgery.

Cardiology, by uniting the art of medicine and technology, has incorporated the progress of science to the needs of healthcare provision, the electrocardiogram being the most eloquent expression of that binomial. João Tranchesi, another character portrayed in the mural, symbolizes the diffusion of modern electrocardiography in Brazil. With incomparable didacticism, he has popularized the learning of that technique. As a tribute, his disciples hold annually the João Tranchesi Session at the Brazilian Congress of Cardiology, where state-of-the-art electrocardiography is discussed in his honor. The contemporaneity of the technique is indisputable, and its digital version is an important Telemedicine tool, reaching remote regions and speeding up the treatment of myocardial infarction.

The change in the illness profile of Brazilians, partially due to demographic transition, with high incidence and prevalence of coronary disease, is represented in the mural. The clenched fist held over the chest, the Levine's sign,[9] a registered mark of the patient with angina, represents the suffering of hundreds of thousands of Brazilians who die from that condition. Cardiac catheterization, which plays an important role in the diagnostic and therapeutic strategy of those patients, has Eduardo Sousa, a pioneer of coronary cineangiography and interventional cardiology in Brazil, as its most remarkable precursor. Eduardo Sousa and Adib Jatene, lifelong partners, have been responsible for the consolidation of the Instituto Dante Pazzanese de Cardiologia (IDPC) as an important research, teaching and healthcare center in Brazil. The first studies in the world on the use of drug-eluting stents in human beings have been conducted at the IDPC. When addressing the evolution of the therapy for coronary artery disease, René Favaloro, responsible for the great boost on coronary artery bypass grafting, should be revered. Those are the contributions of physicians from the southern hemisphere.

At the, the emblematic figure of Professor Eugene Braunwald from Harvard University, a living legend of cardiology and perhaps the most expressive name of modern cardiology, emerges. Even nonagenarian, he continues to influence the specialty worldwide because of his knowledge and experience. His presence in the mural symbolizes the need for permanent scientific exchange with other centers around the world for the development of cardiology in Brazil.[10] In the bottom of the mural, several emblematic figures of Brazilian cardiology are portrayed, all of them taking care of bedridden patients. The scene reminds us of Rembrandt's "The Anatomy Lesson of Dr. Tulp". In addition, the cardiologists Adriano Pondé, Rafael Leite Luna, Rachel Snitcovsky, Betina Ferro, Edgard Magalhães Gomes, Fulvio Pileggi, José Krieger, Ivo Nersralla, Siguemituzo Arie, Arnaldo Elian and Ênio Cantarelli are portrayed. All these remarkable physicians have had a significant role in the development of cardiology in Brazil and some have even been presidents of the SBC.

The characters are displayed according to a fictional timeline, in which those responsible for the first discoveries are on the left-hand side and the most recent ones, on the right-hand side. The proportion of the characters and their sizes have no relation to their hypothetical historical importance but comprise a set that interacts with artistic perspective. According to the painter Flávio Tavares, it is not possible to portray in a painting all the personalities of Brazilian cardiology, and much effort was put into the construction of a plot capable of expressing that history, a stimulating challenge.

Artistic figurative expression has been first registered in rupestrian art, which might have been the first artistic manifestation of mankind. The human need for registering medical knowledge is visceral, and some individuals have even put their own lives at risk for that, such as anatomists Andreas Vesalius and Leonardo Da Vinci, who have desecrated corpse driven by a curiosity prohibited at their times. Thus, the combination of art and medicine has accounted for the advance and spread of medical knowledge. The mural 'Heart of the Tropics' perpetuates in a few meters and in an allegorical way our cardiology. This mural required careful research, whose result underwent several adjustments to harmonize the history of Brazilian cardiology from an artistic perspective capable of mixing real characters with imaginary and sick people, providing a dive into over a century of the development of Brazilian cardiology. A universe of colors, lights and shade has been combined to incorporate the characters into the dreamlike scenario of painting. According to Emilia Viotti da Costa, a nation without history is a nation without memory.

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Lower Prevalence and Severity of Coronary Atherosclerosis in Chronic Chagas' Disease by Coronary Computed Tomography Angiography

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Abstract

Background: **In Chagas' disease endemic regions, there has been for many years a recurrent empirical observation that coronary artery disease (CAD) is uncommon in patients with Chagas' disease. Previous pathological and invasive coronary angiography studies led to controversial results.**

Objective: **We sought to investigate whether CAD is less prevalent and less severe in patients with chronic Chagas' disease when compared with a matched population with a similar CAD risk profile.**

Methods: **A total of 86 participants, 43 consecutive patients with chronic Chagas' disease and 43 asymptomatic individuals, without any prior history of cardiac disease or known CAD (control group), were included. Patients and controls were matched according to gender, age, and Framingham risk score. All participants underwent coronary calcium scoring and coronary computed tomography angiography on a 320-row detector scanner. Statistical significance level adopted was p < 0.05.**

Results: **The coronary artery calcium score (CACS) was significantly lower in patients with Chagas' disease than in controls (p<0.05). The presence of coronary atherosclerotic plaques was significantly less frequent in patients with Chagas' disease than in controls (20.9% versus 41.9%, p=0.037). After adjustment for the Framingham score, the odds ratio for the presence of any coronary artery calcium (CAC) in Chagas patients was 0.26 (95%CI: 0.07-0.99, p=0.048). The pattern is similar for CACS > 10 (OR: 0.11, 95%CI: 0.01-0.87, p=0.04) and for the presence of any stenosis (OR: 0.06, 95%CI: 0.01-0.47, p=0.001). Propensity score matching also indicated an effect of Chagas disease on the CACS (-21.6 points in the absolute score and 25% less of patients with CACS >10, p=0.015).**

Conclusions: **CAD is less prevalent and less severe in patients with chronic Chagas' disease when compared with a matched population with a similar CAD risk profile. (Arq Bras Cardiol. 2020; 115(6):1051-1060)**

Keywords: **Chagas Disease/physiopathology; Atherosclerosis; Coronary Artery Disease; Tomography, Computerized/methods; Score Calcium.**

Introduction

Approximately 20,000 people die annually from Chagas' disease and 100 million people are at risk of contracting the infection worldwide. It is endemic throughout much of Mexico, Central America, and South America, where as many as 6 million people are infected.[1,2] In the United States, an estimated 300,000 individuals are infected with *Trypanosoma cruzi* (*T. cruzi*), most of who acquired the infection in endemic areas and then migrated to North America.[3-5]

Chagas' cardiomyopathy is essentially a myocarditis. The inflammatory process, although more intense in the acute phase, is clinically silent but continuous in patients with chronic infection.[6,7] After the acute illness, patients enter the indeterminate phase, which is asymptomatic and may last indefinitely. About 20 to 30% of people with chronic *T. cruzi* infection eventually develop clinical disease, predominantly cardiac. Cardiac disease usually begins with conduction abnormalities such as right bundle branch block and/or left anterior fascicular block, which may be followed by dilated cardiomyopathy years later.[8] Heart failure and other

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associated abnormalities,[9-14] including sympathetic autonomic dysfunction[15] can be seen at this phase. In later stages, apical aneurysms and thrombus formation can be frequent findings.

Importantly, during the chronic cardiomyopathy phase, a significant proportion of patients complain of atypical chest pain. Yet, the prevalence of coronary artery disease (CAD) in these patients has been found to be consistently low. Therefore, expert investigators in Chagas' disease have raised the hypothesis that patients with Chagas' disease would have less CAD than individuals without Chagas' disease but with an otherwise similar CAD risk profile. Still, the relationship between Chagas' disease and coronary atherosclerotic disease remains controversial.[16] It has been demonstrated that abnormal myocardial perfusion and even extensive myocardial scarring may occur in patients with Chagas' disease in the absence of epicardial coronary stenosis.[17,18] Myocardial fibrosis in Chagas' disease patients can be detected in early phases of the disease and precisely quantified by cardiac magnetic resonance;[19,20] its magnitude has proven prognostic significance.[21]

Despite the high prevalence of CAD risk factors, including smoking, initial reports indicating a very low prevalence of significant CAD by invasive coronary angiography in patients with severe Chagas cardiomyopathy have raised the suspicion of a distinct prevalence of CAD in Chagas patients.[22,23] The influence of Chagas disease on CAD and other chronic degenerative diseases including neoplastic diseases[24] has biological plausibility based on the presence of common mechanistic factors such as chronic inflammation, fibrosis, increase in free radical and low-density lipoprotein levels and decrease in nitric oxide levels. Nonetheless, studies that described the prevalence of CAD in patients with Chagas' disease have reported conflicting results. While some studies have found a prevalence that is similar to that observed in the general population,[23] several studies have suggested that the prevalence of CAD in patients with Chagas' disease could be lower than that of a non-infected population with similar clinical risk scores for CAD.[17,22,25-27] There is also some preliminary basic evidence that *T. cruzi* infection itself might exert a protective effect against the development of CAD in chronically infected subjects.[28] This would be possible by the potential action of trans-sialidase produced by T. cruzi in reducing mycoplasma infection, which could be involved in inflammation associated with CAD.[28]

In the present study, we used state-of-the-art coronary computed tomographic techniques to determine whether patients with chronic Chagas' disease have a lower prevalence and/or severity of CAD when compared with a matched population of asymptomatic and with no previous history of CAD, but with a similar CAD risk profile.

Methods

Population

A total of 43 consecutive patients with chronic Chagas' disease were prospectively recruited from our specialized outpatient clinic. All patients were serologically positive for Chagas' disease by at least two different techniques: ELISA and indirect immunofluorescence. They were classified in three subgroups: (1) patients in the indeterminate phase, (2) patients with electrocardiographic abnormalities, and (3) patients with heart failure. The indeterminate subgroup (15 patients, 34.9%) was defined as asymptomatic patients with chronic Chagas' disease but without abnormalities on chest X-ray, electrocardiogram (ECG), echocardiography or contrasted X-ray studies of esophagus and colon. The ECG subgroup (12 patients, 27.9%) was defined as patients with electrocardiographic abnormalities, but no abnormalities on global or segmental left ventricular (LV) systolic function and with LV ejection fraction ≥ 55% by echocardiography. Patients with LV ejection fraction < 55% were assigned to the cardiomyopathy subgroup (16 patients, 37.2%).

Additionally, a total of 43 asymptomatic individuals, without any prior history of cardiac disease or CAD, and no family history of early CAD, that underwent coronary computed tomography angiography (CTA) for risk stratification only were included as control group. These 43 patients were selected from a larger control group of 124 consecutive individuals that filled the matching criteria for each Chagas disease patient. A second individual who filled the matching criteria was not included and allocated to the backup control group. For selection of the control group, three levels of matching were used for each of the Chagas' disease patients (case-control 1x1): first, a Framingham risk score (FRS) within the same risk strata (low, intermediate and high);[29] second, age differences < 5 years; and third, the same gender. Also, since there were no patients with diabetes mellitus in the Chagas' disease group, we also excluded diabetic patients from the control group. The FRS was calculated using the model described by D'Agostino et al.,[16] and was based on the following clinical parameters: age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status. All 43 individuals underwent serological testing to exclude Chagas' disease.

All patients signed an informed consent form approved by our local institutional ethics committee. In both groups we excluded patients with renal insufficiency, defined as serum creatinine > 1.5mg/dL and/or creatinine clearance of <60mL/min/1.72m^2, by the MDRD formula (Modification of Diet for Renal Disease).

Coronary computed tomographic angiography (Coronary CTA)

All patients underwent coronary CTA on a 320-detector row scanner (*AquillionOne™ – Canon Medical Systems Corporation,* Otawara, Japan) after fasting for at least 4 hours. Prior to the exam, the patients answered a questionnaire on cardiovascular risk and were examined for heart rate (HR) and blood pressure.

Acquisition protocol included the coronary artery calcium score (CACS) and coronary CTA. CACS was determined using a tube rotation time of 370ms, tube voltage of 120 kV, current of 300mA, 320x0.5-mm collimation with 3-mm slice thickness reconstructed images obtained per heartbeat during diastole.

For coronary CTA, participants with heart rate over 65 bpm received up to 20mg of intravenous metoprolol. All participants received sublingual nitrates if their systolic blood pressure were greater than 90 mmHg. Superior and inferior limits for acquisition were defined on the CACS imaging. A real time tracking of contrast bolus propagation (*Sure Start™ – Toshiba Medical Systems Corporation,* Otawara, Japan) was used to detect steep increase in signal intensity on the descending aorta. The acquisition was started at a threshold of 150 HU. Non-ionic iodinated contrast (70mL, with iodine concentration of 370mg/mL) (Iopamiron 370 – Schering, São Paulo, Brazil, under license of BRACCO - Italy) was then administered by a power injector (*Stellant™ – Medrad,* Indianola, PA, USA) at a 5mL/s rate followed by 40mL of saline chaser.

Coronary CTA image acquisition occurred within one single heart beat (HR less than 65 bpm) according to a prospectively ECG-triggered protocol and during inspiratory breath-hold.[30,31] Coronary CTA acquisition parameters depended on participants' body mass index (BMI): up to 23 kg/m^2, tube voltage of 100kV and tube current of 450-550mA; BMI from 24 to 39 kg/m2, 120kV and 400-580mA, respectively; BMI greater than 40kg/m^2, 135kV and 510mA, respectively. Collimation depended on longitudinal size of the heart and varied from 120 to 160mm, with 0.5mm thick slice acquisitions (240x0.5mm to 320x0.5mm). Typical radiation dose for this protocol is below 10 mSv.

Coronary CTA Analysis

CACS analysis used standard protocol described by Agatston et al.,[32] using at least 3 pixels equal to or greater than 130 HU to define calcium.

Coronary CTA images were reconstructed immediately after scan completion in a consistent manner in order to identify motion-free coronary artery images. ECG-gated datasets were reconstructed at 75% of the cardiac cycle. In case of insufficient image quality, additional phases were reconstructed at 5% increments. Multiple phases were used for image interpretation if the phase of minimum coronary artery motion was different for different arteries. All images were analyzed in a *Vitrea™ FX* workstation (*Vital Images Inc,* Plymouth, MN, EUA) by two experienced coronary CTA who were unaware of any clinical information. The observers could use all tools available in the workstation to analyze the images, such as axial views, multiplanar and curved reformatting, maximal intensity projection and 3D volume rendering. For the discrepancies, a consensus between the two readers was reached for the presence and type of atherosclerotic plaque and the degree of stenosis per each coronary segment. For coronary segmentation we used a 19-segment model, previously described in the CorE-64 trial.[33]

CAD was defined as the presence of any coronary atherosclerotic plaque, even in absence of luminal obstruction. Significant obstructive CAD was defined as luminal reduction equal to or greater than 50% of the reference luminal diameter (segment immediately distal without evident disease). Atherosclerotic plaque was classified by a qualitative analysis as: A – non-calcified plaque, B – predominantly non-calcified plaque, C – mixed plaque, D – predominantly calcified plaque and E – calcified plaque. When more than one type of plaque was present, the most predominant type in each patient was considered for analysis. The degree of coronary stenosis was visually classified by the two observers according to the segment stenosis score: 0 – absence of luminal reduction, 1- mild stenosis (< 50%), 2- moderate stenosis (50-69%) and 3 – severe stenosis (≥ 70%). Figure 1 shows two examples of Chagas' disease patients with and without CAD.

Statistical Analysis

All continuous variables are presented as mean ± standard deviation, and all categorical variables are reported as percentage or absolute number. Continuous variables with normal distribution were described using the mean and standard deviation and continuous variables without normal distribution were described using the median and interquartile range. Shapiro-Wilk test was used to check for normal distribution. For comparison between groups, we used the paired Student's *t* test for variables with normal distribution, and the Mann-Whitney test for non-parametric variables. For comparisons of categorical variables, we used Pearsons' chi-square test or Fisher's exact test as appropriate. For the multivariable analysis we performed conditional logistic regression analysis adjusted for the FRS for each of the binary outcomes of CACS equal to or greater than zero; CACS lower than 10 or greater or equal to 10 and presence of coronary obstruction (defined as >50% stenosis on visual assessment). Propensity score matching, using kernel method and bootstrapping was used for additional matching between Chagas' disease and control patients. There are no data in the literature on the prevalence of atherosclerotic coronary plaque in Chagas disease patients measured by computed tomography (CT), therefore we used an exploratory or convenience sample size. The study was designed to have a matched control group, so 43 Chagas patients had to be matched to 43 normal controls with similar sex, age range and FRS. Analyses were performed with Stata software, version 13.0 (StataCorp, College Station, Texas). All tests were two-tailed, and a value of $p<0.05$ was considered indicative of statistical significance.

Results

The clinical characteristics of all participants are shown in Table 1. In Chagas' disease group, 27 women were (62.8%) and the mean age was 54.2 ± 8.3 years, and in the control group, there were also 27 women (62.8%), and the mean age was 55.0 ± 7.1 years. Gender, age, and the FRS were similar, highlighting the effective matching of both groups. The Chagas' disease group was found to have higher levels of HDL cholesterol than the control group (p=0.030, Table 1). No patient was excluded due to limited coronary CTA image quality, and no adverse event related to the procedures of this study was reported.

The CACS was significantly lower in patients with Chagas' disease than in controls. Similarly, the severity of coronary stenosis, number of coronary territories and number of coronary segments with CAD were significantly lower on Chagas' disease group compared to control group ($p < 0.05$ for all comparisons, Table 2 and Figure 1). When stratified by the FRS the prevalence of CAC >0 is higher in the control group across the three FRS tertiles (Figure 2).

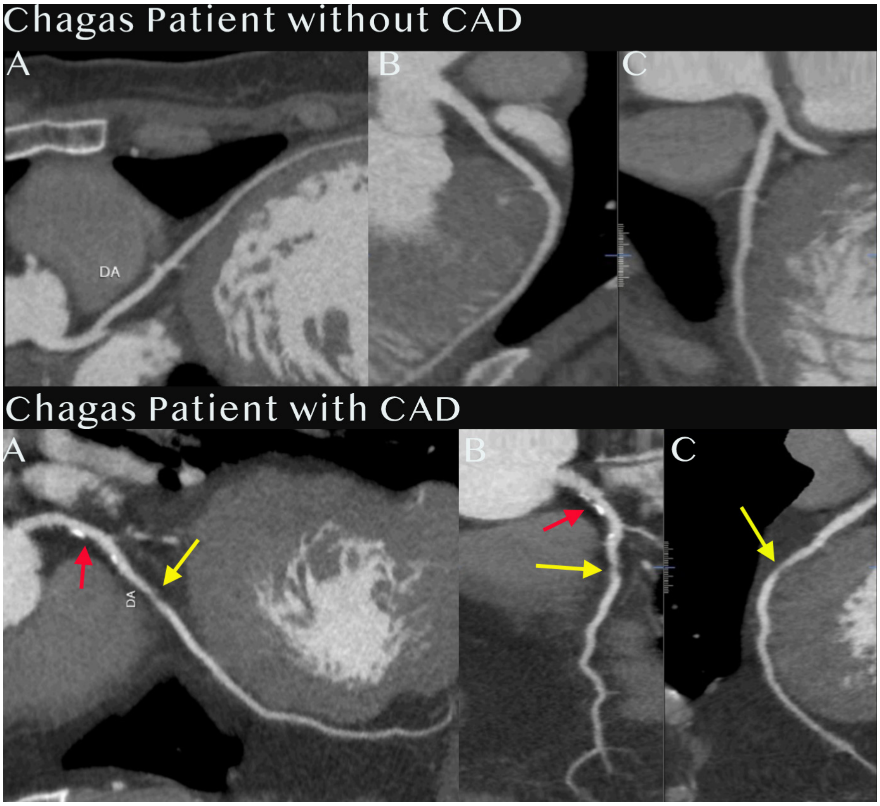

Figure 1 – *Coronary computed tomography angiography (coronary CTA) images of case examples of Chagas' patients without (top row) and with (bottom row) coronary artery disease (CAD). Panels A, B and C show three different views of the left anterior descending artery (LAD) of both patients. On the bottom row, red arrows indicate partially calcified plaque at proximal LAD without stenosis (predominantly cal mixed plaque), and yellow arrows indicate a non-calcified plaque with significant luminal stenosis.*

Table 1 – Clinical characteristics

Characteristics	Groups		p
	Chagas' (n=43)	Control (n=43)	
Age (years)	54.18 ± 8.26	55.00 ± 7.12	0.626*
Male	16 (37.2%)	16 (37.2%)	1.000**
BMI	27.4±4.2	28.9±4.8	0.127*
Coronary CTA HR (bpm)	63.4±5.1	62.2±3.7	0.215*
HDL cholesterol (mg/dL)	51.0 ± 12.4	45.9 ± 9.2	0.030*
Total cholesterol (mg/dL)	201.5 ± 36.3	224.3 ± 84.6	0.108*
Treated hypertension	20 (46.5%)	24 (55.8%)	0.388**
Current smoker	04 (9.3%)	04 (9.3%)	1.000**
Framingham risk score	3 (1; 8)†	4 (1; 8)†	0.682***

*BMI: body mass index; CTA: computed Tomography Angiography; HR: heart rate; bpm: beats per minute; HDL: high density lipoprotein. †: Median (P25; P75); *: Student t test; **: Pearsons' chi-square test; ***: Mann-Whitney test.*

Regarding the presence versus absence of coronary stenosis, 93% of Chagas' disease patients and 58.1% of control group participants did not have any coronary stenosis (p = 0.001, Table 3 and Figure 1).

The presence of coronary atherosclerotic plaques was significantly less frequent in patients from the Chagas' disease group than in subjects from the control group (20.9% versus 41.9%, p = 0.037, Table 4). No significant differences were

Table 2 – Comparison of coronary artery disease (CAD) severity between patients with Chagas' disease and control group

	Groups		p*
	Chagas' disease	Control	
	Mean±SD	Mean±SD	
	Median (P_{25}; P_{75})	Median (P_{25}; P_{75})	
Coronary calcium score	24.7±100.6	49.8± 118.7	0.047
	0 (0; 0)	0 (0; 35)	
Segment stenosis Score	0.12± 0.45	0.56±0.80	0.001
	0 (0; 0)	0 (0; 1)	
Number of coronary territories	0.35±0.81	0.77±1.07	0.032
	0 (0; 0)	0 (0; 1)	
Number of coronary segments	0.63±1.81	1.35±2.14	0.030
	0 (0; 0)	0 (0; 2)	

*SD: standard deviation; (P25: 25th percentile; P75: 75th percentile), * Mann-Whitney test.*

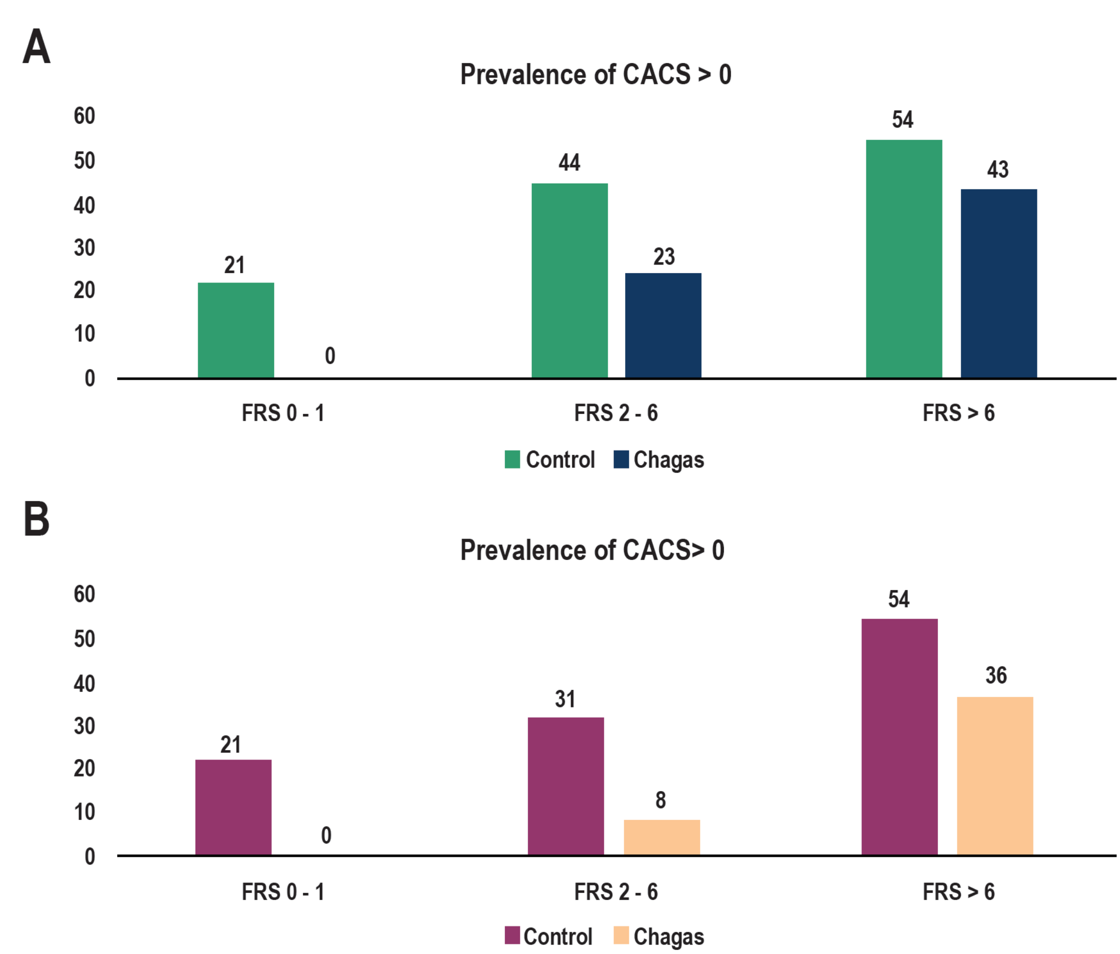

Figure 2 – *Relationship between Chagas' disease and the prevalence of CAD. A. Prevalence of any coronary artery calcium (coronary artery calcium score, CACS > 0) in patients with Chagas' disease and in controls stratified by the Framingham Risk Score (FRS) tertiles. B. Prevalence of CACS > 10 in patients with Chagas' disease and in controls stratified by Framingham Risk Score tertiles.*

Table 3 – Comparison of the degree of coronary stenosis between Chagas disease and control groups

Degree of stenosis*	Groups	
	Chagas' n (%)	Control n (%)
No stenosis	40 (93.0)	25 (58.1)
Mild stenosis	1 (2.3)	14 (32.5)
Moderate stenosis	2 (4.7)	2 (4.7)
Severe stenosis	0 (0)	2 (4.7)

**Fisher's exact test, p = 0.001.*

Table 4 – Characterization of coronary plaques

Atherosclerotic plaques	Groups		p
	Chagas' disease n (%)	Control n (%)	
No plaque	34 (79.1)	25 (58.1)	p = 0.037
Plaque present	9 (20.9)	18 (41.9)	
Type of plaque#			p = 0.237
Non calcified	0 (0)	1 (2.3)	
Mixed – predominat non calcified	2 (4.7)	3 (7.0)	
Mixed	1 (2.3)	0 (0)	
Mixed – predominant calcified	1 (2.3)	2 (4.7)	
Calcified	5 (11.6)	12 (27.9)	

** Fisher's exact test. # Patient-based analysis – the most predominant type of plaque was assigned*

found in the type of coronary plaques between the groups (p=0.237), although 27.9% of participants of the control group had calcified plaque versus only 11.6% in the Chagas' disease group (Table 4). Within the Chagas disease group, there were no differences in CAD burden based on calcium score among groups, including no differences compared to those with ejection fraction less than 55% (cardiomyopathy group).

When the analysis was performed based on the case-control design, the odds ratio for the presence of any CAC in Chagas' disease patients was 0.27 (95%CI: 0.08 – 0.98, p =0.046). The pattern is similar for CACS > 10 (OR: 0.1, 95%CI: 0.13 – 0.78, p=0.028) and for the presence of any stenosis (OR: 0.06, 95%CI: 0.01 – 0.47, p=0.007). These results remained robust even after adjustment for the FRS, with OR of 0.26 (95%CI: 0.07 – 0.99, p=0.048) for CACS>0, 0.11 (95%CI: 0.01 – 0.87, p=0.04) for CACS>10 and 0.06 (95%CI: 0.01 – 0.47, p=0.001) for the presence of any stenosis (Table 5). An additional analysis using propensity score matching, with kernel matching method and bootstrapping, indicated an average effect of – 21.6 points for the absolute CACS and -25% for CACS above 10 in Chagas disease patients when compared to the matched control group.

Discussion

In the present study, using state-of-the-art computed tomographic techniques, we demonstrated a lower prevalence and severity of CAD in chronic Chagas' disease patients when compared with a matched population with a similar CAD risk profile. The prevalence of coronary atherosclerotic plaques in patients with chronic *T cruzi* infection was approximately half of that observed in the control non-infected population. Importantly, in the present study, we studied chronic *T. cruzi* infection in three different stages: (1) the indeterminate phase, (2) ECG abnormality with normal LV function and (3) overt LV dysfunction.

Chagas' disease and CAD

Previous studies have investigated the relationship between Chagas' disease and CAD, and the results have been conflicting. Lopes et al.[23] examined autopsied hearts of 35 chronic Chagas' disease patients and 54 non-infected individuals and found that the prevalence of coronary atherosclerotic plaques (71.4% versus 74.1%, respectively) and myocardial infarction (8.6% versus 7.4%, respectively) was similar in both groups.[23] This is in contrast with our results. We believe the reason for this apparent discrepancy relies on the fact that Lopes et al.[23] performed an autopsy-based pathology study and, therefore, it is likely that they evaluated a population with much more advanced disease. In fact, it is possible that some of the patients in the Chagas' disease group died of CAD complications and not Chagas' disease. Moreover, unlike Lopes et al.[23] who studied male individuals only, we included both genders in the present study.

In another autopsy-based study, de Morais et al. [25] examined 181 hearts of chronic Chagas' disease patients and identified

Table 5 – Odds ratio for the presence of any coronary artery calcium, coronary artery calcium score (CACS > 10), and for the presence of any stenosis in patients with Chagas disease

	OR*	95% CI	p
Unadjusted			
Presence of any CAC	0.27	0.08 – 0.98	0.046
CACS > 10	0.10	0.13 – 0.78	0.028
Presence of any stenosis	0.06	0.01 – 0.47	0.007
Adjusted for FRS			
Presence of any CAC	0.26	0.07 – 0.99	0.048
CACS > 10	0.11	0.01 – 0.87	0.04
Presence of any stenosis	0.06	0.01 – 0.47	0.001

*CAC: coronary artery calcium score; FRS:Framingham risk score. *Multivarate logistic conditional regression.*

only four cases of myocardial infarction. Interestingly, all cases were secondary to thromboembolic coronary events, probably originated in apical LV aneurysms. Most importantly, the pathophysiological substrate most frequently associated with myocardial infarction, i.e. complicated atherosclerosis was not observed in any patient of this large autopsy series.

In a prospective observational study from our group, Ianni et al.[26] followed 160 patients in the indeterminate phase of chronic Chagas' disease for up to 14 years and were able to document the development of CAD in only two individuals; one presented an acute myocardial infarction and the other stable angina. Marin-Neto et al.[17] evaluated 23 subjects with chronic Chagas' disease and demonstrated that myocardial perfusion abnormalities as detected by thallium scintigraphy were present in all patients. Nevertheless, the presence of significant CAD was not observed in any of the 16 patients that underwent invasive coronary angiography.

In another study, Sarabanda et al.[27] performed invasive coronary angiography in 56 consecutive subjects with chronic Chagas' disease and ventricular tachycardia and demonstrated that the presence of significant CAD was not observed in any of those patients. More recently, Carvalho et al.[22] evaluated 61 consecutive patients with severe Chagas' cardiomyopathy (NYHA functional class III or IV). All patients underwent invasive coronary angiography, and the presence of significant CAD (> 50% stenosis) was identified in only one patient (1.6%). These finding are in agreement with our results, which also demonstrated a low prevalence of significant CAD (4.7%) in chronic Chagas' disease patients.

Coronary CTA versus invasive angiography

It is important to highlight that there is an important difference between the present study, that used coronary CTA to evaluate the presence of DAC, and all these previous reports that used invasive coronary angiography. Even though the latter is considered the gold standard for the assessment of coronary anatomy and quantification of coronary stenosis, it consists of a luminography, i.e., it is not able to detect or quantify the amount of non-obstructive atherosclerotic plaques in the arterial wall. In contrast, coronary calcium scoring plus coronary CTA is not only capable of identifying obstructive lesions,[33-37] but also allows for the quantitative assessment of the global atherosclerotic burden of the individual.[38-43] Therefore, it is a much more sensitive tool for the detection of CAD, particularly in the earlier stages of the disease, in which the invasive coronary angiography might miss the diagnosis.

Limitations and selection of the control group

Our study has some limitations that must be recognized. This is a single-center study with a relatively small sample size. The control group was composed of healthy and asymptomatic individuals that underwent coronary CTA for risk-stratification only and not randomly selected from the community. One important aspect of the present study relates to the selection of the control group, which was a critical step. We were able to select individuals comparable to Chagas' disease patients in the risk to develop CAD, so that each individual of the control group was matched to one patient in the Chagas' disease group for gender, age and the FRS. Indeed, except for the *T. cruzi* infection, the baseline characteristics of both groups were very similar. The only significant difference was that patients in the Chagas' disease group demonstrated higher levels of HDL cholesterol than the individuals in the control group. However, we do not believe this difference had a significant influence on our results, particularly because, since the control group was matched regarding the FRS, this small difference in HDL cholesterol level was, at least theoretically, counterbalanced by the other risk factors of the score.[29] The use of the propensity score matching technique added an extra layer of confidence in our matching between Chagas' disease and control group.

Clinical implications

Unfortunately, in the present study, we were not able to investigate the underlying mechanisms of the lower prevalence and severity of CAD in individuals with chronic *T. cruzi* infection. Nevertheless, our results allow us to raise some hypotheses. One possibility is that, despite the careful selection of a matched control group, both populations could have genetic or environmental differences that were not controlled in our study.

Another fascinating possibility is that the *T. cruzi* infection itself could exert some protective effect against the development of CAD. There is some preliminary evidence suggesting that an enzyme derived from the *T. cruzi,* called trans-sialidase, could have the potential to reduce the inflammatory activity and the amount of atherosclerotic plaques in experimental models.[28] It is undeniable that the mere possibility that this line of research could result in the development of a novel therapeutic tool for the prevention of CAD is very exciting.

In the meanwhile, the lower prevalence of CAD in Chagas' disease may suggest that physicians caring for Chagas' disease patients could utilize coronary CTA imaging as a first step diagnostic tool for suspected CAD in this population. Although our data is still not enough to support a change in current patient management, CTA could potentially be a gatekeeper for invasive coronary angiography in these patients, even those with more severe clinical scenario, such as ventricular tachycardia and dysfunction.[44]

Conclusions

In the present study, we used coronary CTA, which is a sensitive tool for the detection of CAD, and conclusively demonstrated that CAD is less prevalent and less severe in patients with chronic Chagas' disease when compared with a matched population with a similar CAD risk profile. Future studies will be necessary to investigate in greater detail the underlying mechanisms of these instigating findings.

Perspectives

Competency in medical knowledge: Chagas' disease and CAD are two prevalent diseases in Latin America, and symptoms such as chest pain, might be similar in patients with either of these diseases. Nonetheless, CAD is less prevalent in patients with Chagas' disease compared to general population with similar Framingham risk scores. This could help clinicians during risk stratification of chest pain.

Translational outlook: Future research is needed to confirm these findings in a large population and to identify potential mechanisms involved in this apparent "protection" for CAD in patients with Chagas' disease.

Author contributions

Conception and design of the research: Cardoso S, Fernandes F, Ianni B, Mady C, Ramires JAF, Rochitte CE; Acquisition of data: Cardoso S, Fernandes F, Ianni B, Torreão JA, Marques MD, Ávila LFR, Santos Filho R, Rochitte CE; Analysis and interpretation of the data: Cardoso S, Azevedo Filho CF, Fernandes F, Ianni B, Torreão JA, Marques MD, Ávila LFR, Santos Filho R, Bittencourt MS, Rochitte CE; Statistical analysis: Azevedo Filho CF, Fernandes F, Ianni B, Torreão JA, Marques MD, Santos Filho R, Bittencourt MS, Rochitte CE; Obtaining financing: Rochitte CE; Writing of the manuscript: Cardoso S, Azevedo Filho CF, Fernandes F, Ianni B, Torreão JA, Marques MD, Ávila LFR, Santos Filho R, Mady C, Ramires JAF, Bittencourt MS, Rochitte CE; Critical revision of the manuscript for intellectual content: Cardoso S, Azevedo Filho CF, Fernandes F, Ianni B, Marques MD, Santos Filho R, Mady C, Ramires JAF, Bittencourt MS, Rochitte CE.

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 doctoral submitted by Savio Cardoso, from Universidade de São Paulo.

Erratum

In Original Article "Lower Prevalence and Severity of Coronary Atherosclerosis in Chronic Chagas' Disease by Coronary Computed Tomography Angiography" with DOI number: https://doi.org/10.36660/abc.20200342, published in the Journal Arquivos Brasileiros de Cardiologia, 115(6):1051-1060, on page 1059, change the information that there was no external funding to: This study was funded by Capes. Change information that is not associated to: This article is part of the thesis of doctoral submitted by Savio Cardoso from Universidade de São Paulo.

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Absence of Atherosclerosis in Chagas' Disease: The Role of Trypanosoma Cruzi Transialidase

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Short Editorial related to the article: Lower Prevalence and Severity of Coronary Atherosclerosis in Chronic Chagas' Disease by Coronary Computed Tomography Angiography

The paper Lower Prevalence and Severity of Coronary Atherosclerosis in Chronic Chagas' Disease by Coronary Computed Tomography Angiography[1] reveals a very important data: patients with Chagas disease have much lower atherosclerosis compared with a carefully matched population of individuals without Chagas disease. Analyzing 43 patients prospectively, 93% of Chagas disease patients had absence of coronary artery disease (CAD) plaques, 7% mild to moderate obstruction and zero cases of severe obstruction. It endorses our previous pathological data[2] in few autopsy hearts, confirming that Chagas disease patients do not have atherosclerosis. Why they do not present atherosclerosis?

The main enzyme produced by *Trypanosoma cruzi* (*T. cruzi*) is trans-sialidase. It removes syalic acid from the tissue to the circulation. Microbiota has been associated with the development of atherosclerosis.[3] Mycoplasma is known to grow in cholesterol-rich media and in our previous study we observed large amounts of mycoplasmas in fat atheroma.[4] Many infectious agents such as mycoplasma and viruses such as SARS CoV-2 uses the syalic acid to enter the host cell, the transialidase from *T. cruzi* may remove mycoplasmas from the atheroma plaques, preventing development of atheroma.[5] We created a nutricosmetic associating the enzyme transialidase and natural antioxidant nanoparticles and decreased experimental atherosclerosis in rabbits.[6,7]

The present study emphasizes the need of other explanation than CAD for myocardial infarction pathogenesis present in Chagas disease patients. Microinfarcts, myocytolysis, hyaline degeneration and fibrosis are common findings in chronic Chagas disease cardiopathy and have been attributed, in varying degrees, to chronic myocarditis, immunoallergic phenomena and microvascular alterations.[8] We also observed that distal right coronary artery was very thin, associated with ventricular wall thinning, which may be interpreted as a consequence of lack of intramyocardial blood pressure due to dilated microcirculation. Injecting 0.5% silver nitrate in 5% aqueous glucose solution to impregnate the endothelial surface of the epicardial arteries and intramural arterioles, it was possible to see that microcirculation in autopsies of patients with Chagas disease heart failure was extremely dilated,[9] possibly due to myocardial inflammation (due to the presence of *T. cruzi* antigens and symbionts).[10,11]

It may cause inadequate balance in the blood flow distribution, worst tissue perfusion in some areas and multiple infarctions. On the other hand, the fibrotic areas may cause obstructions in the vessel trajectory, favoring deviation of blood flow (a "steal" phenomenon), and appearance of ischemic lesions;[10] the characteristic thinning lesions in Chagas disease at the apical and basal posterior left ventricle walls may also be the result of ischemia in the "watershed" lesions between the two main coronary artery branches — the anterior descending and posterior descending arteries causing ischemic lesions, foci of myocardial infarction, aneurysms and myocardial fibrosis. Low perfusion in the watershed region of right coronary and circumflex arteries may result in frequent thinning fibrotic lesion of lateral basal left ventricular wall, raising the hypothesis that this lesion could be a better predictor for ventricular tachycardia and sudden death.[11] This myocardial lesion has an aspect of myocardial infarction healing, containing islands of viable myocytes in the midst of fibrosis, which may induce ventricular arrhythmia.[12]

Chagas disease cardiopathy is a particular disorder that still deserves many research studies.

Keywords

Chagas Disease/physiopathology; Atherosclerosis/physiopathology; Diagnostic Imaging/methods; Computed Tomography/methods

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Short Editorial

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Original Article

Is Current Drug Therapy for Heart Failure Sufficient to Control Heart Rate of Patients?

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Abstract

Background: **Studies have shown that heart failure (HF) patients with heart rate (HR) < 70 bpm have had a better clinical outcome and lower morbidity and mortality compared with those with HR > 70 bpm. However, many HF patients maintain an elevated HR.**

Objective: **To evaluate HR and the prescription of medications known to reduce mortality in HF patients attending an outpatient cardiology clinic.**

Methods: **We consecutively evaluated patients seen in an outpatient cardiology clinic, aged older than 18 years, with diagnosis of HF and left ventricular ejection fraction (LVEF) < 45%. Patients with sinus rhythm were divided into two groups – HR ≤ 70 bpm (G1) and HR > 70 bpm (G2). The Student's t-test and the chi-square test were used in the statistical analysis, and a p-value < 0.05 was considered statistically significant. The SPSS software was used for the analyses.**

Results: **A total of 212 consecutive patients were studied; 41 (19.3%) had atrial fibrillation or had a pacemaker implanted and were excluded from the analysis, yielding 171 patients. Mean age of patients was 63.80 ± 11.77 years, 59.6% were men, and mean LVEF 36.64±7.79%. The most prevalent HF etiology was ischemic (n=102; 59.6%), followed by Chagasic (n=17; 9.9%). One-hundred thirty-one patients (76.6%) were hypertensive and 63 (36.8%) diabetic. Regarding HR, 101 patients had a HR ≤70 bpm (59.1%) and 70 patients (40.93%) had a HR >70 bpm (G2). Mean HR of G1 and G2 was 61.5±5.3 bpm and 81.8±9.5 bpm, respectively (p<0.001). Almost all patients (98.8%) were receiving carvedilol, prescribed at a mean dose of 42.1±18.5 mg/day in G1 and 42.5±21.1mg/day in G2 (p=0.911). Digoxin was used in 5.9% of patients of G1 and 8.5% of G2 (p=0.510). Mean dose of digoxin in G1 and G2 was 0.19±0.1 mg/day and 0.19±0.06 mg/day, respectively (p=0,999). Most patients (87.7%) used angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), and 56.7% used spironolactone. Mean dose of enalapril was 28.9±12.7 mg/day and mean dose of ARB was 87.8±29.8 mg/day. The doses of ACEI and ARB were adequate in most of patients.**

Conclusion: **The study revealed that HR of 40.9% of patients with HF was above 70 bpm, despite treatment with high doses of beta blockers. Further measures should be applied for HR control in HF patients who maintain an elevated rate despite adequate treatment with beta blocker. (Arq Bras Cardiol. 2020; 115(6):1063-1069)**

Keywords: **Heart Failure; Heart Rate; Drug Therapy; Medication Adherence; Digoxine; Morbidity & Mortality; Atrial Fibrillation; Pacemaker, Artificial.**

Introduction

Heart failure (HF) is an increasingly frequent syndrome associated with high morbidity and mortality in severe cases, and a common end-stage of heart diseases.[1]

Despite the severity of HF, an effective guideline-based treatment of HF can improve the quality of life and reduce mortality of patients.[2,3] However, the prescription of medications known to improve HF patients' prognosis is still lower than expected, as shown in recent reports.[4-6] Among the main causes of the under-prescription of medications to HF patients are hypotension, older age, and fear of potential side effects.[6,7] Another possible reason why drug doses that have been proven effective in HF are not achieved is the lack of clear therapeutic objectives, as commonly seen in the treatment of dyslipidemias and hypertension.[8,9] Perhaps we should set some clear targets, including a more strict control of heart rate (HR), which has been shown to be an important guide to assess treatment efficacy. The SHIFT study has shown that reducing HR values to less than 70 beats per minute (bmp) can improve the prognosis of HF patients with reduced left ventricular ejection fraction (LVEF) and sinus rhythm. However, HR values in some of our patients are still higher than expected.[10]

In the present study, we aimed to verify whether HF patients with sinus rhythm, attending the outpatient department of a

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large tertiary hospital in east São Paulo, had controlled HR (i.e., HR≤70 bpm). We also evaluated whether these patients were receiving appropriate drug therapy, in accordance with guidelines on HF management.[2]

Methods

Consecutive patients with HF and LVEF <45% seen at a cardiology outpatient clinic between January 2016 and March 2017, treated for HF for at least six months participated in the study. We assessed demographic data, etiology of heart disease, heart rhythm, blood pressure, HR, and drug treatment, including the doses achieved of each drug.

Inclusion criteria were age older than 18 years, diagnosis of HF, LVEF <45% and sinus rhythm. Patients were divided into two groups – patients with HR ≤70 bpm (G1) and patients with HR >70 bpm (G2).

Prescription of the three groups of medications proven to change the natural history of HF was evaluated – 1) vasodilators: angiotensin converting enzyme inhibitors (ACEI), 2) angiotensin II receptor blockers (ARBs), 3) spironolactone and beta blockers. Patients with renal dysfunction and persistent hyperkalemia, who did not tolerate 50% of ACEI/BRA, used hydralazine and nitrates.

The dose of ACEI considered was 20mg twice daily or equivalent dose of captopril (150mg per day). The dose of ARBs considered was 100-150 mg per day for losartan, and a full dose of 25mg per day for spironolactone. For beta blockers, the full dose was 25 mg twice a day for carvedilol.[2] We also evaluated the percentage of prescription and dose of commonly prescribed drugs for HF treatment, including digoxin, hydrochlorothiazide, and furosemide.[2]

The study was approved by the Research Ethics Committee of Casa de Saúde Santa Marcelina (approval number 13.10.805).

Statistical Analysis

For characterization of the study population, continuous variables with normal distribution were described as mean ± standard deviation. Categorical variables were described as number (percentage). The Kolmogorov-Smirnov test was used to verify normality of data distribution (p>0.05 = normal distribution). For group comparisons, continuous variables were described as mean ± standard deviation; and for comparisons of patients' characteristics, the chi-square or the Fisher exact test was used. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software.

Results

A total of 212 consecutive patients were studied; 41 of them were excluded for having atrial fibrillation or a pacemaker implanted. Therefore, 171 patients with sinus rhythm were assessed. Mean age was 63.8 ± 11.8 years, 59.6% were men, mean LVEF was 36.64 ± 7.79% and mean pro-brain natriuretic peptide level was 1663.95 ± 2158.77 pg/mL. An ischemic etiology of HF was identified in 63 patients (36.84%), and 131 patients (76.6%) were hypertensive. Clinical characteristics and HF treatment of patients are described in Table 1. Doses of prescribed medications are listed in Table 2.

Comparisons between G1 and G2 are described in Table 3.

Discussion

Our study showed that 40.93% of patients with HF had a HR above 70 bpm, despite the use of a high dose (>42 mg/day) of carvedilol by more than 98% of patients. Most patients were correctly prescribed with medications that could change the prognosis of the disease. The frequency of prescription of HF drugs was higher than previously described in international registries as well as in the Brazilian registry of heart failure (BREATHE).[4-6] Most patients were receiving the target dose of the drugs prescribed as recommended in the guidelines.[2,3]

Table 1 – Characteristics and drug treatment of heart failure patients with sinus rhythm (n=171)

Characteristics	
Age (years)	63.80 ± 11.77
Etiology of heart failure	
Ischemic	102 (59.65%)
Chagasic	17 (9.9%)
Idiopathic	29 (17%)
Comorbidities (n)	
Diabetes mellitus	63 (36.84%)
Hypertension	131 (76.6%)
Clinical data	
SBP (mmHg)	119.56 ± 18.69
Heart rate (bpm)	69.81 ± 12.34
NT-proBNP	1663.95 ± 2158.77
Echocardiographic data	
LVDD (mm)	61.34 ±7.79
LVSD (mm)	50.33 ± 8.25
LVEF (%)	36.64 ± 6.73
Drugs prescribed; n (%)	
Furosemide	90 (52.63%)
Hydrochlorothiazide	25 (14.61%)
ACEI/ARB	150 (87.72%)
Beta blocker	169 (98.83%)
Spironolactone	97 (56.72%)
Hydralazine	30 (17.54%)
Nitrates	42 (24.56%)
Digoxin	12 (7.01%)

SBP: systolic blood pressure; NT-proBNP: N-terminal pro–B-type natriuretic peptide; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction; ACEI: angiotensin converting enzyme inhibitors (ACEI), ARBs: angiotensin II receptor blockers.

Table 2 – Mean dose (mg/day) of the drugs prescribed

Medication	Dose (mg/day)
Furosemide	52.31 ± 26.15
Hydrochlorothiazide	26.09 ± 5.10
Enalapril	28.86 ± 12.68
Losartan	87.80 ± 29.80
Carvedilol	42.28 ± 19.65
Spironolactone	25.00 ± 4.77
Hydralazine	96.55 ± 59.35
Isosorbide	53.90 ±15.60
Digoxin	0.19 ± 0.06

Data expressed as mean ± standard deviation

These results allow us to suggest that the main cause of non-prescription of HF drugs by physicians is the lack of attempts to increase the treatment doses. It is important to highlight that the non-prescription of at least 50% of target dose leads to lower protection and higher risk of death and hospitalizations.[6,7]

Our data differ from those previously published in registries such as the BIOSTAT-HF, in which only 60% of patients achieved at least 50% of the recommended treatment dose for beta blockers, which has been shown to reduce mortality.[6] Similarly, the Brazilian registry - BREATHE – showed that 83.4% and 63.1% of HF patients were receiving ACEI/ARB and beta blockers, respectively, at hospital discharge.[5] In the QUALIFY registry, although most patients (87.5%) were prescribed ACEI/ARB, only 14.8% achieved the target dose, and 51.8% were

Table 3 – Comparison of clinical data and drug therapies of patients with heart failure and sinus rhythm by heart rate values (≤70bpm vs. >70 bpm)

	G1 (HR ≤70bpm)	G2 HR>70 bpm	p
Patients; n (%)	101 (59.06%)	70 (40.93%)	
Men; n (%)	62 (61.38%)	40 (57.97%)	
Etiology of heart rate			
Ischemic	59 (58.41%)	43 (61.64%)	0.938
Chagasic	16 (15.84%)	3 (4.28%)	0.009
Non-ischemic	26 (25.74%)	24 (34.28%)	
Comorbidities			
Diabetes mellitus	31 (30.69%)	32 (45.71%)	0.045
Hypertension	82 (81.18%)	50 (71.42%)	0.108
Clinical data			
SBP (mmHg)	119.76 ± 17.87	119.29 ± 19.81	0.871
HR (bpm)	61.53 ± 5.26	81.76 ± 9.52	<0.001
NT-proBNP	1625.09 ± 2258.42	1721.80 ± 1999.91	0.822
Echocardiographic data			
LVDD (mm)	61.26 ± 7.78	61.46 ± 7.82	0.868
LVSD (mm)	49.84 ± 8.42	51.12 ± 7.92	0.356
LVEF (%)	37.46 ± 6.58	35.46 ± 6.78	0.056
Doses of the drugs prescribed			
Furosemide	50.57 ± 25.06	54.74 ± 27.41	0.458
Hydrochlorothiazide	26.92 ± 6.66	25.00 ± 0.00	0.392
ACEI/ARB	29.77 ± 12.38	27.50 ± 12.99	0.361
Betablocker	80.43 ± 33.75	97.22 ± 20.22	0.076
Spironolactone	42.14 ± 18.55	42.48 ± 21.14	0.911
Hydralazine	24.79 ± 4.84	25.35 ± 4.64	0.585
Nitrates	111.11 ± 67.81	72.73 ± 29.11	0.097
Digoxin	55.77 ± 16.21	50.67 ± 13.89	0.325
Furosemide	0.19 ± 0.06	0.19 ± 0.06	0.999

HR: heart rate; SBP: systolic blood pressure; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro–B-type natriuretic peptide.

using a dose greater than 50% of the target dose for ACEI. In this same study, 27.9% of patients were taking the target dose for beta blockers, and 51.8% were receiving a dose greater than 50% of the target dose for beta blocker.[4] In our study group, 79.09% of patients achieved the recommended dose for ACEI, and 53.63% of them were using enalapril 40 mg/day, and 58.47% achieved the recommended dose for beta blockers (15% of them were receiving a dose greater than 50 mg/day of carvedilol. A large majority (97.27%) of patients were prescribed a dose greater than 50% of ACEI, and 88.88% of patients were receiving a dose greater than 50% of carvedilol (Figure 1).

Our study also revealed that many of the patients treated with carvedilol 42.48mg/day, and 40% of the patients with sinus rhythm had a HR greater than 70 bpm (Figure 2). These results are in agreement with the literature, since all studies reporting HR data of HF patients treated with ACEI, beta blockers and spironolactone have shown that a high percentage of them maintain the HR at values above 70 bpm despite treatment. It worth mentioning that in many of these studies, the beta blocker dose used by the patients was lower than 50% of target dose.[6,7]

In the OPTIMIZE-HF registry, that evaluated 10,697 hospitalized patients in the United States, mean HR at hospital discharge was 76 bpm, with no correlation between HR and dose of beta blocker. Patients receiving a dose lower than 25% of the target dose for beta blockers showed a mean HR of 78 bpm, and those who achieved the target dose showed a mean HR of 72 bpm. An elevated HR correlated with the prognosis, with higher morbidity and mortality among patients with HR greater than 70 bpm.[11] At Duke University, most of patients with HF (73%) showed elevated HR (>70 bpm) despite treatment. Elevated HR was associated with higher morbidity and mortality (RR 1.59), and higher treatment cost.[12] Habal et al.[13] reported that the risk of death was 59% higher in patients with a HR above 90 bpm compared with those with HR of 61-70 bpm.[13] The ASCEND-HF study showed that 85% of HF patients had elevated HR (>70 bpm) despite treatment, which was associated with higher mortality.[14]

In our study, although a considerable number of patients showed a HR above 70 bpm, the number was lower than those reported in these previous studies, which may be explained by the different doses of beta blockers used by the patients. In addition, a study on office patients who were receiving carvedilol at a dose near to the target dose reported that 35% of patients with HF had a HR above 70 bpm.[15]

An issue discussed in the literature concerns which is a more important determinant of prognosis, the target dose of beta blocker or the reduction in HR. It is worth pointing out that the HR reduction achieved by beta blockers differs among patients. In the MERIT-HF study, two groups of patients were identified – one group that showed a HR reduction in response to low doses of metoprolol (mean 76 mg/day) and another group that achieve HR reduction in response to high doses of metoprolol (mean 195 mg/day).[16] Such difference may be genetically determined, with some of the patients highly responsive to relatively low doses of medications.[16] The authors pointed out that the reduction in events was not different between the two groups, indicating that HR reduction was a more important determinant to reduction of cardiovascular events compared with the beta blocker dose.[16] Considering HR reduction, the SHIFT study suggested a target HR below 70 bpm,[10] and suggested that HR reduction is also more important than the dose of beta blocker in reducing cardiovascular events.[17] It is of mention that the greater reduction in events is achieved when the HR is reduced to values lower than 64 bpm, as demonstrated in the CHARM and CIBIS-ELD studies.[18,19]

A meta-analysis of several clinical trials with beta blockers showed that the prescription of these drugs was associated with a reduction in mortality of 34%, and that the HR reduction was more strongly associated with a reduction in events that the dose of beta blocker.[20] In addition, the study showed that for every reduction in HR of 5 beats/min, the risk

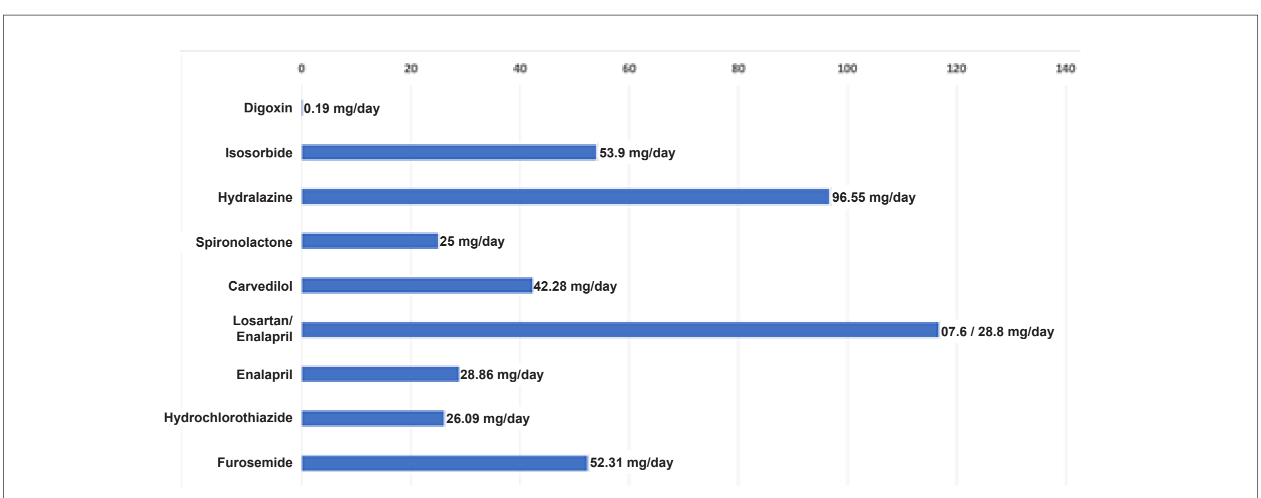

Figure 1 – *Percentage of users and mean dose of the prescribed medications for heart failure treatment in 171 patients (mean left ventricular ejection fraction of 36.6%) seen at the cardiology outpatient clinic of Santa Marcelina Hospital, São Paulo, Brazil.*

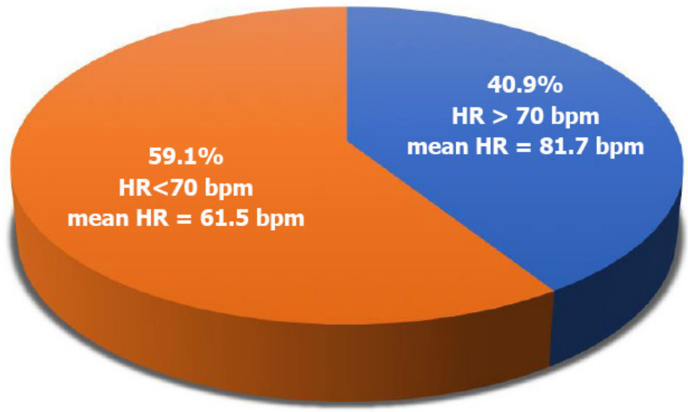

Figure 2 – *Distribution of heart failure patients with sinus rhythm by heart rate (>70 bpm or <70 bpm).*

of death decreased by 18%, and the dose of beta blocker was not determinant to event reduction, with a reduction in the risk of death of 26% in patients receiving a higher dose, and of 22% in those receiving a lower dose.[20]

The BIOSTAT-HF study and the retrospective analysis of the ACTION-HF data revealed a greater reduction in cardiovascular events in patients treated with a higher dose of beta blocekrs.[6,21] In the BIOSTAT-HF study, doses greater than 50% of target dose were associated with greater mortality reduction in 2,516 patients. In the Discussion section, the authors state that they did not detect any difference in the clinical course of patients treated with more than 50% of target dose compared with those treated with the target dose; however, lower doses did not have a protective effect.[6] In the ACTION-HF study, the patients who had a better clinical outcome (greater mortality reduction) were those who achieved HR reduction to lower than 70 bpm with a dose of 50% or more of beta blocker. Patients receiving a lower beta blocker dose showed higher mortality rate. When only patients receiving a low dose of beta blocker were analyzed, those with HR values below 70 bpm showed a better clinical outcome than those with HR values above 70 bpm.[21]

We can conclude that both low doses of beta blocker and a HR above 70 bpm are associated with a worse prognosis. Data of the literature have highlighted the importance of evaluating HR in all HF patients and optimizing the treatment in those with HR above 70 bpm, by either increasing the dose of beta blocker or by prescribing ivabradine in attempt to reduce it, since a HR of more than 70 bpm has been shown an excellent and easy marker of worse course. It is worth remembering that the higher the HF the worse the prognosis. We should be careful to avoid postponing the decision to change the therapy when we see a patient with sinus rhythm and HR above 70 bpm. It is also important to point out that the efficacy of be blockers at low doses has not been proven. Besides, in patients with elevated HR despite treatment with beta blocker, we can use ivabradine, which is a selective *f* current blocker, that reduces HR in patients with sinus rhythm.[2]

One limitation of this study was the fact that it was a single-center study. The strength of this study lies on the fact that it demonstrated that many HF patients treated with adequate dose of beta blocker maintain HR at high levels,[22] which is related to their prognosis.

Conclusion

Of the patients with sinus rhythm evaluated, 98.83% were prescribed a high dose of beta blocker (42.28 ± 19.65 mg/day), but 40.93% maintained HR at levels above 70 bpm. Further measures should be applied for a better HR control of these patients who maintain an elevated HR despite adequate treatment with beta blocker. In our study group, a high frequency of patients was taking vasodilators, at adequate mean dose.

Author contributions

Conception and design of the research: Cardoso J, Cardoso C, Barretto ACP; Acquisition of data: Cunha M, Netto E, Del Carlo CH, Brancalhão E; Analysis and interpretation of the data: Cardoso J, Brancalhão E; Statistical analysis: Brancalhão E; Writing of the manuscript: Cardoso J; Critical revision of the manuscript for intellectual content: Cardoso J, Espíndola MD, Cardoso C, Name AL, Barretto ACP.

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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Heart Rate Control in Heart Failure

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Short Editorial related to the article: Is current drug therapy for heart failure sufficient to control heart rate of patients?

Heart failure (HF) is an important public health issue due to its high prevalence and the severity of clinical manifestations.[1,2] The increment in population longevity has increased the number of hospitalizations and deaths due to HF. Recent data by DATASUS (2020) show the occurrence of 26,482 deaths from HF.[3]

This syndrome has a multifactorial characteristic and its treatment requires a multidisciplinary team to meet the recommendations proposed in the guidelines for the treatment of HF. Follow-up and monitoring of patients are essential for improving the clinical outcomes.[4-6]

Heart rate (HR) is considered a therapeutic target in the treatment of HF, since elevated HR is a marker of events in HF.[4] Several studies have shown the importance of HR control to improve outcomes such as risk of death and hospital admission by HF.[7,8]

Therefore, observational studies are essential to investigate the impact of the treatment of patients with HF. In this sense, a study carried out by Cardoso et al.[9] aimed to assess whether patients monitored in outpatient settings have their HR controlled and receive drug prescriptions according to the guidelines for the treatment of HF.[9]

A recent global study showed that despite satisfactory adherence to the recommendations of guidelines for the treatment of HF, an under-dosage of the recommended drugs is observed. Actions are needed to improve this situation, since high doses of recommended therapies are associated with reduced mortality in observational studies of patients with HF.[10]

In their study, Cardoso et al.[9] mentioned that beta-blockers do not have the same effect reducing HR for all patients. Thus, the authors raised an important question of what would be more important to determine a good outcome for patients with HF, the target dose of the beta-blocker or the reduction in HR?

The study evaluated 171 patients in outpatient settings and showed very relevant data on the effectiveness of the treatment of HF on HR control. Although beta-blockers were prescribed in high doses for 98.8% of patients, a large portion (40.9%) had HR greater than 70 beats per minute. The authors also observed that other classes of drugs recommended for the treatment of HF, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics, were properly prescribed.[9]

Thus, considering the impact of HR on the prognosis of patients with HF, the study conducted by Cardoso et al.[9] suggests that other actions in addition to the prescription of the recommended drug therapy need to be adopted to ensure the control of HR in patients with HF.

Keywords

Heart Failure/treatment; Heart Rate; Patient Care Team; Medication Adherence.

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Atrial High-Rate Episodes and Their Association with Cerebral Ischemic Events in Chagasic Patients

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Abstract

Background: Atrial high-rate episodes (AHREs) are associated with an increased risk of cerebral ischemic events; however, there are no studies related to the presence of AHREs and cerebral ischemic events in Chagasic patients.

Objective: To investigate the association between the presence of AHREs ≥ 6 minutes and cerebral ischemic events in Chagasic patients.

Methods: Cohort study with Chagasic patients with implantable electronic cardiac devices (IECDs), followed at the Arrhythmia Outpatient Clinic of a University Hospital, in the city of Salvador, state of Bahia, Brazil, between May 2016 and June 2017.. Patients diagnosed with atrial flutter / atrial fibrillation, with unicameral IECD and using oral anticoagulation were excluded. AHREs with atrial frequency ≥ 190 beats per minute and duration ≥ 6 minutes (min) were considered, and cerebral ischemic events were identified by computed tomography (CT) of the skull.

Results: The 67 research participants (67.2% females, mean age 63.6 ± 9.2 years) were followed for 98 ± 28.8 days and 11.9% of the patients had AHREs ≥ 6 min. Skull CT showed silent cerebral ischemic events in 16.4% of the patients, 63.6% of whom had AHREs ≥ 6 min in the analysis of IECDs. Advanced age [OR 1.12 (95% CI 1.03-1.21; p=0.009] and the presence of AHREs ≥ 6 minutes [OR 96.2 (95% CI 9.4-987.4; p <0.001)] were independent predictors for ischemic events.

Conclusion: AHREs detected by IECDs were associated with the presence of silent cerebral ischemic events in Chagasic patients. (Arq Bras Cardiol. 2020; 115(6):1072-1079)

Keywords: Chagas Disease/complications; Atrial Flutter; Cerebral Infarction; Brain Ischemia; Pacemaker Artificial; Tomography, Computed/methods.

Introduction

Atrial fibrillation (AF) increases the risk of ischemic stroke by five to six times regardless of other risk factors.[1] In recent years, interest in detecting AF at an earlier stage, before clinical identification, has been growing, mainly detected through an implantable cardiac pacemaker / defibrillator (ICD) and preceding the first disease manifestation,[2,3] the atrial high-frequency episodes (AHREs), which correspond to the occurrence of atrial arrhythmias such as atrial fibrillation and flutter and are characterized by having an atrial frequency ≥ 190 beats per minute (bpm)[4] or ≥ 250 bpm,[3] with duration ≥ 5 to 6 minutes (min). They are asymptomatic episodes and detected only through continuous monitoring and are also called "subclinical AF".[4]

AHREs are associated with an increased risk of stroke[5] and the tendency is that these episodes have the same adverse prognosis as clinical AF; however, the duration, frequency or exact daily load of these episodes at risk of stroke is still unknown; thus, the threshold of AHREs that justifies oral anticoagulation is not yet clear.[6]

The incidence of AHREs is 30-70%, depending on the clinical profile of the population studied and the detection algorithms used in each study protocol.[7] When excluding patients with a history of AF and using oral anticoagulation, that number drops to around 30%.[8-10]

However, in some specific populations who are vulnerable to thromboembolic complications, such as patients with Chagas'

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disease (CD), there are no data related to the investigation of the presence of these episodes and their incidence.

Approximately 30% of CD patients develop cardiac changes, and more than 10% develop neurological changes.[11] Complications of heart disease are mainly due to arrhythmias and heart failure, responsible for more than 35% of deaths.[12] In CD, AF is the most frequent supraventricular arrhythmia, being found in 4 to 12% of cases,[13] being one of the main causes of cerebral embolic events,[14] and of which incidence affects 3% of the Chagasic population.[15]

Investigating the presence of AHREs and their association with stroke in patients with CD may allow the inclusion of these patients to those using oral anticoagulants. The objective was to investigate the association between the presence of AHREs ≥ 6 minutes and cerebral ischemic events in Chagasic patients.

Methods

Study Design and Population

This is an observational, prospective cohort study. All 77 patients were included, of both genders, aged ≥ 18 years, followed at the arrhythmia outpatient clinic of a University Hospital, a referral in Cardiology, in the city of Salvador, state of Bahia, Brazil, between May 2016 and June 2017. The patients had Chagas' disease and IECD's (pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices) capable of monitoring atrial activity. Patients diagnosed with atrial fibrillation / atrial flutter, with unicameral IECD, those with chronic indication for oral anticoagulation for any reason, or those with a contraindication to cranial tomography were excluded.

The research was performed in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee of Hospital Universitário Prof. Edgard Santos UFBA-HUPES (under number: 1,426,885, on 26/02/2016). The consent form was obtained from all participants.

Data on gender, age, ethnicity, comorbidities, type and indication of IECD's, IECD stimulation mode ' drug therapy and characterization of Chagas disease were collected, in addition to data related to chest radiography, transthoracic echocardiogram ((TTE) and long-term electrocardiogram - 24-hour Holter. In each patient, CD was classified according to the criteria of the Brazilian Consensus on Chagas Disease.[14] Data were collected through interviews with patients and from medical records.

The risk score used was CHA_2DS_2-VASc (C- Congestive heart failure (or Left ventricular systolic dysfunction) – 1 point, H- Hypertension – 1 point, A_2 - Age ≥75 years - 2 points, D - Diabetes Mellitus – 1 point, S_2 - Prior Stroke or transient ischemic attack or thromboembolism- 2 points, V - Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) – 1 points, A - Age 65–74 years – 1 point and Sc - Sex category (female sex) - 1 point).[16]

The risk classification of cerebrovascular events, according to the score CHA2DS2-VASc is defined as follows: High risk (2 points or more), intermediate risk (1 point) and low risk (0 points).

Study Procedures

After signing the informed consent form, patients underwent a 12-lead electrocardiogram (ECG), aiming at confirming the absence of atrial fibrillation / atrial flutter, in addition to identifying cardiac rhythm and intraventricular conduction disorders. Then, the patients were evaluated by an arrhythmologist and had their IECDs adjusted to a specific schedule, aiming at detection and recording of atrial arrhythmias.

After a period of approximately 3 months after the schedule implementation, the patients returned to the clinic to have devices analyzed (reading of the IECD's), to identify and classify the occurrence of atrial arrhythmias, the AHREs.

During the period between the programming and the reading of the IECDs, patients underwent a non-contrast-enhanced skull computed tomography (CT) aiming to identify cerebral ischemic events. Silent cerebral infarction was identified in those patients who showed changes in cerebral infarction in the CT reports and who did not show any clinical changes in ischemic events or neurological deficits. CT scans were performed and evaluated by the Neuroradiology Department of the Hospital. This examination was performed on a Toshiba Medical Systems Corporation device, 1385 (Shimo Ishigami, Otawara-Shi, Tochigi, Japan).

IECDs Programming

The choice of device manufacturer did not influence patient inclusion / exclusion. Manufacturers' devices that have been included were Medtronic®, St. Jude Medical® and Biotronik®, of which models were available for use in this population.

The device was programmed to identify AHREs lasting at least 190 bpm, for ≥ 6 min, recognized as an appropriate cutoff point to select AHREs and rule out premature atrial contraction or false events,[17] throughout the monitoring period. This duration was chosen because it is consistent with the methodology of two large studies, the "Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)"[4] and the "The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk (TRENDS)",[3] which demonstrated the association between AHREs, lasting at least five or six min, and cerebral ischemic events. The storage electrogram was activated to confirm the occurrence of AHREs. Patients had atrial sensitivity set at 0.1 - 0.5 millivolts (mV).

All AHREs detected by IECD lasting ≥ 6 min and with frequency ≥ 190 bpm were documented and sent for blind assessment by the specialist (electrophysiologist). The activation of other electrogram storage triggers was left to the physician's discretion but was not supported by the study protocol.

In addition to device programming, data related to stimulation / detection parameters, percentages of atrial and ventricular utilization, as well as the minimum and maximum heart rate were collected.

Monitoring

Approximately three months after IECD programming, the patient returned for the subsequent consultation, and at this time data related to the detection of AHREs were collected.

The atrial electrograms corresponding to the detected AHREs were evaluated by an electrophysiologist blinded to the results of cranial CT scans. These electrograms were categorized as adequate or inadequate detections. Inadequate detections (noise, ventricular Far-field R wave detection, or repetitive, non-reentrant ventricular-atrial synchrony),[17,18] were excluded.

Three categories were defined, without overlapping the duration of AHREs: (1) without AHREs; (2) AHREs lasting <6 min; (3) AHREs lasting ≥ 6 min. Based on the detection of AHREs lasting ≥ 6 min, 4 subgroups were defined: (1) AHREs between 6 min - 29 min; (2) AHREs between 30min - 5h59min; (3) AHREs between 6 am - 11:59 pm and (4) AHREs ≥ 24 h. These cutoffs were defined according to the positive predictive values established by the ASSERT study analysis.[19]

For AHREs ≥ 6 minutes and ≥ 190 beats / min, the positive predictive value was 82.7%. The positive predictive value increased to 93.2%, 96.7% and 98.2% when the threshold duration was extended to 30 minutes, six hours and 24 hours, respectively. Increasing the threshold heart rate to 250 beats / min decreased false positive detections, but to a lesser extent, and added only marginally to the positive predictive value when long threshold durations were used.[19]

Ischemic Events in Cranial Tomography

All CT scans were performed and evaluated by the Department of Neuroradiology of the Hospital where the study was conducted, with the aim of identifying areas compatible with ischemic events (ischemic areas, lacunar infarctions, localized glioses or hypodense areas). For patients with no medical history or previous neurological deficits, ischemic events were considered to be silent. The cranial CTs were performed on a Toshiba Medical Systems Corporation device, 1385, Shimoishigami, Otawara-Shi, Tochigu, Japan.

Statistical Analysis

The statistical analysis was performed using the IBM SPSS program, version 21.0 (IBM, Armonk, New York). The data was submitted to descriptive statistical analysis, using frequency measurements (absolute and relative) for qualitative variables. For quantitative variables, mean and standard deviation, or median and interquartile range were used, depending on the variable distribution, which was tested using the Shapiro-Wilk test.

For the categorical variables, the χ^2 test or Fisher's exact test was applied. The unpaired Student's t test was used for the mean ages of patients with AHREs ≥ 6min and without AHREs ≥ 6min and for the comparison of LVEF means, whereas the Mann-Whitney test was used to compare the time since the IECD implantation in months.

The results were presented using Odds Ratio (OR) and their respective 95% confidence intervals (95%CI). A value of $p < 0.05$ was considered statistically significant.

Results

Population Characteristics and Detection of AHREs

A total of 77 patients were included in the cohort, of which ten were excluded; seven had AF at the time of the cardiac device programming , and oral anticoagulation was started (as defined by the patient's attending physician); two died before the reading of the device and in one patient, ventricular Far-field R-wave detection was identified during IECD reading. In the end, 67 participants completed all stages of the research.

The mean age was 63.6 ± 9.2 years; all participants were in the chronic phase of CD, 89.6% of whom had developed the Cardiac form and 10.4% the Cardiodigestive form of the disease. The clinical manifestations of the cardiac form of CD included the Arrhythmic Syndrome (100% of patients), Heart Failure - HF (38.8%) and Thromboembolic Syndrome (3% - corresponding to two patients with previous stroke). The clinical manifestations related to the Cardiodigestive form was the occurrence of Chagasic Megaesophagus in seven patients.

As for data related to IECDs, we found that 46.3% of patients were in DDD stimulation mode (double-chamber stimulation), followed by 41.8% in DDD-R mode (DDD with frequency response - R); the minimum heart rate was 61.8 ± 3.9 bpm, and the maximum was 124.4 ± 5.5 bpm. The percentage of atrial utilization averaged 52.8 ± 37.4%, whereas the ventricular was 65.6 ± 42.5%.

The mean follow-up was 98 ± 28.8 days and AHREs were detected in 24 (35.8%) patients, with varying durations. The incidence of AHREs lasting ≥ 6 minutes or "subclinical AF" was 11.9% (n = 08).

The median time to reach the first AHRE was 26.2 days (ranging from 0.08 to 83.25 days), and the median duration of the AHREs was 135.4 minutes (ranging from 22.8 to 5811.8 minutes).

Comparisons of the demographic and clinical characteristics of patients with AHREs ≥ 6min *versus* patients without AHREs or with duration <6 min are shown in table 1.

Detection of Ischemic Events

Eleven patients (16.4%) had an ischemic event on cranial CT and had no history of previous stroke. It was observed that 87.5% of the patients, who had AHREs ≥ 6 min, also had ischemic events on cranial CT. Table 2 shows the clinical characteristics of patients with and without ischemic events.

It was observed that 45.5% of the patients with ischemic events had AHREs lasting between 30min and 05h59 min, and the average number of AHREs ≥ 6 min was 3.88 ± 2.58, with 50% of patients having between 1 and 3 episodes.

In addition to considering the longest AHRE identified by the IECD, the total daily load of AHREs (the maximum time that the patient remained in "subclinical AF" during a 24-hour period) and its possible association with ischemic events were also measured. It was demonstrated that the Chagasic patient with daily load lasting ≥ 06 minutes, is more likely to develop ischemic events [OR: 46.67 (6.57 - 331.67; $p < 0.001$)]. The median maximum daily load that was associated with the occurrence of ischemic events was 4,554 seconds (75.9 minutes) [OR: 1.001; $p < 0.026$).

Table 1 – Demographic and clinical characteristics of patients with AHREs ≥ 6 min *versus* patients without AHREs or duration <6 min

Demographic and clinical characteristics	Population total (n=67)	With AHREs ≥ 6min (n= 08)	Without AHREs or < 6min (n= 59)	P value
Age (years) – mean ± SD	63.6 ± 9.2	69.9 ± 10.4	62.8 ± 8.8	0.040†
Sex– n (%)				0.103
Female	45 (67.2)	3 (6.7)	42 (93.3)	
Male	22 (32.8)	5 (22.7)	17 (77.3)	
Ethnicity – n (%)				1.000
White	4 (6)	0(0.0)	4 (100)	
Nonwhite	63 (94)	8 (12.7)	55 (87.3)	
IECD Type				1.000
Pacemaker	62 (92.5)	8 (12.9)	54 (87.1)	
ICD	5 (7.5)	0(0.0)	5 (100)	
IECD Indication – n (%)				1.000
AVB/ TAVB	52 (77.6)	7 (13.5)	45 (86.5)	
SND	10 (14.9)	1 (10.0)	9 (90)	
Secondary prevention SCD	5 (7.5)	0(0.0)	5 (100)	
Implant OF IECD (months)§	108 (48-168)	144 (54-165)	96 (36-180)	0.757*
HF (NYHA)	26 (38.8)	4 (15.4)	22 (84.6)	0.701
HF functional class				1.000
I	7 (26.9)	1 (14.3)	6 (85.7)	
II	13 (50)	2 (15.4)	11 (84.5)	
III	6 (23.1)	1 (16.7)	5 (83.3)	
AMI– n (%)	4 (6)	8 (12.7)	4 (100)	1.000
SAH – n (%)	50 (74.6)	6 (12)	44 (88)	1.000
Diabetes – n (%)	6 (9)	1 (16.7)	5 (83.3)	0.549
Dyslipidemia – n (%)	21 (31.3)	2 (9.5)	19 (90.5)	1.000
LVEF % - mean ± SD	58.5 ± 14.1	58.1 ± 11	58.6 ± 14.5	0.495
LA ≥ 40mm – n (%)	22 (32.8)	3 (13.6)	19 (86.4)	1.000
CHA2DS2-VASc Score				0.346
Low risk	12 (17.9)	1 (8.3)	11 (91.7)	
Intermediate risk	37 (55.2)	3 (8.1)	34 (91.9)	
High risk	18 (26.9)	4 (22.2)	14 (77.9)	

Source: The author.
*Data is presented as mean ± standard deviation or the number of patients (%); § Data presented as median and interquartile range. P values were calculated using the Chi-square test, * Mann-Whitney and the † Student's t test, as appropriate. IECD: Implantable electronic cardiac device. ICD: Implantable cardioverter defibrillator. AVB/TAVB: Atrioventricular block / Total atrioventricular block. SND: Sinus node disease. SCD: Sudden cardiac death. HF: Heart Failure (NYHA: New York Heart Association). AMI: Acute myocardial infarction. SAH: Systemic arterial hypertension. LVEF: Left ventricular ejection fraction. LA: Left atrium. CHA2DS2-VASc: risk score for thromboembolic events (C- Congestive heart failure (or Left ventricular systolic dysfunction) – 1 point, H- Hypertension – 1 point, A_2 - Age ≥75 years- 2 points, D - Diabetes Mellitus – 1 point, S_2 - Prior Stroke or transient ischemic attack or thromboembolism- 2 points, V - Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) – 1 point, A - Age 65–74 years – 1 point e Sc - Sex category (female sex) - 1 point).*

Table 2 – Clinical characteristics of patients with and without ischemic events

Clinical characteristics	Ischemic events (n= 11)	Non-ischemic events (n= 56)	P value
Age (years) – mean ± SD	70.6 ± 10.9	62.2 ± 8.3	0.005†
Sex– n (%)			0.483
Female	6 (13.3)	39 (86.7)	
Male	5 (22.7)	17 (77.3)	
HF	6 (23.1)	20 (76.9)	0.315
Classification of HF -(NYHA)			0.843
I	1 (14.3)	6 (85.7)	
II	3 (23.1)	10 (76.9)	
III	2 (33.3)	4 (66.7)	
AMI – n (%)	1 (25)	3 (75)	0.521
SAH – n (%)	8 (16)	42 (84)	1.000
DM – n (%)	1 (16.7)	5 (83.3)	1.000
Dyslipidemia – n (%)	5 (23.8)	16 (76.2)	0.301
LVEF % - mean ± SD	57.2 ± 14	58.7 ± 14.2	0.553†
LA ≥ 40mm – n (%)	6 (27.3)	16 (72.7)	0.157
Score CHA2DS2-VASc			0.050
Low risk	-	12 (100)	
Intermediate risk	5 (13.5)	32 (86.5)	
High risk	6 (33.3)	12 (66.7)	
AHREs			< 0.001
Without AHREs	3 (7)	40 (93)	
AHREs < 6minutes	1 (6.3)	15 (93.8)	
AHREs ≥ 6minutes	7 (87.5)	1 (12.5)	

Source: The author.
Data is presented as mean ± standard deviation or the number of patients (%); § Data presented as median and interquartile range. P-values were calculated using the Chi-square test and † Student's t test. AHREs: Atrial high-rate episodes. IECD: Implantable electronic cardiac device. PM: Cardiac pacemaker. AVB/TAVB: Atrioventricular block / Total atrioventricular block. SND: Sinus node disease. SCD: Sudden cardiac death. HF: Heart Failure (NYHA: New York Heart Association). AMI: Acute myocardial infarction. SAH: Systemic arterial hypertension. DM: Diabetes mellitus. LVEF: Left ventricular ejection fraction. LA: Left atrium. CHA2DS2-VASc: risk score for thromboembolic events (C- Congestive heart failure (or Left ventricular systolic dysfunction) – 1 point, H- Hypertension – 1 point, A_2 - Age ≥75 years- 2 points, D - Diabetes Mellitus – 1 point, S_2 - Prior Stroke or transient ischemic attack or thromboembolism- 2 points, V - Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) – 1 point, A - Age 65–74 years – 1 point e Sc - Sex category (female sex) - 1 point).

Table 3 shows the description of the daily load of AHREs in patients with and without ischemic events.

Advanced age and the presence of AHREs ≥ 6 minutes were associated with ischemic events, as shown in Table 4.

Discussion

There was an association of AHREs ≥ 6 min with silent ischemic events. The study by Benezet-Mazuecos et al.[20] showed that silent cerebral ischemic events occur more in patients with AHREs (42%) than in those without AHREs (19%), finding an OR of 3.4. Benezet-Mazuecos et al.[21] also described that silent cerebral ischemic events occurred more in patients with AHREs (32%) than in those without AHREs (13%) finding an OR of 2.45. In addition, brief episodes of subclinical AF (48 hours) documented by Holter monitoring were associated with a significantly increased risk of silent cerebral ischemic events and stroke.[22]

The incidence of AHREs in patients without a history of AF is around 30%, with different monitoring periods.[4,9,10] In our study, the incidence found in the Chagas population (also without a history of AF), with a monitoring period of about 03 months, was 11.9%. This finding is very similar to that found in a large study of 2,580 non-Chagasic patients with no history of AF, where AHREs ≥ 6 min were found in 35% of patients in an average follow-up of 2.5 years, and in 10% of patients in the first three months of the study.[4] However, it is important to note that the median time to detect episodes in our study with Chagasic patients (26.2 days) was lower than the one in other studies, as in the MOde Selection Trial (MOST) - 100 days[2] and

Table 3 – Description of the daily load of AHREs in patients with and without ischemic events

Description of daily load	With ischemic events (n= 11)	No ischemic events (n= 56)	P value
Daily load of AHREs - n (%)			< 0.001
Without daily load	3 (27.3)	40 (71.4)	
< 6 minutes	1 (9.1)	14 (25)	
≥ 6 minutes	7 (63.6)	2 (3.6)	

Data is presented as the number of patients (%); The P-value was calculated using Fischer's exact test. AHREs: Atrial High Rate episodes.

Table 4 – Factors associated with ischemic events

Associated factors	OR	CI 95%	P value
AHREs ≥ 6 minutes	96.2	9.4 - 987.5	< 0.001
Advanced age	1.12	1.03 - 1.21	0.009
HF	2.16	0.58 -7.98	0.241
Dyslipidemia	2.08	0.56 – 7.80	0.270
SAH	0.89	0.21 -3.82	0.874

OR: Odds Ratio; 95%CI: 95% confidence interval; χ2 test. AHREs: Atrial high-rate episodes. HF: Heart Failure. SAH: Systemic arterial hypertension.

ASSERT - 36 days,[4] and additionally, the average number of AHREs in our study was higher (3.9) than that in the ASSERT study (2.0).[4]

In this study, all patients had a double-chamber IECD; however, no association was found between the dual-chamber stimulation mode and the presence or absence of AHREs, and this may be due to the fact that many episodes were short-lived. However, it is possible that in a larger sample of patients, a reduction in AHREs can be detected, with double-chamber stimulation. The MOST[2] study also did not show this association.

The detection of AHREs was higher in patients with advanced age, females, of black ethnicity, with a history of AMI, whose indication for IECD implantation was AVB / TAVB; however, only advanced age was associated with the ischemic event. The aging of the population results in an increase in the underlying heart disease, and the improvement in diagnostic techniques has shown a high prevalence of AF in people over 70 years of age.[23] This also happens with the Chagasic population,[24] where the prevalence of AF was markedly higher in individuals with advanced age. Studies have shown that AHREs were more prevalent in the elderly population, but no statistical significance was found in this association.[4,20]

In addition to the silent ischemic events associated with AHREs ≥ 6 min in older patients, there was also an association of the high-risk CHA2DS2-VASC score with silent ischemic events, similar to what was observed in other studies.[20,21,25]

Although AHREs detected by IECDs are associated with a 2- to 2.5-fold increase in stroke risk, compared to individuals without AHREs,[3,4] the absolute risk of stroke in these patients is lower than in those with detected clinical AF.[26]

Detection studies of "subclinical AF" using IECDs have tried to identify the ideal time limit (considering the longest episode or daily load) and its clinical consequences, such as thromboembolic events. The duration of the thresholds described in the studies have been highly variable, 5 min,[2,3] suggesting an increase of 2.8 in the risk of stroke or death; 6 min,[4] with a 2.5-fold increased risk for thromboembolism; 24 h[8] with an increase of 3.1, with a greater risk for thromboembolic events. Likewise, the daily load of 3.8[27] and 5.5 h,[3] has also been associated with a significant increase in stroke risk (9 and 2-fold increase, respectively).

In our study, the daily load of AHREs lasting ≥ 6 minutes, suggests a greater chance for the Chagasic patient to develop a silent ischemic event, a higher risk than that described by other studies. In patients with IECDs,[28] an OR of 2.11 was demonstrated for the occurrence of ischemic events in the patient who had at least 1 day with at least 1 hour of the "subclinical AF" load (95% CI: 1.22-3.64, p = 0.008). Another study,[20] describes that the load detected by the IECDs was shown to be significantly associated with silent cerebral ischemic events, with an OR o 5.38.

The duration of the longest episode or the daily load of AHREs that sufficiently increases the risk of ischemic events to justify anticoagulation is uncertain. The current recommendation is to follow the AHRE Management Algorithm[7], since there are no studies published so far on this subject.

Limitations

The present study has limitations related to the small number of patients included in it and its development in a single observation center, but it is worth mentioning that there are no studies being carried out with the Chagasic population and with this purpose. In addition, unlike other previously performed studies, the three brands of IECDs most often used by the studied population were included here, not limited to a single type of device and their evaluation (programming performed and analysis of records) did not interfere with other configurations, therefore meeting the needs of patients during the entire monitoring time, with the study being easily reproducible.

The absence of a control group also corresponds to a limitation; however, even without the control group, it is worth emphasizing the relevant contribution of the study to obtain unprecedented information on patients with Chagas disease and ischemic events.

The investigation of ischemic events was performed through skull CT, and the sensitivity for the detection of ischemia is greater than that of skull magnetic resonance. However, the use of specific magnetic resonance imaging methods for patients using IECDs is not yet a reality for patients treated by the Brazilian public health system and analyses of intra and inter-observer variability have not been carried out by neurologists.

Conclusions

We observed that in patients with Chagas disease and IECDs, AHREs ≥ 6 min are frequent and their association with silent ischemic events was significant. The occurrence of silent ischemic events was also associated with a higher maximum daily load. This association was more prevalent in elderly patients, and the other characteristics of Chagas disease did not interfere with the evaluated results.

These are the first published results about Chagasic patients, and may offer subsidies for professionals who routinely monitor these patients, making them aware of the relevance of these episodes and directing them in the search and application of algorithms for this specific population.

Author Contributions

Conception and design of the research: Freitas EL, Sampaio ES, Oliveira MMC, Aras R; Acquisition of data: Freitas EL, Oliveira LH, Guimarães MSS, Pinheiro JO, Magalhães LP, Albuquerque GSB, Aras R; Analysis and interpretation of the data: Freitas EL, Oliveira MMC, Oliveira LH, Guimarães MSS, Pinheiro JO, Magalhães LP, Albuquerque GSB, Macedo C, Aras R; Statistical analysis and Writing of the manuscript: Freitas EL, Sampaio ES, Oliveira MMC, Aras R; Critical revision of the manuscript for intellectual content: Aras R.

Potential Conflict of Interest

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

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Causing Mechanisms of Embolic Strokes in Chagas Heart Disease: Autonomic Dysfunction, a Working Hypothesis

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Short Editorial related to the article: Atrial High-Rate Episodes and Their Association with Cerebral Ischemic Events in Chagasic Patients

In Brazil, to date, Chagas disease (Chd) is still a major public health problem and a frequent cause of chronic Chagas cardiomyopathy (CCC) and stroke.[1] It is still the leading cause of DALYs — disability-adjusted life-years (in 2016, of 141,640), a measure of health loss due to fatal and non-fatal disease burden.[2] Chd is strongly associated with Chagas association-embolic strokes (CAS)[3] with an incidence ranging from 0.56 to 2.67 per 100 person/year.[4,5] It is closely related to the presence of CCC.[6] Diagnosis of Chd may be established after stroke presentation in around 40% of patients. Classically, the cause of CAS was thought to be cardioembolic, with intracardiac thrombus resulting from poor ventricular function and atrial arrhythmia. Risk factors for CAS include apical aneurysm, left ventricular (LV) thrombus, severe atrial dilation, LV systolic dysfunction, older age, and atrial arrhythmia.[5] Although it remains true that the majority of CAS is thromboembolic, other types, including small vessel disease, among others (i.e. vessel atherosclerosis and cryptogenic stroke), have been observed.[7] Hypotheses on the mechanisms of these noncardioembolic strokes include the presence of autonomic dysfunction in most or all patients with CCC in various stages.[8] Concerning autonomic dysfunction, our group showed that CCC patients, even in the early stages and without cardiac dysfunction, present signs of a parasympathetic nervous system disorder that correlate significantly with subcortical white matter abnormalities of the brain. This was demonstrated by an inverse and significant correlation between reduced cardiac frequency variability (evaluated by the respiratory sinus arrhythmia test and the presence and number of white matter hyperintensities seen on brain magnetic resonance imaging (MRI). A total of 52% of our patients revealed hyperintensities on MRI, compared with about 13% in the general population. However, there was no correlation with cerebral hemodynamics, which was tested with a transcranial Doppler, including vasoreactivity evaluated by the breath-holding index. Based on these results, we suggested that a properly functioning parasympathetic system protect the brain against white matter hyperintensities. We speculated that imbalance between sympathetic and parasympathetic systems could promote electrical instability of the heart that could contribute to noncardioembolic CAS.[9] To answer whether the parasympathetic dysfunction is a mediator of neurologic consequences of CCC or just a bystander, we conducted another study where we found no correlation between the presence of serum functional circulating antibodies with β-adrenergic or muscarinic activity and the autonomic system function or the presence of white matter hyperintensities (seen on MRI) in CCC patients. The antireceptor antibodies were tested in rabbit isolated hearts. We concluded that autonomic dysfunction is possibly a mediator of neurologic consequences of CCC apparently related to promote atrial arrhythmias as epiphenomena of stroke.[10] An important feature of CCC is the fact that not all patient with risk factors for noncardioembolic CAS will have stroke. The complicated development and pathology of the disease, coupled with the complexities of the parasite life cycle and its interactions with the host, make it a very difficult task to identify which group of patients with CCC is susceptible to stroke. Although there is no absolute proof that autonomic dysfunction is synonymous with noncardioembolic CAS, i.e., halting autonomic dysfunction to prevent noncardioembolic CAS, there is a consensus that cardiac autonomic dysfunction is needed for this event.

In this edition, Freitas et al.[11] presented a study to help understand an important clinical presentation in CCC, i.e. stroke. They draw attention to the arrhythmic mechanism, particularly atrial arrhythmia. The justification is that a consensus is lacking about the contribution of atrial high-rate episodes in this event. To answer this question, the authors performed a longitudinal study between 2016 and 2017 to check the existence (or not) of an association between high-rate atrial episodes (HRAE) and stroke in patients with chronic CCC. All 67 Chagas patients had implantable electronic cardiac devices (IECDs) (92.5% had pacemakers and 7.5% had implantable cardioverter-defibrillators) to monitor atrial activity. HRAE was considered as atrial frequency ≥190 beats per minute and duration ≥6 minutes and cerebral ischemic events were identified by brain computed tomography (CT) scans. The results were summarized and analyzed in the groups with and without atrial high-rate episodes.

Mean age of 63.6±9.2 years, follow-up for 98±28.8 days; and 11.9% of the patients had HRAEs ≥6 min. CT showed silent brain ischemic events in 16.4% of the patients, 63.6% of whom had HRAEs ≥6 min in the analysis of IECDs. Advanced age [OR 1.12 (95% CI 1.03–1.21; $p<0.009$] and the presence of HRAEs ≥6 minutes [OR 96.2 (95% CI 9.4–987.4; $p<0.001$)] were independent predictors for ischemic events. They concluded that HRAEs

Keywords

Stroke; Chagas Heart Disease.

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detected by IECDs were associated with the presence of silent brain ischemic events in Chagas patients.

The interpretation of these results should consider the small number of patients previously mentioned by the authors, uncontrolled confounding factors and the uncertainty introduced by the large 95% confidence interval observed in the patients with HRAEs ≥6 minutes. Different stages of CCC was possibly used since there is a wide spectrum of clinical and pathological manifestations in CCC patients leading to different profiles of patients included in the groups.[12] Possibly, the study refers to noncardioembolic CAS, since left ventricular ejection fraction (LVEF) and left atrial (LA) diameter were normal (only 27.3% LA ≥40 mm) and it does not contain any information about existence of intracardiac thrombus and apical aneurysm. An important question is that the level of noncardioembolic CAS reported was very high for a mean follow-up of only 3 months. We are not aware of any study or registries that show such a high incidence in CCC patients of similar age and clinical characteristics.[4,5] Another important question is the clinical applicability of the study since its main result does not change decision-making in CCC patients. There is no evidence that patients with non-embolic CAS should undergo a different diagnostic workup than other stroke patients and antiplatelet agents for noncardioembolic CAS. Actual data on effective treatments are lacking in this rather large subgroup of patients. However, it is important to understand why such patients without overt left ventricular systolic dysfunction (LVEF 58.5±14.1) seemed to have increased non-embolic CAS. One putative explanation is the presence of autonomic dysfunction observed in nondilated CCC patients, which is related to reduced vagal heart variability indexes. Vagal heart dysfunction can occur even in CCC patients in the early stages, but it worsens as the left ventricular function deteriorates with disease progression[13,14] and a properly functioning parasympathetic system to protect the brain against noncardioembolic CAS.

Although several aspects of non-embolic CAS in CCC have been elucidated in the last decades, important questions remain unresolved as to its mechanisms. While some studies in the pre-clinical area have documented the role of autonomic modulation disorders in noncardioembolic CAS, this still represents a preliminary hypothesis and the translational aspects of these studies have not been fully achieved. A better understanding of the function of autonomic modulation in the clinical severity of non-embolic CAS in CCC is an important area of research for future studies.

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Original Article

Prevalence of Trypanosoma Cruzi Infection in Blood Donors

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Abstract

Background: **Chagas disease (CD) is considered a public health problem in Latin America. The northeastern region, especially the state of Ceará, still represents a major concern in terms of the risk of transmission of CD.**

Objective: **To estimate the prevalence of T. cruzi in blood donors from the state of Ceará.**

Methods: **This is a retrospective descriptive study that was performed in the period from 2010 to 2015 from data recorded in the computerized system of the Hematology and Hemotherapy Center of Ceará (HEMOCE in Portuguese).**

Results: **Of the 763,731 potential blood donors, 14,159 were serologically ineligible; 1,982 (0.33%) were serologically ineligible due to positive / inconclusive diagnosis for CD. A total of 425 individuals came to the HEMOCE to repeat the test, with 28.2% (120/425) declared ineligible for donations due to CD.**

Conclusion: **No significant reduction of positive / inconclusive serology was observed in the period between 2010 and 2015, but a reduction was observed when compared to 1996/1997 in the state. The determination of the prevalence of CD in blood banks may be relevant as an indicator of the risk of CD transmission through blood transfusions in a given region. New serological tests for triage with better accuracy in screening are needed, in an attempt to reduce the unnecessary disposal of blood bags, reduce costs for the Brazilian Unified Health System, and diminish insecurity for the patient and family members. (Arq Bras Cardiol. 2020; 115(6):1082-1091)**

Keywords: **Chagas Disease/complications; Chagas Disease/epidemiology; Trypanosoma Cruzi; Blood Banks; Sorologic Tests.**

Introduction

Chagas disease (CD) is considered to be a public health problem in Latin America. This disease used to be exclusive to the Americas, but, in recent decades, it has spread to other continents, due to the internalization of the disease caused by the migration of people from endemic regions to these locations.[1] In Brazil, it is estimated that there are some two to three million infected people.[2]

In the northeast region of Brazil, the state of Ceará is one of the states in which there is still a great concern in terms of the transmission of CD. This concern is due to three main factors: the region is still, from a social point of view, quite needy. It also has the highest indices of homes conducive to the colonization of triatominae bugs, along with the low operational level of Chagas Disease Control Program (CDCP) throughout Brazil.[3,4]

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As regards CD transmission, the two most important epidemiological forms are the vectorial and blood transfusions.[2,5,6] As of 1940, the practice of blood transfusions became widespread throughout Latin America, which contributed of the risk of CD by blood transfusion.[7-12] In this light, blood transfusions began to take on epidemiological importance as of 1944 and became technically approved in 1951. In 1969, the obligation of serological triage for CD was instituted in blood banks in Brazil. This action was established by the Brazilian Health Ministry in an attempt to control and increase safety against related diseases.[13]

Governmental decree number 158, ratified on February 04, 2016, by the Health Ministry, considers an ineligible donor to be those who have had home contact with the triatominae in an endemic area, and those with a clinical or laboratorial diagnosis for CD. In addition, in Article 130 of the same governmental decree, the conducting of serological tests of high sensitivity for CD became mandatory in every blood donation.[14]

Therefore, the present study sought to estimate the prevalence of *T. cruzi* in blood bank donors in the state of Ceará, given that the region has scarcely been explored. The results of the present study will serve as a warning to the epidemiological surveillance agency teams, so that they may establish measures for the prevention, treatment, and follow-up of individuals infected by *Trypanosoma cruzi* as well as for individuals who live in high-risk areas.

Metodology

Study design, location, and sample

This work is a retrospective descriptive study conducted through the collection of data recorded in the information technology (IT) system of the Hematology and Hemotherapy Center of the state of Ceará (HEMOCE in Portuguese) of all of the potential blood donors of the state's Public Blood Bank Network from 2010 to 2015 (Figure 1). The donors' personal data were preserved, and these were identified by their registration number to guarantee confidentiality.

The state's Public Blood Bank Network consists of a Blood Bank Coordinator, with its headquarters located in the city of Fortaleza; four Regional Blood Banks, located in the municipalities of Sobral, Quixadá, Crato, and Iguatu; one Blood Bank Nucleus, in Juazeiro do Norte; one Blood Bank Collection Clinic at the Dr. Jose Frota Institute (IJF in Portuguese); and 64 Blood Transfusion Agencies, located in the hospitals attended to by the Blood Bank Network of Fortaleza and the municipalities throughout the countryside of Ceará. Each blood bank is responsible for receiving blood donors and patients in the coverage area, with jurisdiction to conduct all of the blood cycle steps, with the exception of serology, which, for than a decade, has been centralized in the Blood Bank of Fortaleza, where the data referent to the blood donors was collected.

The serological triage for CD during the study period was performed by the chemiluminescence technique, which consists of the interaction of the antibodies present in the serum of the infected patients with antigenic epitopes present in the plaque, which, after incubation of biotinylated anti-gamma globin and streptoavidin conjugated with the enzyme, in the presence of a luminal reagent, are capable of emitting light.[15,16]

If the result is positive or inconclusive, the test is repeated in duplicate in the same sample. If the result remains positive or inconclusive, the patient is called to the blood bank service for a second blood collection. After the collection, the triage test (chemiluminescence) is again performed, and, if the result is positive or inconclusive in the repetition of the test, a confirmatory test will be performed and the donor is already definitively refused, even if the confirmatory test is negative. The confirmatory test must be a highly specific test, with the HEMOCE using indirect immunofluorescence (IIF) or *western blot,*[15] depending on the bidding processes, since this is a governmental agency.

The IIF consists of a detection of antibodies in the infected serum, which, when incubated upon a slide with fixed *T. cruzi* antigens, connect themselves, forming the antigen-antibody compound, and which are revealed by a human anti-gamma globulin marked with fluorescein isothiocyanate. The *western blotting* test consists of a method in molecular biology and biochemistry to detect proteins in a homogenate or a biological tissue extract. This technique uses a gel electrophoresis to separate the denatured proteins by mass. The proteins are then transferred from the gel to a nitrocellulose membrane, where they are used as specific protein antibody probes.[15]

If the result is positive or inconclusive in the confirmatory test, the patient is referred to the medical clinic of the Walter Cantídio University Hospital or to Messejana Hospital, which are reference units for the clinical follow-up of individuals with chronic CD in the state of Ceará (Figure 2).

Data analysis

The occurrence of ineligible donors due to CD was calculated, and a descriptive statistical analysis was conducted from the absolute and relative frequencies. For the epidemiological characterization of individuals who are blocked from donating blood due to a confirmed diagnosis of CD, the following parameters were considered: gender (male and female), age range (18 – 29 years of age and over 30 years of age), profession, hometown, and city from which the individual came (Fortaleza or other municipality). The descriptive analysis was performed using Microsoft Excel, version 2013.

Figure 1 – *Maps showing the location of the study. Source: Drafted by the author.*

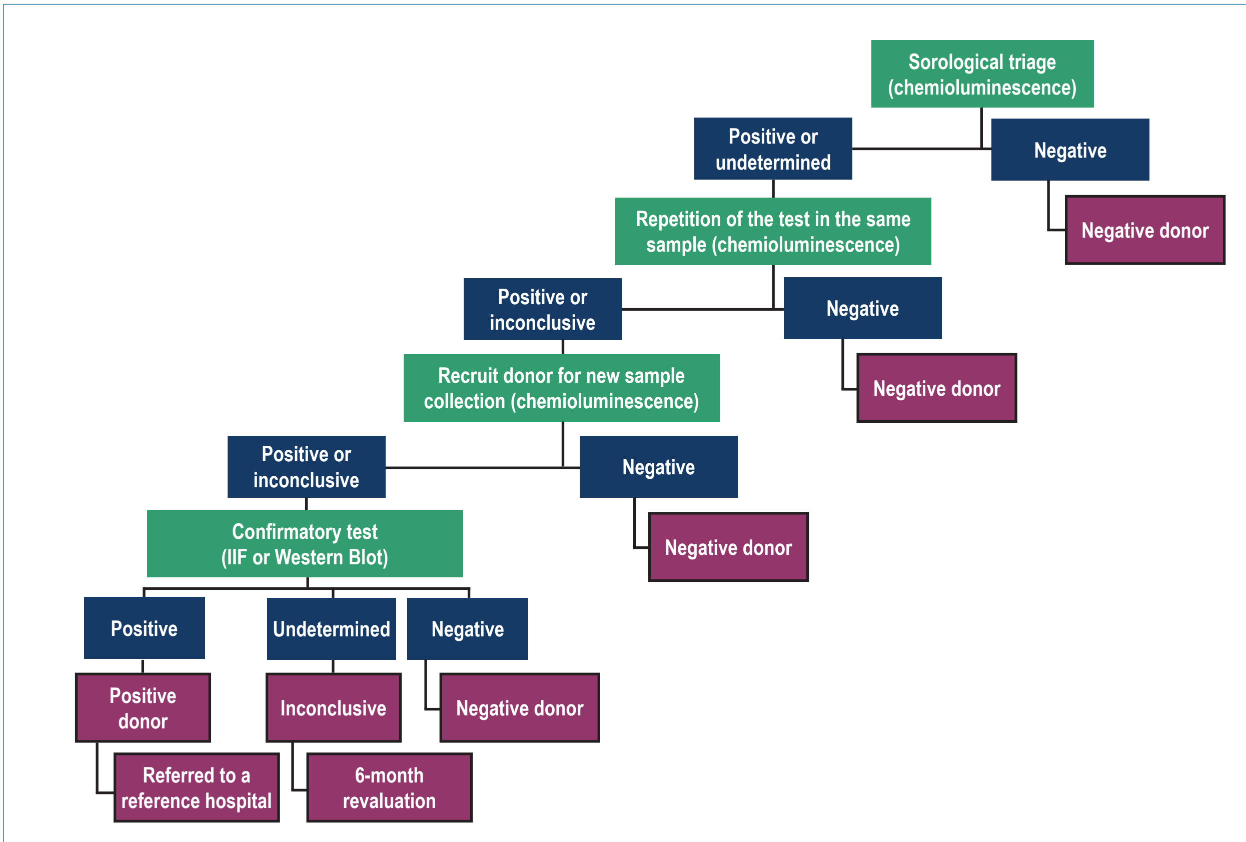

Figure 2 – *Fluxogram of the triage of potential blood donors for CD at the state´s Public Blood Bank in 2017. IIF: indirect immunofluorescence. Source: Drafted by the author.*

Ethical aspects

The present study was approved by the Research Ethics Committee of the Federal University of Ceará (COMEPE-UFC in Portuguese), logged under protocol number 1.482.674, CAAE: 53833816.5.0000.5054, which was judged according to the guidelines for research with human beings from the National Health Council (Resolution CNS 466/12).

Results

During the period of the study (January 2010 to December 2015), the state's Public Blood Bank Network of the state of Ceará received a total of 763,731 potential blood donors. Of these, 155,378 (20.3%) were excluded in the clinical triage, and among the reasons for exclusion were: anemia, hypertension, alcoholism, drug use, high-risk behavior for sexually transmitted diseases, hepatitis, malaria, CD, among other causes. This study rejected 38 (0.02%) potential donors, of which 21 (55.2%) were men and 17 (44.8%) were women. Hence, the research on antibodies against *T. cruzi* (Serological triage) was conducted with 608,353 (79.6%) individuals.

During the period of the study, 14,159 blood bags were discarded, because they were believed to be inappropriate for donation due to positive serology for some type of disease traced at the blood bank, representing 2.32% of the total number of blood bags collected during the period. Of the 608.353 blood donor candidates approved in the clinical triage, 1,982 (0.32%) were considered ineligible for blood donation due to positive/inconclusive serology due to CD by means of the chemiluminescence test. Of these, 602 (30.37%) were positive and 1,380 (69.62%) were inconclusive (Table 1). The inconclusive results corresponded to 9.75% (1,380) of the discarded bags.

The results showed an increase of 16.35% in the number of potential donors, when compared to 2010 to 2015. As regards the prevalence per year, a reduction of 50% (0.34% in 2010, 0.17% in 2015) was observed.

To verify if CD is still present in historically endemic areas, the prevalence was analyzed in the blood banks of Sobral, Quixadá, and Iguatu, considering positive and inconclusive results. The blood bank of Sobral presented the highest prevalence for CD in 2010 at 0.57% (78/13,674). In 2011, blood bank of Quixadá also presented 0.55% (29/5312), and in 2012 this same blood bank presented 0.71% (43/6,075), and 0.56% (33/5,914) in 2013 (Figure 3).

The blood banks of Quixadá, Sobral, and Iguatu presented the highest indices of serum prevalence for infection by *T. cruzi* in the period studied – 0.51% (171/33,413), 0.42% (356/85,150), and 0.40% (140/35,286), respectively.

The years of 2012 and 2013 presented the highest percentages of blood donors declared ineligible due to CD, 0.47% and 0.49%, respectively, with a subsequent reduction in

Table 1 - Total number of ineligible donors in the serology triage due to CD at the state´s Public Blood Bank from 2010 to 2015

YEAR	DONORS*	POS (N)	POS (%)	IND (N)	IND (%)	TOTAL INELIGIBLE (N)	TOTAL INELIGIBLE (%)
2010	94,847	86	0.09	244	0.25	330	0.34
2011	100,019	89	0.09	231	0.24	320	0.33
2012	98,815	89	0.09	374	0.38	463	0.47
2013	99,037	114	0.12	365	0.37	479	0.49
2014	105,281	112	0.11	84	0.08	196	0.19
2015	110,354	112	0.1	82	0.07	194	0.17
TOTAL	**608,353**	**602**	**0.1**	**1380**	**0.23**	**1982**	**0.33**

*POS: positives; IND: undetermined. *Total number of donors who did the serology test. Source: Ceará Public Blood Bank (2010 – 2015).*

the following years of 2014 and 2015, with the lowest values recorded of 0.19% and 0.17% (Table 1). Of the ineligible donors due to CD, 847 (42.73%) had already donated blood some time before the period of this study.

Of the 1,982 donors selected to repeat the test (positive or inconclusive diagnosis in the serological triage due to CD), 757 (38.19%) individuals did not return to the Blood Bank to repeat the test. Hence, 1,225 (61.8%) individuals repeated the test.

In the repetition of the chemiluminescent triage test, 92 individuals presented inconclusive results, while and 333 presented positive results. These sample reagents were submitted to the confirmatory test (IIF or *western blot*). Of these, 305 individuals presented a negative confirmatory test, 48 an inconclusive result, and 72 a positive result (Table 2). Thus, 120 (28.23%) individuals were declared ineligible for blood donation due to CD.

Of these ineligible individuals due to CD (n=120), 78 (65%) were male, 100 were over 30 years of age, 100 (83.3%) were first-time donors, and 20 (16.7%) had already donated blood before. Forty-five (37.5%) of these individuals had completed high school and 32 (26.7%) had not completed elementary school, while 88 (73.3%) came from municipalities in the countryside of the state of Ceará and 62 (51.7%) came from the capital city of Fortaleza (Table 3).

Discussion

Chagas disease, little by little, is becoming less relevant than it used to be in the realm of Brazilian sanitation. Even so, it still represents a challenge in some key aspects. Fiusa-Lima & Silveira in 1984[16] found an overall prevalence of 3.05% of CD infection in the northeastrne region (Brazil = 4.40%). Alencar conducted the first studies on CD in Ceará in 1987 and detected an estimated prevalence of 14.8%, highlighting the municipality of Limoeiro do Norte which presented 16.7%.[17] Despite the significant reduction in the vectorial transmission as of the 1990s, CD is considered by the World Health Organization (WHO) as “neglected”, which makes it part of a political and planned agenda of control, which should be followed by endemic countries.[18]

From the point of view of blood banks, the disease continues to be the object of continuous surveillance, given that the population of donors encompasses a considerable number of individuals who have already lived in sanitary and environmental conditions that were favorable to the transmission of the disease, and some of these individuals still live in these conditions. Thus, epidemiological studies in hemotherapy services becomes important, not only because of the relevance in blood transfusions, but also as an option to evaluate the transmission of the disease in specific municipalities.

In the present study, the prevalence of CD was of 0.33% in the serological triage of the Public Blood Bank Network of the state of Ceará. Similar results were also found in other regions of the country, such as in the study conducted at the Blood Bank of the city of Ituiutaba, in the Triângulo Mineiro region, which detected that 0.23% of the candidates presented a positive serology for CD, while 0.27% presented inconclusive serological results in the period of 2011 to 2011.[19] In the period from 1995 to 2009, a study was conducted in the Blood Bank of the Center Region of Uberaba (HRU in Portuguese) and a serum prevalence of 0.2% of ineligible donors due to CD was found.[20]

A bibliographic review conducted by Costa et al.[21] analyzed the ineligibility of candidates for blood donation due to seropositivity for CD in different regions of Brazil (northeast, southeast, south). In this sense, the greater prevalence of the ineligible donors due to seropositivity for CD occurred in the Northeast, specifically in the sity of Iguatu, CE, while in the southeast region, in the city of Patos de Minas, MG, the recorded percentages were of 1.90% and 1.20%, respectively. In the southern region of the country, the percentages of prevalence for ineligible donors due to seropositivity for CD varied between 0.40% and 0.47% in Porto Alegre and Pelotas, respectively.

The present study observed that the blood bank of Iguatu presented one of the highest prevalence of the studied period (0.41%); however, when compared to the findings from Costa et al.[21] a reduction was observed in the prevalence of ineligible donors due to seropositivity for CD in Iguatu, CE, between 2010 and 2015.

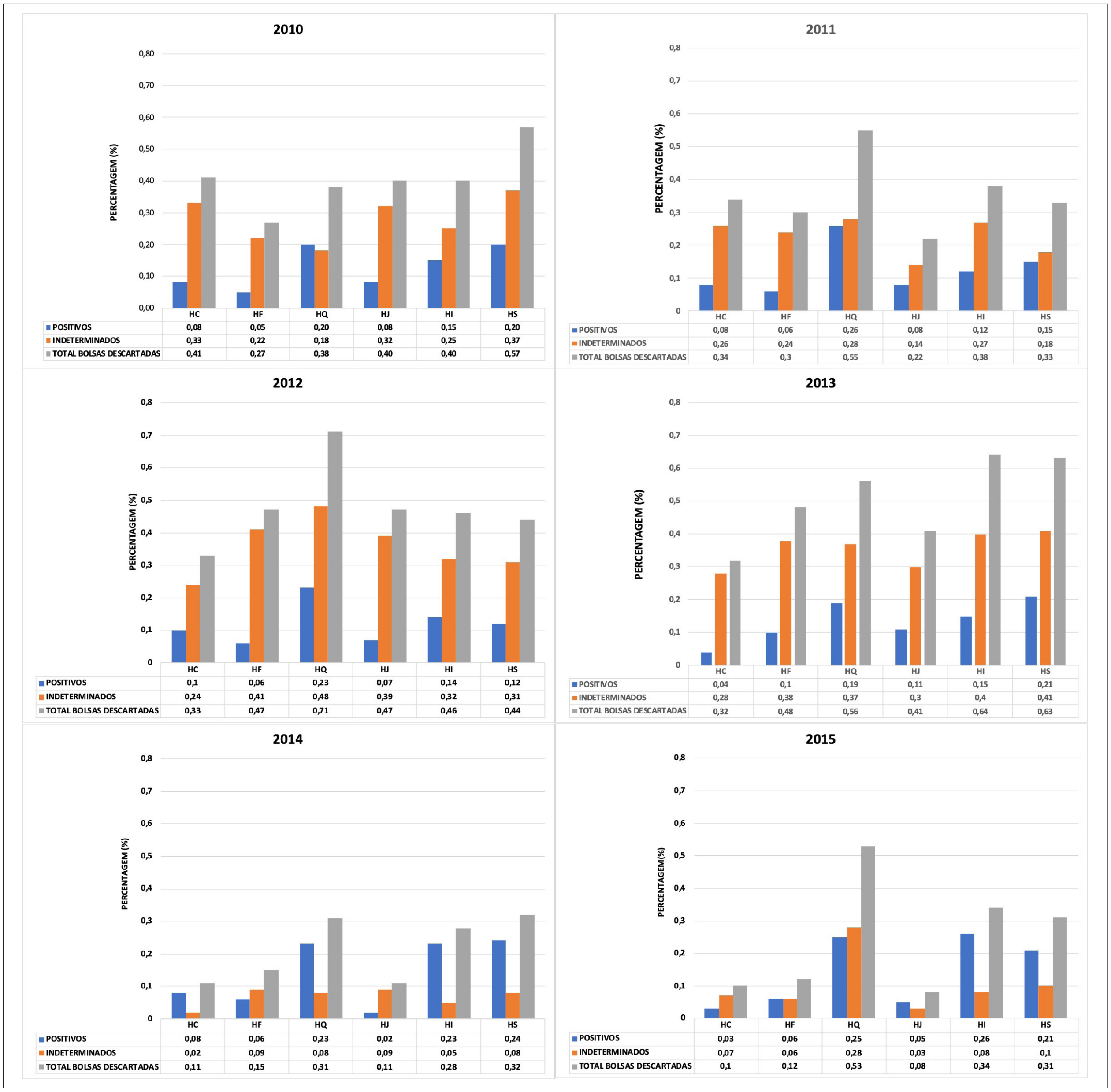

Figure 3 – *Prevalence of CD in the state´s Public Blood Banks, from 2010 to 2015. Source: Drafted by the author.*

The blood bank of Sobral presented one of the highest prevalence of the studied period when compared to the other blood banks of the state (Figure 3). These data can be explained by the fact that the city of Sobral is considered a high-risk region for vectorial CD. This municipality presents a unique eco-epidemiological scenario, characterized by foci of triatominae in informal urban settlements with low-quality housing. Species of native triatominae, such as *Triatoma brasiliensis* and *Triatoma pseudomaculata* can often be seen inside of houses, and are often infected with *T. cruzi*. These foci have the potential to develop acute cases of CD, illustrating that this region still represents a real concern for the population.[22]

Santana et al.[23] analyzed the positivity for CD among blood donors in Piauí between 2004 and 2013. The prevalence of the reagent serology for CD in the triage of blood donors was greater than that observed in the present study, at approximately 1%. Only 34.5% of the positive samples in the triage were referred for complementary tests. In the confirmatory tests, 84.4% presented negative results.[23]

In the state of Ceará, Silva et al.[24] studied the seroprevalence for CD in public blood banks from 1996 to 1997, where 34,943 donors were observed, of which 377 (1.1%) presented seropositivity for CD.[24] When compared to the present study, it could be observed that there was a reduction in the ineligibility of donors due to CD in the sorological triage that, until 2015,

Table 2 – Blood donors considered ineligible in the serology triage and recruited to repreat the test and take the confirmatory test from 2010 to 2015 (n: 1982)

	REPETITION OF THE TRIAGE TEST (chemiluminescence)					CONFIRMATORY TEST (IIF ou Western Blot)			
YEAR	DID NOT RETURN	REPETITION NEG	REPETITION IND	REPETITION POS	TOTAL	CONF. NEG	CONF. IND	CONF. POS	TOTAL
2010	103	142	11	26	282	21	8	10	39
2011	124	126	13	47	310	49	11	11	71
2012	145	131	21	101	398	102	10	9	121
2013	160	235	18	54	467	41	1	6	48
2014	105	80	20	39	244	45	7	19	71
2015	120	86	9	66	281	47	11	17	75
TOTAL	**757**	**800**	**92**	**333**	**1.982**	**305**	**48**	**72**	**425**

NEG: negativo; IND: indeterminado; POS: positivo; CONF: confirmatório. IIF: indirect immunofluorescence. Fonte: Hemorrede Pública Estadual do Ceará (2010 – 2015).

could be observed in 0.33% (Table 1). This outcome possibly represents a reflection of the measures taken to improve the quality of hemotherapy services since the 1980s in many Brazilian states, which gave priority to the practice of return blood donations with fidelity and volunteer donors. Moreover, as the transmission in the rural areas has been diminishing due to anti-vectorial measures, it was expected that, over time, this new population of donors would present lower rates of infection.[24]

In addition to these factors, it should be highlighted that the techniques for serology have greatly progressed, which can be contributed to the reduction in the false positive results.[25-27]

In this context, the disease control policies must continue to exist, so as to avoid sporadic outbreaks, such as that which occurred in 1998 in the state of Ceará, due to the difficulties in continuing the anti-vectorial program (lack of insecticide and qualified professionals), which provoked a spike in the number of captured vectors and high frequency of reagent serology among the donors.[28]

One should be aware of the fact that the application of insecticides in homes does not seem to hinder the continuous reintroduction of wild triatominae species, and, as is well-known, the *Trypanosoma cruzi* circulates within a domestic zoonotic cycle, representing a challenge for the authorities involved in CD control. Concentrating efforts of sanitary surveillance in the three realms of government is necessary to eradicate this disease and its transmission via blood transfusion.[29,30]

It should also be emphasized that the hemotherapy services are not obligated by law to performed confirmatory tests for any of the diseases detected by routine exams. However, as set forth in Resolution RDC number 343, passed on December 13, 2002, as in other regulations, any donor presenting a non-negative serological result should be called to receive the necessary medical advice.[31]

The present study verified that many donors did not return for the repetition of the test, and this fact represents a limitation of the present study, as many potential donors did not perform the confirmatory tests. The non-return of the potential donors represents a loss of information, such as the more precise prevalence of CD in blood banks.

The blood bank network should formulate new strategies to recruit these individuals so as to confirm the diagnosis and, in the case of a negative result, allow them to become blood donors once again.[31]

This loss of information is worrisome and can result from a combination of factors, among which is the place of origin of many donors. In addition to the difficulty of the donors travel from his/her city of origin to the capital, the letter of summons is an instrument that scares people, as it indicates that the result of the exam was not normal, and many end up not wanting to know the true result.[15]

The present study observed that the majority of ineligible donors due to CD (positive/inconclusive) was of the male sex, over 30 years of age, from the capital city of Fortaleza, but born in the municipalities in the countryside of the state of Ceará. Although other studies also show this predominance of males in individuals diagnosed with CD, there is no positive correlation between the sex of the donor and the reagent serology for the disease, as it indistinctly affects both men and women, which can be justified by the fact that many men work in rural areas, with greater chances of coming into contact with the triatominae, as well as due to cultural differences in the practice of blood donations, which commonly attribute to the best donor role to the men.[28,32-34]

As regards the place of origin, it is well-known that many knowingly infected individuals live or have lived in countryside regions that constitute the natural ecotopes of the insect vector and, later, many end up migrating to large urban centers, such as Fortaleza, fleeing from droughts and in search of jobs and opportunities.[35] Despite the certificate of the eradication of CD by *Triatoma infestans*, it is important to clarify that this species was never found in the state of Ceará; therefore the risk of transmission of CD in Ceará is due to the most prevalent species of triatominae, the *Triatoma brasiliensis* and the *Triatoma pseudomaculata*. Thus, the state of Ceará still presents a high risk for the transmission of the disease.[3,35-37]

Table 3 – Sociodemographic characteristics of the donors considered ineligible with confirmation of CD at the Ceará Public Blood Bank from 2010 to 2015

	Positives		Undetermined		Total ineligible	
Variables	**n**	**%**	**n**	**%**	**n**	**%**
Sex						
Male	43	59.7	35	73	78	65
Female	29	40.3	13	27	42	35
Total	72	100	48	100	120	100
Age	**n**	**%**	**n**	**%**	**n**	**%**
≤ 30 years	8	11.1	12	25	20	16.7
>30 years	64	88.9	36	75	100	83.3
Total	72	100	48	100	120	100
N of prior donations	**n**	**%**	**n**	**%**	**n**	**%**
0	69	95.8	31	64.6	100	83.3
≥ 1	3	4.2	17	35.4	20	16.7
Total	72	100	48	100	120	100
Education	**n**	**%**	**n**	**%**	**n**	**%**
Illiterature	4	5.5	1	2.1	5	4.2
Elem. Incomplete	21	29.2	11	23	32	26.7
Elem. Complete	8	11.1	3	6.2	11	9.2
High School Incomplete	10	13.9	1	2.1	11	9.2
High School Complete	24	33.3	21	43.7	45	37.5
University Incomplete	0	0	5	10.4	5	4.2
Univeristy Complete	2	2.8	5	10.4	7	5.8
Not informed	3	4.2	1	2.1	4	3.3
Total	72	100	48	100	120	100
Place of origin	**n**	**%**	**n**	**%**	**n**	**%**
Fortaleza	7	9.7	15	31.2	22	18.3
Metropolitan region	3	4.2	4	8.3	7	5.8
Other municipalities	61	84.7	27	56.3	88	73.3
NI	1	1.4	2	4.2	3	2.5
Total	72	100	48	100	120	100
City where they came from	**n**	**%**	**n**	**%**	**n**	**%**
Fortaleza	30	41.7	32	66.6	62	51.7
Metropolitan region	16	22.2	6	12.5	22	18.3
Other municipalities	25	34.7	10	21	35	29.2
NI	1	1.4	0	0	1	0.8
Total	72	100	48	100	120	100

Elem.: elementary; NI: not informed. Source: Ceará Public Blood Bank (2010 – 2015).

In addition to the vectorial form, the form of transmission has been especially attacking the northern and northeastern regions of the country. In the case of men, this transmission can occur in a sporadic manner, through the ingestion of food contaminated with the parasite or its feces.[38]

As regards the age range, during the period of study, a reduction in the number of younger infected individuals could be observed, which can be evaluated as a reflection of the vectorial control measures implemented in the state of Ceará. With the overall reduction of the incidence of the disease, the entrance of individuals diagnosed with CD became less frequent in the age group of people who donate blood, parallel to the progressive exit of infected individuals from the list of donors by age or by morbidity due to CD. However, it is important to highlight that the increase in the launching of blood donation campaigns generates a greater demand for people of highly varied age groups, making it difficult to identify a greater difference between the analyzed age ranges.[39,40]

Parallel to the reduction in blood donors diagnosed with CD in Ceará, what calls attention is the high proportion of inconclusive reactions. During the period of the study (2010-2015), we observed that, in the serological triage, 70.9% (1,380) of the results of ineligible donors due to CD were inconclusive, representing 5.99% of the total number of bags discarded during the period. Many studies demonstrate that the inconclusive reactions often represent more than 50% of the cases of donor ineligibility due to seropositity for CD in blood banks, with this rate being higher than 70% in some services.[41,42]

In Brazil, it is estimated that 60% of the occurrences of inconclusive reactions in the three million annual blood donations, of which 0.6% of the collected blood bags are discarded due to a positive serology for *T. cruzi*, that is, 10,800 bags are being discarded due to inconclusive serology.[34] The significant number of inconclusive reactions is worrisome, especially since, in addition to the high costs caused by the disposal of blood bags, there is also the consequence that this brings to the donor, who is labeled as an individual diagnosed with a severe disease such as CD.

Discrepancies in the results of the serological tests occur quite often, sometimes questionable in a given text and positive or negative in another. The present study verified that 847 individuals had previously donated blood and such discrepancies become even more evident and conflicting in repeat donors, when more than a dozen repeatedly negative serological reactions in previous donations now present an inconclusive or eventually positive serology in a subsequent donation.[43-45]

The present study verified that of the 1,982 ineligible donors due to CD, 1,225 (61.8%) returned to repeat the test, and of these, only 72 (5.8%) were positive in the confirmatory test (IIF or *western blot*) and 48 (3.9%) were inconclusive. The occurrence of inconclusive reactions and false-positive reactions in the tests of serological triage show flaws in the specificity of the serological tests, as there may be many individuals co-infected with other diseases, and therefore sensitized with other antigens, which can entail crossed reaction in the serological tests.

Consequently, many healthy individuals end up being labeled as CD carriers, when in fact they are not actually infected with the disease, leading to psychological, social, and economic issues for the donor who was excluded for wrongly being considered infected with CD, in addition to promoting the unnecessary disposal of blood bags in blood banks and important financial losses for the Brazilian Unified Health System.[40]

The data obtained in this study reflect the difficulties in the approach and guidance of donors with inconclusive serological reactions, who are almost all non-chagasic, as well as the indispensability of the implementation of measures that allow one to minimize, or even eliminate, the questionable or false-positive serological results for CD in serological triage tests.

The confirmatory tests present good sensitivity and specificity; however, the triage tests, such as chemiluminescence, present a high sensitivity, and it is well-known that tests with a high sensitivity have their specificities compromised, generating false-positive results. Due to this factor, it is important to implement more specific tests in the serological triage of blood donors.[28,30,31]

The determination of the prevalence of the disease in blood banks can be relevant as an indicator of the risk for CD in blood transfusions and of the level of transmission of the disease in a determined region, as well as allow one to evaluate the vectorial control indirectly, providing up-to-date information about the disease in the state.

In this sense, it is possible to trace local strategies that involve the efforts of all of the sectors related to the area, such as sanitation agencies, blood banks, and laboratories, unified in the effort to eliminate the transmission through blood transfusions and improve the quality of the transfused blood.

In addition, the results from this study warn of the need in the blood banks to introduce a complementary serological method that is more specific, in an attempt to minimize the unnecessary disposal of blood bags and consequently indicate the real values of the disease in blood donors. Hence, there is a need for studies that propose new measures for the improvement in the accuracy of the serological tests, which could consequently reduce the unnecessary disposal of blood bags, thus diminishing the costs for the Brazilian Unified Health System.

Conclusions

Of the potential donors in the studied period, 1,982 were considered ineligible donors due to a positive/inconclusive serology for CD. Confirmed as ineligible (positive or inconclusive) were 28.2% (120/425) due to CD. No significant reduction in positive/inconclusive serology was observed in the period between 2010 and 2015; however, a reduction was observed in relation to 1996/1997 in the state. The determination of the prevalence of CD in blood banks can be relevant as an indicator of risk for transmission through blood transfusion in a given region. New serology tests for triage, with a better accuracy, are necessary in order to reduce the unnecessary disposal of blood bags, reduce the costs for the Brazilian Unified Health System, and diminish the insecurity for patients and family members.

Author contributions

Conception and design of the research, Obtaining financing and Writing of the manuscript: Costa AC, Oliveira MF; Acquisition of data: Costa AC, Silva Filho JD, Fidalgo ASOBV, Gomes VBAF, Oliveira MF; Analysis and interpretation of the data: Costa AC, Rocha EA, Silva Filho JD, Oliveira MF; Statistical analysis: Costa AC, Rocha EA, Silva Filho JD, Viana CEM, Oliveira MF; Critical revision of the manuscript for intellectual content: Costa AC, Rocha EA, Fidalgo ASOBV, Nunes FMM, Viana CEM, Oliveira MF.

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

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Serological Tests in Chagas Disease: Another Enigmatic Evidence in a Disease Largely Neglected

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Minieditorial referente ao artigo: Prevalência da Infecção pelo Trypanosoma cruzi em Doadores de Sangue

Cardiologists and Gastroenterologists acting in distinct environments of our institution in Ribeirão Preto, not infrequently face patients with epidemiologic, clinical and laboratorial features of Chagas Disease (CD) in whom serological evaluation is negative for the disease.[1] In a series of 65 patients evaluated between 07/01/2011 and 12/31/2012 by invasive coronary angiography to elucidate the cardinal symptom of chest pain, all with wall motion abnormalities (including 28 presenting the typical apical aneurysm at contrast ventriculography), two distinct serological tests were positive in only 11(17%) patients.[2] How can we elucidate this enigma and provide guidance in this situation? The answer may be, in part, in the experience with this entity and in the knowledge and confidence in the diagnostic accuracy of the serological tests employed.

The hitch point begins with the asymmetrical concepts leading to uncertainty that involve the routine diagnostic procedures of CD by using serological verification of antiparasite antibodies. In accordance to current guidelines,[3,4] only one negative test is enough to exclude the diagnosis (granting blood donation or solid organ transplantation), while two distinct positive serological tests are needed to confirm CD diagnosis. This is an ancient practice in clinical and research routines, due to the heterogeneous accuracy (mean of sensibility and specificity) of the tests/ e. g. complement fixation, indirect hemagglutination, indirect immunofluorescence and direct agglutination).[5] Even after the development of chemiluminescence methods based on ELISA, capable of automated reading to avoid subjective interpretation as seen in the above-mentioned tests, the rule of two simultaneous distinct tests followed by a third one if a discordant result is obtained, remains in the latest PAHO guidelines for diagnosis of CD.[6] A conflicting technical note from the WHO recommended a single ELISA test for screening in blood banks, supported by its alleged high sensitivity (nearly 99%) and as a way of cost reduction when dealing with a high volume of screening as occurs in blood centers and blood banks.[7] Nevertheless, well-documented evidence exists suggesting that this protocol may not be entirely adequate.[8]

Keywords

Chagas Disease; Epidemiology; Sorologic Tests; Percutaneous Coronary Intervention/methods.

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The study published in this issue of Arquivos Brasileiros de Cardiologia,[9] presents data from blood centers in Ceará state related to CD serological tests in an extensive period and renew the evidence leading to some unsettling reflections:[10]

1. Since it is an endemic region with vectorial transmission still present by the Authors report, the strikingly high number of inconclusive tests (70%) in those donors considered ineligible, rises the possibility of a cross reaction with *leishmania spp*, also endemic in the region, that could be responsible, at least partially, for those so intriguing results.[11] It is relevant, from now on, to emphasize that from the Authors report, the initial inconclusive result was based in only one ELISA neither positive nor negative. This is distinct from an inconclusive result of two tests, one positive and other negative, a common finding in clinical guidelines.
2. Characteristically in the present paper, the repetition of the ELISA test in a second sample in 1,225 previously positive or inconclusive results, only in 425 samples remained positive or inconclusive. This result suggests low reproducibility, a concerning result reinforced by their report that 43% of those excluded in the first test had previously donated blood. This indicates that the negative result in the first screening test led to the potential acceptance of a CD false-negative donor.
3. Furthermore, those 425 donors with positive (333) or inconclusive (92) results after two ELISA tests in two distinct samples, had their second sample submitted to another serological test (immunofluorescence or *Western blot*). In this third test, 305 were negative, 48 inconclusive and only 72 remained positive.
4. In summary, there was a concordance of only 28% between the first and last tests. Can we state that those approved as donors are free of CD? What about those excluded as donors, what is their basic probability of having the disease?

There is clearly the necessity of improvement in serological diagnostic tests since transfusional transmission of CD in our country remains uncertain, due to the paucity of symptoms in the acute phase of CD, mainly a non-specific febrile condition commonly seen in hospitalized patients. The transition to the indeterminate form and its ulterior clinical forms occurs lately and may not be identified if not actively scrutinized. In ancient times a description of transfusional contamination in 6 (25%) of 24 recipients of one contaminated bag had only one case with clinical signs of the acute phase myocarditis.[12] Recently, severe cases have been described in other countries.[13] When occurring in solid organ transplants recipients, due to the concomitant immunosuppression, it is not rare severe and potentially lethal manifestations of the acute phase of CD.[14] In addition, reactivation of the disease may occur in an organ recipient not suspected of having CD. The absence of a gold-standard diagnostic test contributes to the above occurrences.

The definition by the World Health Organization of Chagas disease as "neglected" certainly acquires more strength by the recognition that 50 years after the establishment of mandatory tests in blood donors in our country, the number of discarded bags due to the number of inconclusive results is huge. Financial and social impact of this serological inconsistency are still to be established.

Anyway, these two pathways of the dilemma imposed by uncertainty are immanent to the context of enigmatic situations involving diagnosis when no gold-standard exists and accuracy of every test applied to the "real-world" will be assessed in a diverse environment from the one it was standardized. Therefore, it rests to be properly established the sufficiency of only one high sensibility serological test to exclude CD.[15] Besides, even a two-step algorithm (a positive high sensibility test followed by a high specificity one) to establish diagnosis[16] seems challenged by evidence now published by researches from the state of Ceará.

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Chagas Cardiomyopathy as the Etiology of Suspected Coronary Microvascular Disease. A Comparison Study with Suspected Coronary Microvascular Disease of Other Etiologies

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Abstract

Background: **Chagas disease (CD) as neglected secondary form of suspected coronary microvascular dysfunction (CMD).**

Objectives: **Comparison of patients with CMD related to CD (CMD-CE) versus patients with CMD caused by other etiologies (CMD-OE).**

Methods: **Of 1292 stable patients referred for invasive coronary angiography to elucidate the hemodynamic pattern and the cause of angina as a cardinal symptom in their medical history, 247 presented normal epicardial coronary arteries and 101 were included after strict exclusion criteria. Of those, 15 had suspected CMD-CE, and their clinical, hemodynamic, angiographic and scintigraphic characteristics were compared to those of the other 86 patients with suspected CDM-OE. Level of significance for all comparisons was $p < 0.05$.**

Results: **Patients with suspected CMD-CE showed most anthropometric, clinical, angiographic hemodynamic and myocardial perfusion abnormalities that were statistically similar to those detected in the remaining 86 patients with suspected CMD-OE. LV diastolic dysfunction, expressed by elevated LV end-diastolic pressure was equally found in both groups. However, as compared to the group of CMD-OE the group with CMD-CE exhibited lower left ventricular ejection fraction (54.8 ± 15.9 vs 61.1 ± 11.9, $p= 0.049$) and a more severely impaired index of regional wall motion abnormalities (1.77 ± 0.35 vs 1.18 ± 0.26, $p= 0.02$) respectively for the CMD-OE and CMD-CE groups.**

Conclusion: **Chronic Chagas cardiomyopathy was a secondary cause of suspected coronary microvascular disease in 15% of 101 stable patients whose cardinal symptom was anginal pain warranting coronary angiography. Although sharing several clinical, hemodynamic, and myocardial perfusion characteristics with patients whose suspected CMD was due to other etiologies, impairment of LV segmental and global systolic function was significantly more severe in the patients with suspected CMD related to Chagas cardiomyopathy. (Arq Bras Cardiol. 2020; 115(6):1094-1101)**

Keywords: **Chagas Cardiomyopathy; Coronary Microvascular, Dysfunction; Dysfunction Ventricular, Left; Diastolic Dysfunction, Wall Motion Abnormality Index; Left Ventricular Ejection Fraction.**

Introduction

More than one century after its discovery in 1909 Chagas disease (CD) is still a major public health problem in Latin America and, due to migratory moves during the last decades, also in non-endemic areas, such as the United States and some European countries.[1,2] Chronic Chagas cardiomyopathy (CCC) is the most prevalent and more ominous of the clinical manifestations of CD, being essentially due to a low-grade but virtually incessant form of infectious myocarditis that is characteristically diffuse but with focal myocitolytic necrosis and intense reparative fibrosis.[3,4] Since in experimental models of ischemia/reperfusion myocitolytic necrosis is usually associated with low intensity but repetitive hypoxic or ischemic damage, this type of myocardial lesion has been interpreted as a consequence of microvascular ischemic disturbances and constitute one of the four main pathogenetic mechanisms that lead to CCC.[5,6]

The occurrence of microvascular ischemia in patients chronically infected with the *T. cruzi* has been demonstrated by various pathological, clinical and experimental laboratory evidence.[7-9] An estimated 20-40% of patients with CCC complain of angina, usually atypical in character since the symptom has no constant relation to physical or emotional stimulation, and variable duration and response to nitrates.[10] Also, several independent investigators have shown that these patients have striking myocardial perfusion abnormalities that are elicited by exercise and reversible with rest, in the presence of coronary arteries that have no epicardial

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obstructive lesions at invasive angiography[11-13] These perfusion abnormalities are therefore attributable to microvascular ischemia and are corroborated by studies in experimental models of *T. cruzi* infection.[14,15]

On the basis of such evidence, many patients with CCC could now be classified as having a secondary class of coronary microvascular disease (CMD), related to a cardiomyopathic process caused by an inflammatory infectious disease.[16-18]

There have been no specific studies focusing on the comparison of patients with CMD related to CD versus patients with CMD linked to other etiologies. Thus this was the objective of the present investigation.

Methods

General Design of the Study and Sample Population

This was a transversal, observational, unicentric investigation with prospective inclusion of stable patients who were referred to our tertiary academic hospital from January 01 to December 31 of 2018 for invasive contrast coronary angiography to elucidate the hemodynamic pattern and the cause of angina as a cardinal symptom in their medical history. Of 1292 such patients 601 were excluded because of: previous treatment with coronary angioplasty (200); previous confirmed acute coronary syndrome (137); valvular heart disease (113); hypertrophic or idiopathic dilated cardiomyopathy (99); previous coronary artery bypass surgery (49) and cardiac transplantation (3).

In the remaining 691 patients coronary angiography indicated to specifically evaluate the primary possibility of coronary artery disease, revealed: significant obstructive epicardial lesions (stenoses > 40% of luminal diameter reduction): (n = 367); angiographycally normal coronary arteries: (n = 247); non-significant epicardial coronary artery disease - stenosis < 40%: (n = 77); miscellaneous coronary artery conditions - congenital abnormalities, myocardial bridge, excessive tortuosity or ectasia, coronary-cavitary fistula, slow flow: (n = 81).

Of the 247 patients who were clinically stable, with no structural cardiac disease and whose cardinal symptom was angina severe enough to warrant the indication of invasive coronary angiography but that did not show any abnormalities, 101 agreed to participate in the study and signed the informed consent. The research protocol was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - USP - Processes : 8430/2011 and CAEE 07494618.3.0000.5440 Doc 3.252.539.

Clinical and Laboratory Assessment

The 101 patients enrolled into the study had a clinical assessment performed in the same day as the hemodynamic and the invasive coronary evaluation, comprising the characterization of angina, the presence of associated symptoms such as dyspnea, fatigue, edema, palpitation, syncope, disfagia, intestinal constipation, and epidemiological hints of having been exposed to the *T. cruzi* infection. Also included was a questionnaire regarding the occurrence of risk factors for coronary artery disease, such as: systemic hypertension, diabetes mellitus, dyslipidemia, current smoking, and familial history of early coronary disease. All patients had a 12-lead ECG recorded, and a sub-sample of 33 (9 and 24 in each group) was examined with a transthoracic rest echocardiogram. All 101 patients had a serological examination for the detection of circulating antibodies against the *T. cruzi*. Also, a peripheral blood sample was collected from all patients, to allow the examination of serum levels of creatinine, and exclude the presence of renal and liver damage, as well as of severe anemia and diabetes mellitus.

Cardiac Catheterization, Hemodynamic Assessment and Coronary Angiography

These procedures were performed under local anesthesia preferably using the radial approach with conventional guide-wires and catheters. Manual injections of 3-7ml of radiological contrast were selectively done in each coronary ostium,[19] with recording at 15-30 frames/sec, in several projections. Left ventricular end-diastolic pressure (LVEDP) was recorded at rest, followed by two automatic injections of 20-30ml of dye at 8-10ml/sec and recording at 15 frames/sec, in the right and left oblique projections. The contrast ventriculography was then analysed according to a 9-segment model using a quantitation score that ascribed 1 to normal wall motion, 2 to hypokinesis, 3 to akinesia and 4 to dyskinesis.[20] An index of the global wall motion was obtained by summing the segmental scores divided by the number of segments analysed.[21] The ventriculogram also allowed the qualitative assessment of LV hypertrophy and dilation.

SPECT Myocardial Scintigraphy

A subset of 19 patients were submitted to rest-exercise SPECT myocardial scintigraphy. The images were acquired in the camera range (Philips BrightView XCT - Cleveland, OH) of a double detector with the patient in the supine position during rest and stress phases. The acquisition occurred in semicircular orbit (180 degrees, from right anterior oblique projection to the left posterior oblique projection), in 32 projections synchronized with the electrocardiogram, 8 frames per cardiac cycle in 60 seconds by projection ("accepted" heartbeat) with 50% acceptance window around of average R-R. The detectors were equipped with collimators of parallel holes of low energy and high resolution, using a 64 x 64 pixel acquisition matrix.[22]

Physical exercise was used as the preferred stress test, beta-blockers, calcium channel blockers and other anti-ischemic drugs were interrupted 48 hours before the nuclear tests. Sestamibi-Tc99m was used as a radiotracer to assess regional myocardial perfusion, at a dose of 12 to 15 mCi at rest and 25 to 30 mCi at stress. Images were acquired 1 hour after each intravenous injection of the radiotracer.

Polar maps using the 17-segment model were generated to assess the perfusion abnormality according to a score defined as 0= normal, 1= slight uptake reduction, 2= moderate uptake reduction, 3= marked uptake reduction, and 4= no tracer uptake. Perfusion abnormalities in stress (SSS- Summed Stress Score) and rest (SRS- Summed Rest

Score) were quantified to differentiate between reversible, when Summed Difference Score (SDS) ≥ 1 and irreversible perfusion defects.[23]

Statistical Analysis

On the basis of the specific serology tests for diagnosing antibodies against the *T. cruzi*, 15 patients were classified as having suspected CMD due to Chagas etiology (CMD-CE) - two positive serological tests with different methods.[24] The other 86 patients, with negative serology tests, composed the group of patients with suspected CMD caused by other etiologies (CMD-OE). The Shapiro-Wilk tests were used to check if variables had a normal distribution, in which unpaired variables were compared with Student's "t" tests, otherwise the Mann-Whitney unpaired tests were used. Continuous variables with normal distribution were described as mean ± standard deviation while non-normal distributed variables were described as median and IQ or range interval. Categorical variables were described as absolute or relative values (percentages or proportions). Proportions within each group were compared using Fisher exact tests. All tests were bicaudal, with p< 0.05 considered significant. All analyses were done with the Stata software *(StataCorp, EUA, versão 14.2)*.

Results

Clinical Features - (Table 1)

Of the 247 stable patients who were initially eligible since they presented no exclusion criteria to enter the study and fulfilled the inclusion criteria of having epicardial coronary arteries that were normal at angiography, 101 (40.9%) were actually enrolled. Of those, only 15 (14,8%) had two serologic tests positive for *T. cruzi*, and composed the group CMD-CE with 40% of males and average age of 61.3 ± 6.7 years). The other 86 (85.2%) composed the group CMD-OE with 32.5% men and higher mean age of 68.9 ± 11.0 years.

On the date of entry into the study, atypical angina was referred by 9 (60%) of the group CMD-CE versus 57 (66%) patients of the group CMD-OE, with typical angina referred by the other patients of each group. In group CMD-CE dyspnea and palpitation, were also frequent, with 8 (53%) and 7(47%) patients respectively, versus 55 (64%) with dyspnea and only 30 (35%) with palpitation in group CMD-OE.

Systemic arterial hypertension was the most prevalent risk factor for coronary artery disease in both groups, with 93.3% vs 81.3%, followed by diabetes mellitus with 40.0% vs 33.7%, dyslipidemia with 33.3 vs 41.8% and active smoking in 13.3 vs 24.4% respectively in the CMD-CE and CMD-OE groups. Both groups were using statistically similar proportions of pharmacological drugs against hypertension, diabetes mellitus, statins and agents to control myocardial ischemia symptoms, such as antiplatelets and calcium antagonists. (Table 1). However, ACE-inhibitors/ARBs were more used by the CMD-CE group while antiplatelet agents were more used by the CME-OE patients.

ECG abnormalities were frequent in the group CMD-CE, with only 33.3% of patients having a normal ECG on the date of the catheterization. In contrast, the group of CMD-OE had non-significantly more patients with a normal ECG (46.7%). While RBBB (26.6%), LAHB (13.3%) and LV overload (13.3%) were the most frequent abnormalities in the CMD-CE group, LV overload (20%) and complete LBBB (6.7%) were predominant abnormalities in the CMD-OE group. Both groups had a similar prevalence of atrial fibrillation (6.7%). None of those differences was statistically significant.

Table 1 – Demographic and baseline clinical characteristics of patients enrolled according to the etiology of coronary microvascular disease

	CMD-CE n = 15	CMD-OE n = 86	p-value
Age (years)	61.3 ± 6.7	68.9 ± 11.0	0.01
Female Gender (%)	60.0	67.4	0.65
Body weight (kg)	77.0 ± 13.1	80.7 ± 15.3	0.18
BMI (kg/m^2)	31.0 ± 7.3	31.9 ± 5.6	0.72
Atypical angina (%)	60.0	66.3	0.86
Dyspnea (%)	53.0	64.0	0.62
Palpitation (%)	47.1	35.2	0.56
Hypertension (%)	93.3	81.3	0.46
Diabetes mellitus (%)	40	33.7	0.77
Dyslipidemia (%)	33	53.5	0.58
Smoking (%)	13.3	24.4	0.51
Use of medications			
ACEI/ARB	100	71	0.037
Beta-blockers	53	54	0.79
Statins	47	53	0.90
Antidiabetics	40	42	0.88
Diuretics	47	40	0.82
Nitrates	20	12	0.63
Calcium antagonists	20	26	0.89
Antiplatelets	53	85	0.013
Normal EKG (%)	33.3	46.7	0.51

CMD-CE: coronary microvascular disease - Chagas etiology; CMD-OE: coronary microvascular disease - other etiologies. BMI: body mass index; ACEI: angiotensin converter enzyme inhibtors; ARB: angiotensin receptor blockers; EKG: electrocardiogram.

Hemodynamic and Contrast Ventriculography Assessment. (Table 2).

Diastolic dysfunction as suggested by increased LVEDP > 12 mmHg at rest was diagnosed in 13 (86.6%) and 64 (74.4%) of patients respectively in the groups CMD-CE and CMD-OE, respectively; p= 0.511. The mean values of LVEDP were similar in the groups. In addition, 9 (60%) and 45 (52.3%) patients had LVEDP > 20mmHg respectively in the CMD-CE and CMD-OE groups.

Using ventriculography to assess LV morphological features that suggest the presence of chamber hypertrophy this alteration was observed in 3 patients (20%) of the group CMD-CE versus 26 patients (30.2%) of the group CMD-OE (p= 0.545). In contrast ventricular dilatation by ventriculography was observed in significantly higher proportion of patients, 26% (n = 4) of the group CMD-CE versus 4.7% (n = 4) of the group CMD-OE (p= 0.04).

Overall most patients had preserved global LV systolic function in both groups, with a minority of patients in both groups showing reduced LVEF values (< 50%). LVEF was marginally significant lower in the CMD-CE (54.8 ± 15.9) as compared to the CMD-OE group (61.1 ± 11.9), p= 0.049 (Figura 1). In addition, regional wall motion abnormalities were detected in a significantly higher proportion of patients in the CMD-CE group (86.6%; n = 13) as compared with that of patients in the CMD-OE group (52.2%; n = 45), p= 0.02 (Figure 2). LV wall motion score index that computs the extent and severity of the segmental systolic abnormality was also higher in the CMD-CE, of 1.77 ± 0.35 than in the CMD-OE group of 1.18 ± 0.26; p= 0.01.

Table 2 – Hemodynamic, angiographic and myocardial perfusion evaluation in the groups of patients with coronary microvascular dysfunction associated to Chagas cardiomyopathy versus CMD due to other etiologies

	CMD-CE n = 15	CMD-OE n = 86	p
LV hypertrophy (%)	20	53.3	0,128
LV dilation (%)	26.0	4.7	0.04
LVEDP (mmHg)	20.13 ± 5.43	19.0 ± 5.1	0.44
LVEF	54.8 ± 15.9	61.1 ± 11.9	0.049
LV segmental abnormalities (%)	86.6%	53.3%	0.02
LVWMSI	1.77 ± 0.35	1.18 ± 0.26	0.01
Ischemic perfusion defects (%)	45.5	62.3	0.31
SDS	0 (0 - 8)	3 (0 - 19)	0.23

CMD-CE: coronary microvascular disease - Chagas etiology; CMD-OE: coronary microvascular disease - other etiologies; LV: left ventricle; LVEDP: left ventricular end-diastolic pressure; LVEF: left ventricular ejection fraction; LVWMSI: left ventricular wall motion score index; SDS: summed difference score. Ischemic perfusion defects, with their correspondent SDS values were evaluated in 11 and 8 patients respectively of the CMD-CE and CMD-OE groups.

Assessment of Myocardial ischemia with myocardial perfusion scintigraphy

After the results of the hemodynamic evaluation were obtained, 11 patients of the CMD-CE group and 8 patients of the CMD-OE group underwent functional assessment with SPECT-myocardial perfusion scintigraphy. (Table 2).

The proportion of patients exhibiting ischemic reversible perfusion abnormalities for the CMD-CE and CMD-OE groups were 45.5% and 62.3% respectively (p= 0.31). The SDS was also similar for the CMD-CE (1.91 ± 3.05) and the CMD-OE (5.63 ± 7.03) groups (p= 0.134).

Discussion

During the whole year of 2018, following the implementation of our inclusion and exclusion criteria to a consecutive series of 247 clinically stable patients who had no structural cardiac disease and complained of anginal symptoms that were severe enough to warrant referral to our tertiary center for invasive coronary angiography but that eventually showed normal epicardial coronary arteries, a sizable sample of 101 of them (40.9%) agreed to participate in this prospective study and signed the respective informed consent. Out of the 101 about one sixth tested positive for chronic *T. cruzi* infection, and composed the group of patients with suspected coronary microvascular disease due to Chagas cardiomyopathy etiology (CMD-CE), while the other 86 patients comprised the group whose suspected coronary microvascular disease must be ascribed to other etiologies (CMD-OE). This is the first report on the relative prevalence of Chagas cardiomyopathy as an etiology for suspected coronary microvascular dysfunction among patients who are otherwise generally considered as having a primary form of coronary microvascular disease. This figure of roughly 15% of is likely to correspond to the real estimate for that etiology, considering that our institution still receives many patients from regions endemic for Chagas disease. Also, our sample of 247 patients with angiographically normal coronary arteries was selected among 691 consecutive patients in whom other abnormalities had been excluded, and correspond to nearly 36% of such individuals who are referred for elective coronary angiography. This finding is inferior to 45% recently reported by another Brazilian hospital,[25] but is quite similar to the reported 39% of patients with coronary stenoses < 20% as the general yield by elective coronary angiography during the years 2004-2008 from an American College of Cardiology national registry.[26]

With the exception of slightly higher mean age in the CMD-OE group, it is noteworthy that the two groups in our study had essentially similar anthropometric and clinical characteristics, including a higher prevalence of female gender, with slightly obese patients who, in addition to atypical angina, also complained of dyspnea and palpitation. The traditional risk factors for coronary artery disease - hypertension, diabetes mellitus, smoking, dyslipidemia - were also present in comparably high proportions of patients of both groups.

Another important finding from our study is that using contrast ventriculography for evaluation of left ventricle morphology, signs of chamber hypertrophy were found in several patients from both groups. In line with these findings, LV diastolic dysfunction, as expressed by striking elevation of the LV end-diastolic pressure occurred similarly in the CMD-CE and CMD-OE groups.

In regard to this important derangement, our patients with CMD due to Chagas disease at the stage of the disease they are when enrolled in this study, show abnormalities that are described in the recent classification of coronary microvascular dysfunction as occurring mostly in the scenario

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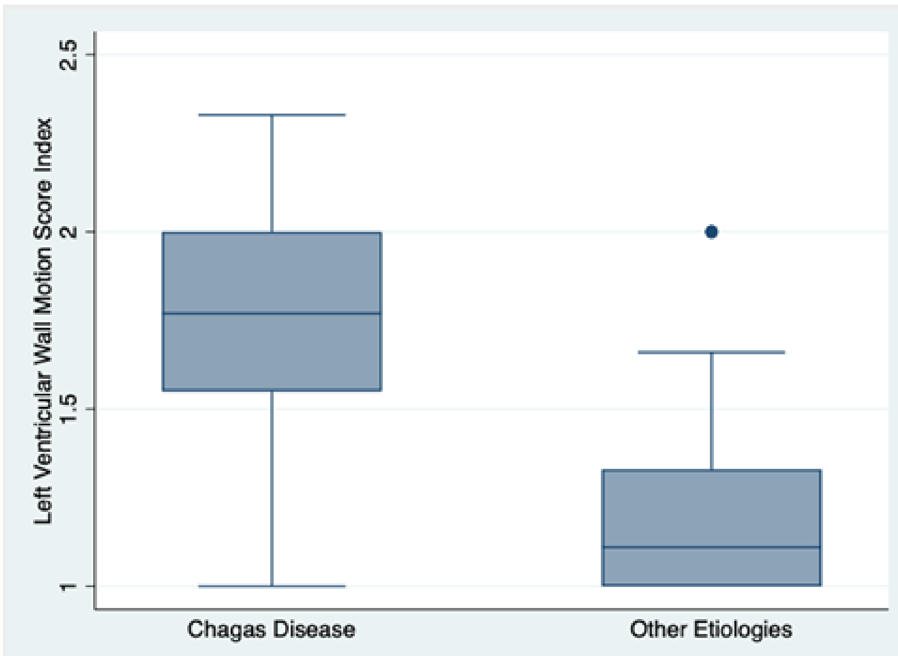

Figure 1 – *Left Ventricular Wall Motion Score Index according to etiology.*

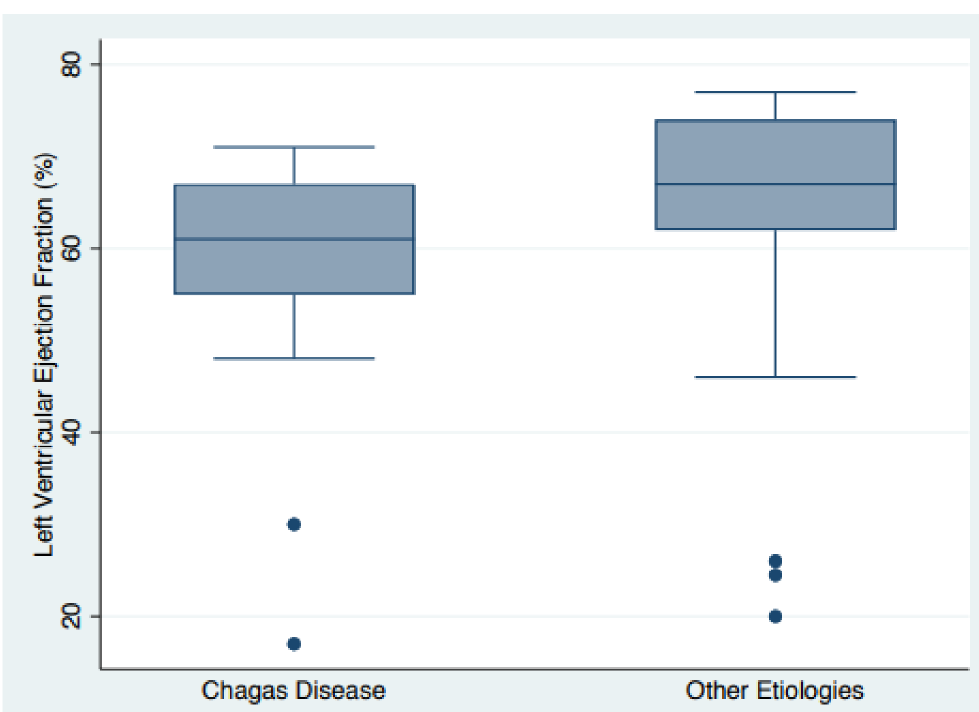

Figure 2 – *Comparison of Left Ventricular Ejection Fraction in both groups of patients with coronary microvascular dysfunction.*

of heart failure with preserved LV ejection fraction.[27] Although diastolic dysfunction also occurred in the group with CMD due to other etiologies, it is likely that myocardial fibrosis, a hallmark of Chagas cardiomyopathy, contributes to the diastolic dysfunction hereby detected in our patients.[6]

However, there were relevant differences between the two groups regarding LV systolic function. Mean LV ejection fraction was significantly lower in the CMD-CE, in keeping with more deteriorated segmental wall motion index and more LV dilation that was significantly more prevalent in the CMD-CE as compared to the CMD-OE group.

Both groups exhibited comparable proportions of patients with ischemic perfusion defects and their SDS between stress and rest myocardial scintigraphy were also similar. It is worthy pointing out that the objective detection of myocardial perfusion abnormalities indicative of myocardial ischemia induced by stress, represents the third criteria for classifying the patients in our study series as having the suspected syndrome of coronary microvascular disease according to a standardized recent classification.[28] Although in this standardization it is suggested that a fourth criterium could be used when the presence of microvascular angina is suspected, in our investigation we did not apply any additional tests to certify the occurrence of impaired coronary microvascular function, such as measurement of resistance indices or of reduced flow reserve.[28] However it is probable that at least some of our patients with CMD-CE could have such abnormalities, as reported by other investigators.[29]

It is reasonable to assume that patients from both groups included in this research share common pathophysiological characteristics that are involved in the appearance of the syndrome of anginal pain with angiographically normal sub-epicardial arteries, thus implying the presence of disturbances at the coronary microvascular level. This concept is supported by the finding in both groups of factors such as hypertension, ventricular hypertrophy, and diastolic dysfunction. However, in the group whose coronary microvascular disease is associated with the chronic *T. cruzi* infection, it is likely that the inherent peculiarities of Chagas cardiomyopathy be responsible for the relatively more serious manifestations of left ventricular systolic dysfunction, in comparison with those exhibited by the group with coronary microvascular disease due to other etiologies.

It is relevant to emphasize that none of the patients who tested positive for antibodies against the *T. cruzi* in our study had previous knowledge about harboring Chagas disease. Moreover, the sample of patients eventually selected to participate in the study was composed primarily of people who were referred to invasive coronary angiography, without previous assessment of myocardial ischemia with exams such as ECG-based tests, or stress echocardiography or nuclear scintigraphy tests. Thus, it is likely that most of those patients could benefit from therapeutic measures directed by both the knowledge of their baseline disease and of the functional consequences of the microvascular disturbances.[30]

Limitations

No specific investigations were carried out to determine the possible etiology in the patients without Chagas cardiomyopathy, although most probably they would be classified as having primary coronary microvascular dysfunction. Also, no invasive tests were done to directly explore the mechanisms responsible for the impairment of microvascular function in any patient included in this study. "Another limitation is the fact that only 19 of the 101 patients had myocardial pefusion assessed with SPECT scintigraphy. Hence, although similar proportions of the patients had perfusion defects, the small number of patients in both groups may have prevented detection of differences in regard to this important characteristic of their coronary microvascular derangements".

Conclusions

Chronic Chagas cardiomyopathy was found in association with the suspected syndrome of coronary microvascular disease in one sixth of a sample of 101 stable patients whose cardinal symptom was anginal pain warranting invasive coronary angiography. These patients chronically infected with the *T. cruzi* showed anthropometric, clinical, and angiographic characteristics, as well as hemodynamic and myocardial perfusion abnormalities that were similar to those detected in the remaining 86 patients with other etiologies for the suspected microvascular dysfunction. However, impairment of LV segmental and global function was signficantly more severe in the patients with symptoms of possible microvascular dysfunction related to Chagas cardiomyopathy.

Author contributions

Conception and design of the research: Magalhães ML, Schmidt A, Marin-Neto JA; Acquisition of data: Campos FA, Magalhães ML, Moreira HT, Pavão RB, Lima-Filho MO, Lago IM, Badran AV, Chierice JRA, Marin-Neto JA; Analysis and interpretation of the data: Campos FA, Magalhães ML, Moreira HT, Pavão RB, Lima-Filho MO, Lago IM, Badran AV, Chierice JRA, Schmidt A, Marin-Neto JA. Statistical analysis: Moreira HT, Schmidt A, Marin-Neto JA, Obtaining financing: Magalhães ML, Marin-Neto JÁ, Writing of the manuscript: Campos FA, Magalhães ML, Moreira HT, Schmidt A, Marin-Neto JA, Critical revision of the manuscript for intellectual content: Campos FA, Moreira HT, Pavão RB, Lima-Filho MO, Lago IM, Badran AV, Chierice JRA, Schmidt A, Marin-Neto JA.

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.

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Coronary Microvascular Dysfunction: Does it Really Matter in Chagas Disease?

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Short Editorial related to the article: Chagas Cardiomyopathy as the Etiology of Suspected Coronary Microvascular Disease. A Comparison Study with Suspected Coronary Microvascular Disease of Other Etiologies

There is a growing recognition that disorders affecting the structure and function of the coronary microcirculation can act as key mediators of patient symptoms and prognosis.[1] The subset of disorders affecting the microcirculation is termed coronary microvascular disease (CMD), which is expressed as either the inability of the coronary arteries to dilate appropriately to meet myocardial oxygen demand and/or as the abrupt reduction in coronary blood flow related to coronary spasm.[2]

For the past 2 decades, CMD has been actively investigated in various cardiac conditions across a broad spectrum of cardiovascular risk factors.[2,3] Microvascular dysfunction is triggered by low-grade systemic inflammation induced by conventional cardiovascular risk factors, including hypertension, diabetes, obesity, dyslipidemia, and older age.[1,4] This spectrum of abnormalities may likely be magnified by the presence of epicardial atherosclerosis.

Despite extensive investigations, the mechanisms underlying CMD are not fully understood.[1] Several mechanisms operating alone or in combination have been proposed to explain the pathogenesis of this disorder. There is increasing evidence demonstrating that functional abnormalities including endothelial and smooth muscle cell dysfunction have a fundamental role in the regulation of coronary blood flow in response to cardiac oxygen requirements.[2] Additionally, diffuse atherosclerosis in the epicardial coronary arteries also plays a role in affecting the microvasculature function. Indeed, contemporary evidence supports the coexistence of CMD with obstructive coronary atherosclerosis in most affected patients.[1]

Although there is no universally accepted definition for CMD,[5] it is usually defined as the clinical syndrome of angina, evidence of myocardial ischemia in the absence of obstructive coronary artery disease.[6] Since coronary microcirculation is beyond the resolution of coronary angiography, the diagnosis of CMD is based on the functional assessment of the coronary arteries, which can be performed using both invasive and non-invasive methods. Invasive coronary angiography with tests of coronary artery function is the preferential approach to evaluate patients with CMD. A comprehensive assessment of microvascular function includes testing the two main mechanisms of microvascular dysfunction. Impaired endothelium microvascular vasodilatation is measured by coronary flow reserve (CFR) and by the index of microcirculatory resistance (IMR), and impaired endothelium-dependent dysfunction, which evaluates the induction of epicardial or microvascular spasm after an intracoronary injection of acetylcholine.[2] Non-invasive testing can only evaluate surrogate markers of coronary function.

In contrast to obstructive coronary artery disease, in which perfusion abnormalities have regional distribution, myocardial impairment in CMD may be a generalized process resulting in diffuse myocardial perfusion abnormalities.[2] Positron-emission tomography (PET) is the reference standard for non-invasive assessment of myocardial blood flow.

In the setting of Chagas disease, experimental and clinical studies support the hypothesis that CMD may be implicated in the pathogenesis of myocardial damage.[7-10]. *T. cruzi* infection may lead to functional and structural microvascular abnormalities, which contribute to myocardial ischemia and symptoms. Similar to coronary artery disease, Chagas cardiomyopathy may affect the myocardium in a regional manner, with localized segmental wall motion abnormalities. However, despite these findings suggesting myocardial ischemia, coronary angiography invariably demonstrate the absence of obstructive atherosclerosis affecting the epicardial coronary arteries.[8] Additionally, impairment of endothelium-dependent coronary vasodilatation in response to acetylcholine has been reported in patients with Chagas cardiomyopathy.[11] Moreover, previous studies showed myocardial perfusion abnormalities in patients with normal epicardial coronary arteries, supporting the concept of abnormal myocardial flow regulation at the microvascular level.[8,9]

With this revision in mind, it is interesting to read the paper from Campos et al.[12] in this issue of *Arquivos Brasileiros de Cardiologia*. In this study, the investigators evaluated patients referred for invasive coronary angiography presenting with angina and suspected of myocardial ischemia. Of the 1,292 patients undergoing coronary angiography, 247 had non-significant epicardial coronary artery disease, 101 patients met the inclusion criteria and were enrolled in the study. Subsequently, these patients with suspected CMD were stratified into two groups according to the diagnosis of Chagas

Keywords

Chagas Diseases/physiopathology; Microcirculation; Risk Factors; Inflammation; Atherosclerosis; Myocardial Ischemia.

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disease, being 15 patients with Chagas and 86 with non-Chagas disease. The patients with Chagas disease showed a higher prevalence of regional wall motion abnormalities and lower left ventricular ejection fraction, when compared with those who had suspected CMD related to other cardiovascular risk factors. This study highlighted the importance of Chagas disease as a potential etiology for CMD, regardless of conventional risk factors for this disorder.

In the current study, the diagnosis of CMD was based on the absence of obstructive epicardial coronary obstructive disease. However, CMD is defined by the presence of limited coronary flow reserve and/or coronary endothelial dysfunction associated with the classic triad of persistent chest pain, absence of obstructive coronary artery disease and objective evidence of myocardial ischemia induced by stress tests. Indeed, myocardial perfusion assessed with SPECT scintigraphy was performed only in a subset of 19 patients (18.8%), which was a limitation of the study. Therefore, further studies on CMD in the context of Chagas cardiomyopathy are needed to advance our understanding on this field.

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Original Article

Early Changes in Circulating Interleukins and Residual Inflammatory Risk After Acute Myocardial Infarction

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Abstract

Background: **Patients with acute myocardial infarction may have a large infarcted area and ventricular dysfunction despite early thrombolysis and revascularization.**

Objective: **To investigate the behavior of circulating cytokines in patients with ST-segment elevation myocardial infarction (STEMI) and their relationship with ventricular function.**

Methods: **In the BATTLE-AMI (B and T Types of Lymphocytes Evaluation in Acute Myocardial Infarction) trial, patients with STEMI were treated with a pharmacoinvasive strategy. The plasma levels of cytokines (IL-1β, IL-4, IL-6, IL-10, and IL-18) were tested using enzyme-linked immunosorbent assay (ELISA) at baseline and after 30 days. Infarcted mass and left ventricular ejection fraction (LVEF) were examined by 3-T cardiac magnetic resonance imaging. All p-values < 0.05 were considered statistically significant.**

Results: **Compared to baseline, lower levels were detected for IL-1β ($p = 0.028$) and IL-18 ($p < 0.0001$) 30 days after STEMI, whereas higher levels were observed for IL-4 ($p = 0.001$) and IL-10 ($p < 0.0001$) at that time point. Conversely, no changes were detected for IL-6 levels ($p = 0.63$). The levels of high-sensitivity C-reactive protein and IL-6 correlated at baseline (rho = 0.45, $p < 0.0001$) and 30 days after STEMI (rho = 0.29, $p = 0.009$). At baseline, correlation between IL-6 levels and LVEF was also observed (rho = -0.50, $p = 0.004$).**

Conclusions: **During the first month post-MI, we observed a marked improvement in the balance of pro- and anti-inflammatory cytokines, except for IL-6. These findings suggest residual inflammatory risk. (Arq Bras Cardiol. 2020; 115(6):1104-1111)**

Keywords: **ST Elevation Myocardial Infarction; Interleukin-6, Interleukin-10, Interleukin-18; C-reactive Protein; Magnetic Resonance Spectroscopy.**

Introduction

Following acute myocardial infarction (MI), patients are at risk of higher rates of hospitalization and death due to heart failure associated with higher levels of high-sensitivity C-reactive protein (hsCRP), but these cardiovascular events can be decreased by anti-inflammatory therapy.[1] Interleukin-6 (IL-6) has been described as having a relevant role in ventricular remodeling in pressure overload models[2] and orchestrating the immune response after acute MI.[3]

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In addition to IL-6, other interleukins such as IL-18[4] and IL-1β[5,6] seem to contribute to adverse ventricular remodeling after MI. Interestingly, IL-4 appears to contribute to fibrosis and ventricular dysfunction in arterial hypertension when induced by angiotensin II administration.[7] Conversely, IL-10 markedly attenuates the inflammatory microenvironment after MI, thus improving ventricular function.[8]

Given the growing interest in the role of inflammation in ventricular remodeling after acute MI, we examined cytokine-mediated inflammatory response during the early phase of acute MI and its relationship with ventricular remodeling using cardiac magnetic resonance imaging (cMRI).

Materials and Methods

Study population

This report is part of the BATTLE-AMI (B And T Types of Lymphocytes Evaluation in Acute Myocardial Infarction) trial (ClinicalTrials.gov, NCT02428374). BATTLE-AMI is a randomized trial in which the effects of combined statin and antiplatelet therapies on infarcted mass and left ventricular ejection fraction (LVEF) in patients with ST-segment elevation myocardial infarction (STEMI) treated with a pharmacoinvasive strategy are compared.[9] The ongoing study includes patients with first STEMI who underwent thrombolysis with tenecteplase in the first 6 hours of onset of symptoms and were transferred to a tertiary care hospital in southeastern Brazil (Hospital São Paulo) in the first 24 hours for coronary angiography and invasive procedures. Patients with previous history of coronary events, coronary revascularization, contraindication to cMRI, or showing hemodynamic instability were excluded from the study.

The project was approved by the local Ethics Committee (Universidade Federal de São Paulo, Hospital São Paulo, IRB:0297/2014, CAAE: 38692514.1.1001.5505), and all patients provided written informed consent before inclusion.

Laboratory measurements

Blood samples were collected in the morning of the first day and between 27-33 days after STEMI. All samples were assayed in the Laboratory of Lipids, Atherosclerosis, and Vascular Biology (Universidade Federal de São Paulo). Cytokine levels in plasma were tested using the enzyme-linked immunosorbent assay (ELISA). IL-4, IL-6, and IL-10 were assayed using the BD Pharmingen kits (BD Biosciences, San Diego, California, USA), and IL-1β and IL-18 were assayed using the R&D Systems kits (Minneapolis, Minnesota, USA). The results were expressed in terms of absorbance using the EnSpire Multimode Plate Reader (PerkinElmer) and/or the iMark Microplate Absorbance Reader (Bio-Rad Laboratories, Hercules, California, USA), according to the manufacturers' instructions. HsCRP was measured by immunonephelometry.

Cardiac magnetic resonance imaging

All cMRI examinations were performed at Hospital São Paulo or Instituto Dante Pazzanese de Cardiologia. The first examination was done within the first 10 days (baseline), usually after hospital discharge. The second examination was performed after 27-33 days of acute MI.

The amount of infarcted mass, LVEF, and microcirculation were determined by 3-T cMRI. For left ventricular function, cMRI images were acquired using a 3-T scanner, as previously reported.[9] Briefly, quantitative assessment was performed in an offline workstation with the software Argus LV function (Siemens Healthineers). For quantification of myocardial necrosis, planimetry was performed manually by contouring late gadolinium enhancement areas, and infarcted tissue volume was calculated as the sum of those areas multiplied by the thickness of each slice.

Cine cMRI was performed using a steady-state free-precession technique (fast imaging employing steady-state acquisition). Ischemia was detected using first-pass perfusion imaging only in the short-axis orientation, with at least three slices (the maximum number of slices are limited by heart rate). Infarct detection and quantification images were acquired using the myocardial delayed enhancement technique after injection of a commercially available gadolinium-based contrast agent. Contrast-enhanced images were acquired in the same views as those used for cine cMRI, using a segmented inversion-recovery sequence. Each cMRI image was reviewed by two independent blinded readers using a dedicated software. Left ventricular function was estimated using cine cMRI images to measure LVEF volumes and mass according to standard methods. Delayed enhancement images were used for infarct characterization. In each patient, myocardial tissue was classified as hyperenhanced (scar tissue) or normally enhanced myocardium after the observer, who used manual interaction, defined a region of interest (ROI) within a remote non-infarcted territory.

Statistical analysis

Data are presented as mean ± standard deviation or median (interquartile range, IQR) according to data normality. Continuous variables were analyzed for normality using the Kolmogorov-Smirnov test. Baseline and 30-day samples were compared using the nonparametric Wilcoxon signed-rank test. Comparisons between groups were made using the Kruskal-Wallis test. Interleukin titers and cMRI parameters were correlated using the Spearman's rank correlation analysis calculator. Sample size was estimated based on previous studies involving early changes in cytokine titers.[10,11] The software SPSS, version 18.0 (IBM, Armonk, New York, USA), was used for statistical analysis. All p-values < 0.05 were considered statistically significant.

Results

Study population

In total, 139 consecutive individuals with STEMI were included in the study. The main characteristics of the study population at baseline are described in Table 1.

Measurement of circulating cytokines

Figure 1 shows that, compared to baseline, levels of IL-1β and IL-18 decreased 30 days after STEMI. Conversely, increased levels of IL-4 and IL-10 were observed 30 days after STEMI. No significant changes were observed for IL-6 levels over time.

Relationship between cytokines and cardiac magnetic resonance imaging

At baseline, no significant correlations were observed between IL-1β, IL-4, IL-10, and IL-18 levels and cMRI parameters, such as the amount of infarcted mass or LVEF; however, there was a negative correlation between IL-6 levels and LVEF (Spearman's rho = -0.50, p = 0.004). A trend for correlation between IL-6 levels and the percentage of infarcted left ventricular mass was also noted (rho = 0.41, p = 0.05) (Table 2).

There was a positive correlation between baseline levels of IL-4 and the amount of infarcted mass as measured by cMRI (rho = 0.24; p = 0.03) at 30 days (Table 3). No other correlations between cytokine levels and cMRI parameters were found when they were assessed 30 days after STEMI.

Relationship between cytokines and high-sensitivity C-reactive protein

The levels of hsCRP correlated with those of IL-6 at baseline (rho = 0.45; $p < 0.0001$) and 30 days after STEMI (rho = 0.29, p = 0.009). No other cytokine showed correlation with hsCRP levels either at baseline or after 30 days of STEMI (data not shown).

Relationship between IL-6 and culprit coronary artery

Right coronary artery was the most common culprit coronary artery related to STEMI (46%), followed by left anterior descending artery (42%) and left circumflex artery (12%). IL-6 levels examined in the first day after STEMI did not differ between the culprit arteries (p = 0.063, Kruskal-Wallis test), as well as after 30 days of STEMI (p = 0.131, Kruskal-Wallis test).

Cardiac magnetic resonance imaging

Table 4 shows the results of cMRI according to the culprit coronary artery. No significant differences were seen for infarcted mass (%), left ventricular mass, or LVEF at baseline or 30 days after STEMI.

Table 1 – Baseline characteristics of the study population

Parameters	N = 139
Age, years*	56 (50-63)
Male gender, n (%)	92 (66)
Smoking, n (%)	28 (20)
Diabetes, n (%)	32 (24)
HbA1c, %**	6.4 ± 1.4
Hypertension, n (%)	82 (60)
SBP, mm Hg**	128 ± 21
DBP, mm Hg**	80 ± 14
Weight, kg**	75 ± 13
BMI, kg/m2**	27.2 ± 4.78
Cholesterol, mg/dL**	208 ± 45
LDL-C, mg/dL**	138 ± 41
HDL-C, mg/dL**	41 ± 12
Triglycerides, mg/dL*	124 (86-213)
hsCRP, mg/L*	15 (7-63)
Myocardial infarction location	
Anterior, n (%)	60 (43)
Inferior, n (%)	73 (53)
Lateral, n (%)	6 (4)

**median (interquartile range); **mean ± standard deviation; BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure.*

Discussion

Our study shows the behavior of cytokine concentrations in the early phase of STEMI in patients who were treated with a pharmacoinvasive strategy and received standard medical care. Our main findings were a marked decrease in the titers of proinflammatory cytokines (IL-1β and IL-18), but not IL-6, and an increase in the titers of protective cytokines (IL-10 and IL-4). Interestingly, LVEF obtained by cMRI showed a correlation with IL-6 concentrations at baseline, but not 30 days post-STEMI. In addition, the infarcted mass quantified by cMRI at 30 days showed a correlation with IL-4 levels at baseline. Together, these data suggest an important role of the interleukin profile on the first day after acute MI, which seems to have some relationship with the infarcted mass and ventricular remodeling. Moreover, the substantial decline in some inflammatory cytokines combined with the remarkable increase in IL-10 appears to attenuate, at least in part, the harmful effects of IL-6 on ventricular remodeling.[12]

Early coronary recanalization and use of both antithrombotic and highly effective lipid-lowering drugs are well-established strategies in the treatment of patients with MI. However, improved knowledge of the residual inflammatory risk during the early follow-up of MI may contribute to creating new therapeutic opportunities.[13]

In our study, IL-6 concentrations were inversely associated with left ventricular function. Mendelian randomization studies have suggested a causal role of IL-6 in coronary heart disease[14,15] and in the development of abdominal aortic aneurysm.[16] Two recent large prospective studies involving individuals after acute coronary events showed an independent association between higher concentrations of IL-6 and main cardiovascular outcomes, including cardiovascular death, even after multiple adjustments to classical biomarkers of cardiovascular disease.[17,18] The interaction of IL-6 with its receptor seems to modulate the inflammatory microenvironment in cardiovascular diseases related to both plaque destabilization and long-term prognosis.

This inflammatory microenvironment involving endothelial and inflammatory biomarkers may be modulated by the antiplatelet therapy chosen.[19,20] However, in the large DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2) study,[21] comparing ticagrelor with clopidogrel after recent acute coronary syndrome, no differences were found in inflammatory biomarkers at baseline, at discharge, and after 4 weeks. The marked decrease in the levels of other inflammatory markers, such as IL-1β and IL-18, and the increase in the levels of protective IL-10 may have contributed to a more favorable inflammatory response, despite persistently high levels of IL-6. Furthermore, these patients received an effective lipid-lowering treatment of proven anti-inflammatory action, with either rosuvastatin[22] or simvastatin/ezetimibe combination.[23] Interestingly, only the level of IL-6 showed no change after the medical treatment, suggesting that the control of this cytokine requires additional therapy, such as the use of a monoclonal antibody or a drug that can reduce IL-6-triggered inflammatory activity.[24,25]

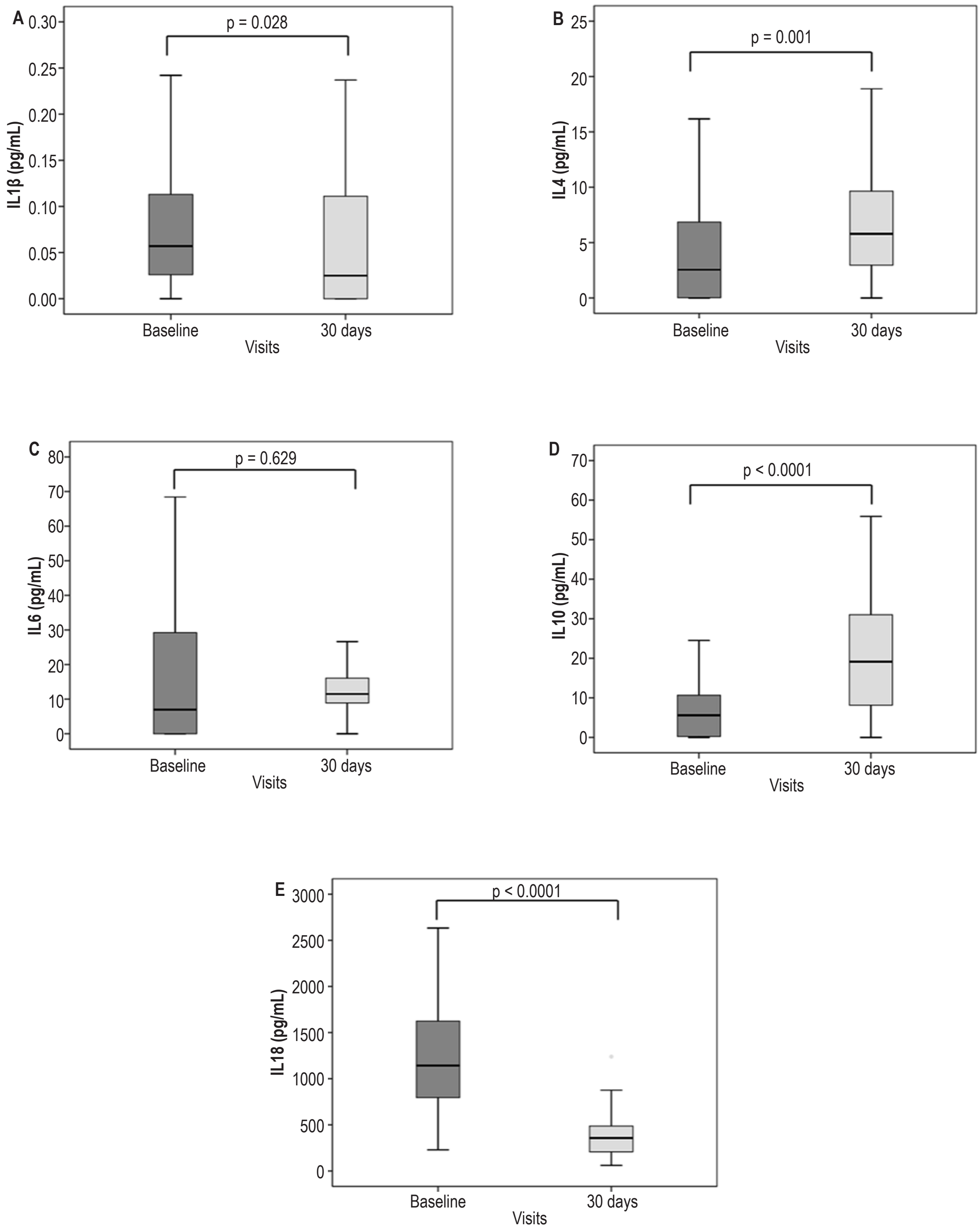

Figure 1 – *Box-plots of interleukin (IL) concentrations at baseline and 30 days after STEMI. (A) IL-1ß; (B) IL-4; (C) IL-6; (D) IL-10; (E) IL-18. Significant changes were observed in all cytokines, except for IL-6. Titers were compared using the Wilcoxon test.*

Table 2 – Correlations between baseline interleukin concentrations (pg/mL) and cardiac magnetic resonance imaging parameters in the acute phase of myocardial infarction

Variables	Spearman's rho	P-value
IL-1β and infarcted mass*	0.16	0.43
IL-1β and infarcted mass**	-0.05	0.84
IL-1β and LVEF	0.12	0.55
IL-4 and infarcted mass*	-0.26	0.19
IL-4 and infarcted mass**	-0.20	0.37
IL-4 and LVEF	0.15	0.44
IL-6 and infarcted mass*	0.16	0.39
IL-6 and infarcted mass**	0.41	0.05
IL-6 and LVEF	-0.50	0.004
IL-10 and infarcted mass*	0.30	0.10
IL-10 and infarcted mass**	0.24	0.28
IL-10 and LVEF	-0.31	0.09
IL-18 and infarcted mass*	-0.11	0.57
IL-18 and infarcted mass**	-0.24	0.28
IL-18 and LVEF	0.01	0.96

**grams; **percentage of left ventricular mass; IL: interleukin; LVEF: left ventricular ejection fraction.*

Table 3 – Correlations between baseline interleukin concentrations (pg/mL) and cardiac magnetic resonance imaging parameters after 30 days of myocardial infarction

Variables	Spearman's rho	P-value
IL-1β and infarcted mass*	-0.02	0.85
IL-1β and infarcted mass**	-0.07	0.59
IL-1β and LVEF	0.19	0.10
IL-4 and infarcted mass*	0.24	0.03
IL-4 and infarcted mass**	0.14	0.20
IL-4 and LVEF	-0.14	0.19
IL-6 and infarcted mass*	0.13	0.23
IL-6 and infarcted mass**	0.13	0.22
IL-6 and LVEF	-0.17	0.10
IL-10 and infarcted mass*	0.13	0.23
IL-10 and infarcted mass**	0.07	0.55
IL-10 and LVEF	0.09	0.40
IL-18 and infarcted mass*	0.14	0.31
IL-18 and infarcted mass**	-0.12	0.38
IL-18 and LVEF	0.07	0.52

**grams; **percentage of left ventricular mass; IL: interleukin; LVEF: left ventricular ejection fraction.*

Table 4 – Cardiac magnetic resonance imaging results by culprit coronary artery at baseline and 30 days after acute myocardial infarction

Culprit coronary artery	Baseline	30 days
Left anterior descending artery		
Infarct size, % LV	10.0 (5.5-19.0)	12.7 (8.0-21.0)
LV mass, grams	117.3 (101.0-171.8)	90.5 (69.0-127.9)
LVEF, %	46.0 (43.3-59.0)	51.6 (40.5-59.3)
Right coronary artery		
Infarct size, % LV	12.0 (10.0-18.5)	10.0 (6.0-17.9)
LV mass, grams	96.0 (86.5-123.0)	99.0 (80.0-113.0)
LVEF, %	48.0 (42.0-50.5)	55.5 (50.0-60.0)
Left circumflex artery		
Infarct size, % LV	11.5 (5.0-18.0)	7.0 (4.0-8.7)
LV mass, grams	103.0 (76.0-130.0)	103.0 (75.0-106)
LVEF, %	51.0 (50.0-52.0)	54.0 (51.0-58.0)

Data presented as median (interquartile range). LV: left ventricular; LVEF: left ventricular ejection fraction. Baseline cardiac magnetic resonance imaging was obtained within 10 days of myocardial infarction. At baseline, no differences were observed for infarct size between culprit coronary arteries (p = 0.59) as well as for LV mass (p = 0.08) or LVEF (p = 0.62) (Kruskal-Wallis test for all analyses). No differences were observed between culprit coronary arteries at 30-days for infarct size (p = 0.13), LV mass (p = 0.86), or LVEF (p = 0.10) (Kruskal-Wallis test was used for comparisons).

IL-4 has several biological properties, including differentiation of Th1 lymphocytes into cells with less inflammatory activity (Th2).[25] In addition, chronically elevated IL-4 was reported to have a causal relationship with cardiac fibrosis and adverse cardiac remodeling.[26] Furthermore, dilated cardiomyopathy induced by angiotensin II is modulated by IL-4 levels.[27] In our study, we observed an association between baseline IL-4 levels and the amount of infarcted mass after 30 days of MI. These findings suggest an important role for this cytokine, possibly by attenuating the myocardial inflammatory process through greater cell differentiation into less inflammatory phenotypes (M2 macrophages and Th2 lymphocytes). In this setting, IL-4 may influence the entire ventricular remodeling process. It may take several weeks to occur and seems to depend on the crosstalk between inflammatory cells and cardiomyocytes, thus determining elimination of necrotic cells and promoting cell replacement and formation of the fibrotic scar.[28]

Inflammasomes are a family of the innate immune system that includes NLRP3, which has been recognized as a relevant trigger for the inflammatory cascade related to cardiovascular disease.[29] This platform can be activated by many stimuli, including hypoxia, promoting the release of the highly inflammatory cytokines IL-1β and IL-18.[30] Furthermore, metabolic syndrome and diabetes are related to IL-18 concentrations. Whereas IL-1β is related to the inflammatory cascade of cardiovascular disease, IL-18 seems to be associated with inflammatory mechanisms, favoring cancer development and showing higher concentrations in subjects with diabetes and insulin resistance.[31,32] Our study showed a decrease in both cytokines (IL-1ß and IL-18), suggesting a decrease in the stimuli for NLRP3 activation after 30 days of STEMI.

Our study also reinforces the important role of IL-6, the only unmodified cytokine 30 days after MI, showing a significant correlation with hsCRP at baseline and 30 days after STEMI, a previously reported association.[33] In our study, only patients with STEMI undergoing thrombolysis in the first 6 hours and referred to coronary angiography in the first 24 hours were included. Thus, this is a highly homogeneous population receiving standard medical care. Taking into account the association of chronically elevated levels of IL-6 with the recurrence of coronary events, heart failure, cardiovascular mortality, and all-cause mortality, an additional decrease in the residual inflammatory risk seems to be a promising target for intervention.[34,35]

Study limitations

The study population received lipid-lowering and antiplatelet therapies whose anti-inflammatory effects may have contributed to the study results. However, these treatments are part of the standard of care for these subjects. Some inflammatory cytokines capable of activating the inflammatory pathway mediated by IL-6, such as tumor necrosis factor-alpha (TNF-α) or IL-1R, were not measured and may have relevance in host tissue responses and ventricular remodeling.[36,37] In fact, MI per se could be related to an increase in IL-6 as a response to injury. However, IL-6 titers remained elevated while other cytokines changed their serum levels after 30 days of STEMI. Another important inflammatory biomarker not evaluated in the study was IL-1α, which is released from necrotic cardiomyocytes and activates the immune responses from fibroblasts.[38] IL-1α blockade decreases chemoattractant activity for many cells mediated by CCL2/MCP-1 and IL-6.[38] In addition, monocyte and lymphocyte recruitment in ischemic heart can be stimulated by several chemoattractants such as CCL2 and CCL5, thus influencing tissue healing.[39] Finally, the transforming growth factor beta (TGF-β), which is highly expressed after acute MI, was not evaluated in our study as well but has been implicated in cardiomyocyte survival and ventricular remodeling.[40]

The results presented herein refer to a relatively early period after acute MI, but this is the time when inflammatory infiltrate seems to be more relevant to cell recovery or reperfusion injury.

Conclusions

During the first month post-MI, we observed a marked improvement in the balance of pro- and anti-inflammatory cytokines, except for IL-6. These findings suggest residual inflammatory risk.

Highlights

- Current strategies in the care of patients with acute myocardial infarction seem to be insufficient to modify the inflammatory pathway mediated by interleukin-6.
- Higher concentrations of this cytokine appear to be associated with decreased left ventricular ejection fraction.
- Therapies targeting interleukin-6 seem promising for their additional decrease in residual inflammatory risk in subjects with acute myocardial infarction.
- The great challenge for reducing residual inflammatory risk lies in the development of safe and affordable therapies.

Author contributions

Conception and design of the research: Izar MC, Maugeri IL, Pinto IM, Szarf G, Caixeta AM, Berwanger O, Fonseca FAH; Acquisition of data: Coste MER, Izar MC, Teixeira D, Ishimura ME, Bacchin AS, Bianco HT, Moreira FT, Pinto IM, Szarf G, Caixeta AM, Gonçalves Jr. I, Fonseca FAH; Analysis and interpretation of the data: Coste MER, França CN, Izar MC, Teixeira D, Ishimura ME, Maugeri IL, Bacchin AS, Bianco HT, Moreira FT, Pinto IM, Szarf G, Caixeta AM, Berwanger O, Gonçalves Jr. I, Fonseca FAH; Statistical analysis: Coste MER, França CN, Fonseca FAH; Obtaining financing: Fonseca FAH; Writing of the manuscript: Coste MER, Fonseca FAH; Critical revision of the manuscript for intellectual content: Izar MC, Maugeri IL, Fonseca FAH.

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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Inflammation Post-Acute Myocardial Infarction: "Doctor or Monster"

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Short Editorial related to the article: Early Changes in Circulating Interleukins and Residual Inflammatory Risk After Acute Myocardial Infarction

As in the short story "The Strange Case of Dr. Jekyll and Mr. Hyde ", inflammation has a good side, which is the protection against pathogens, and helps in the process of cellular and tissue repair after an injury; on the other hand, it may also perpetuate and worsen the injury and, in the case of acute myocardial infarction (AMI), it may be the trigger of coronary occlusion. In the acute phase of AMI, the immune system is activated in the process of myocardial repair, in which the necrotic tissue is replaced by the scar tissue (fibrosis). From anatomopathological studies, we know that in the first hours after coronary occlusion, neutrophils are mainly recruited to the injury site. The local neutrophil population peaks around the third day, then a progressive decline is observed. From the fifth day, they are replaced by macrophages and both are responsible for clearing non-viable myocytes. In addition to this role, together with smooth muscle cells macrophages are responsible for angiogenesis and collagen production. The scarring process begins at the periphery of the infarcted area and extends to the nucleus, and this repair mechanism is completed in about 4–8 weeks, depending on the infarction size.[1,2]

If we know how the inflammatory process occurs at the cellular level post-AMI, why do we continue to study inflammation? And why concentrating efforts on studies on cytokine expression? Whereas, on the one hand, the inflammatory process is necessary for the repair process, in the context of AMI, inflammation also plays an important role in complications. Such effect is observed in cardiogenic shock (causing vasodilation, vasoplegia and worsening shock),[3] mechanical complications (papillary muscle rupture and ventricular free wall, and interventricular communication), in ventricular remodeling (fibrotic expansion and replacement of the affected wall) and, in the long run, it has been related to new cardiovascular events. Cytokines are molecules that mediate immune and inflammatory reactions and are responsible for activating inappropriate pathways or exaggerated responses (hypersensitivity).[4] Therefore, understanding its kinetics can help to clarify the pathways associated with favorable outcomes and the pathways that, when activated, may lead to an increase in unfavorable events and have the potential to be the target of future therapeutic approaches.

Keywords

Myocardial Infarction; Inflammation/complications; B-Lymphocytes; Cytokines; Vasoplegia; Shock, Cardiogenic.

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In the elegant subanalysis of the BATTLE-AMI study (B and T Types of Lymphocytes Evaluation in Acute Myocardial Infarction), conducted by Maria Coste et al.[5] the main objective was to study the behavior of the immune system during the early and late phase of AMI trying to correlate it with the area at risk in AMI. For this, blood samples were collected from 138 patients (from among the 300 participants from the original study sample), and pro-inflammatory cytokines IL-1β (IL – Interleukin), IL-4, IL-6 and IL-18, and anti-inflammatory IL-10 were dosed. As expected, pro-inflammatory cytokines (IL-1β and IL18) prevailed in the first days and, after four weeks, pro-cytokine declines were observed and an increase in those associated with an anti-inflammatory profile (IL-10). But the levels of IL-4 and IL-6 remained high. Subanalyses should be analyzed carefully and, due to the risk of type I error, they have a primary role in generating hypotheses.[6] In this study, less than half of the patients in the original sample were analyzed, and we observed a lower average age than that found in the literature, and, thus, the immune response observed could be different with the expansion of the sample.[7] This possibility is even more possible if we consider the significant variability in the measured values of cytokines.

Multiple analyses should also be looked at very carefully, especially when you have a limited sample. In the present sub-study, cytokine levels were correlated with three myocardial resonance variables, which increases the possibility that the finding had been by chance. This could explain, for example, the negative correlation between IL6 and the left ventricular ejection fraction, but without an association with the LV mass affected in AMI.[5] As the area of necrosis was of moderate size (around 10% in late enhancement), probably few patients had cardiogenic shock and/or remodeling with ventricular expansion. It would be interesting to further evaluate the behavior of cytokines in these clinical situations. The data, however, add to the literature hitherto available, and their major contribution is to try to correlate the main cytokines — already widely studied in the acute phase of AMI — with cardiac resonance data.

The study of tissue inflammation has drawn attention mainly after the CANTOS study (Canakinumab Antiinflammatory Thrombosis Outcome Study),[8] in which IL-1 block was associated with a reduction in cardiovascular events (hazard ratio 0.83; 95% CI, 0.73–0.95; p=0.005) in post-AMI patients.β Recently, the COLCOT study (Colchicine Cardiovascular Outcomes Trial)[9] demonstrated that colchicine (non-specific and diffuse inflammation block) reduced the primary composite outcome (death, AMI, cardiac arrest, stroke and emergency hospitalization) (hazard ratio 0.77; 95% CI, 0.61–0.96; p=0.02). IL-6 has thus received special interest,[10-12] because its high levels are associated with activation of macrophages, release of C-reactive protein, activation of smooth muscle cells and action on lipid metabolism — processes classically associated with acute coronary events. Indirect data, mainly from patients with rheumatoid arthritis, suggest that the increase of IL-6 could be the link between this disease and cardiovascular events.

As these studies demonstrated the relationship of IL-6 with cardiovascular events, the next step is to carry out specific clinical trials. Tolicizumab is a monoclonal antibody that specifically blocks IL-6,[13] and has been shown to be beneficial for patients with rheumatoid arthritis, but, on the other hand, it was ineffective in the acute phase of infection by the SARS-COV-19 virus (during the so-called "cytokine storm").[14] We do not yet know what the consequences of its blockage on the cardiovascular system would be. Although it is highly associated with pro-inflammatory effects, IL-6 can also have anti-inflammatory effects.[4] As in Stevenson's tale, to get rid of the monster, doctor Jerkill killed the host. We have to be careful with the immune system, looking for beneficial effects such as better ventricular remodeling and secondary prevention of events because, without knowing all the consequences and in the absence of robust clinical evidence, we might kill more than save.[15]

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Effectiveness and Safety of Transvenous Removal of Cardiac Pacing and Implantable Cardioverter-defibrillator Leads in the Real Clinical Scenario

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Abstract

Background: **Transvenous lead extraction (TLE) of cardiac implantable electronic devices (CIED) is an uncommon procedure and requires specialized personnel and adequate facilities.**

Objectives: **To evaluate the effectiveness and safety of the removal of CIED leads and to determine risk factors for surgical complications and mortality in 30 days.**

Methods: **Prospective study with data derived from clinical practice. From January 2014 to April 2020, we included 365 consecutive patients who underwent TLE, regardless of the indication and surgical technique used. The primary outcomes were: success rate of the procedure, combined rate of major complications and intraoperative death. Secondary outcomes were: risk factors for major intraoperative complications and death within 30 days. Univariate and multivariate analysis were used, with a significance level of 5%.**

Results: **Procedure success rate was 96.7%, with 90.1% of complete success and 6.6% of clinical success. Major intraoperative complications occurred in 15 (4.1%) patients. Predictors of major complications were: lead dwelling time ≥ 7 years (OR = 3.78, p = 0.046) and change in surgical strategy (OR = 5.30, p = 0.023). Functional class III-IV (OR = 6.98, p <0.001), renal failure (OR = 5.75, p = 0.001), CIED infection (OR = 13.30, p <0.001), number of procedures performed (OR = 77.32, p <0.001) and major intraoperative complications (OR = 38.84, p <0.001) were predictors of 30-day mortality.**

Conclusions: **The results of this study, which is the largest prospective registry of consecutive TLE procedures in Latin America, confirm the safety and effectiveness of this procedure in the context of real clinical practice. (Arq Bras Cardiol. 2020; 115(6):1114-1124)**

Keywords: **Electrodes Implanted; Pacemaker; Cardiac Pacing Artificial; Transvenous lead extracion; Infection; Effectiveness; Surgical complications; Mortality.**

Introduction

Cardiac implantable electronic device (CIED) lead extraction is an uncommon procedure, which requires long-term professional training and adequate facilities.[1-5] Although its indications are well established in medical guidelines, its use varies according with the expertise of each center, being almost exclusively used for the treatment of CIED-related infections in low volume centers and on a larger scale in centers with greater experience.[2-9]

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Since most implantable devices use the venous access for lead placement, the transvenous techniques are the most commonly used. Nowadays, opening the chest is not frequently used in lead extraction, being almost exclusively limited to epicardial lead placement. For transvenous leads, the open surgery is restricted to cases where large lead vegetations are found or for correction of complications during transvenous lead extraction.[3]

Lead adhesion to the myocardium, to the veins or lead-to-lead adhesion are quite frequent. Several factors are related with adhesion formation, including: dwelling time of implanted leads, lead type, the number of leads, the patient's age and sex.[6] In order to disrupt these adhesions, specific tools have been employed, each with its indications, advantages and disadvantages.[3,7] In general, the reported success rates for extractions range from 90 to 98%.[1,7,10,11] In spite of the satisfactory results obtained, catastrophic complications may occur during extraction, and when they do occur, open heart surgical procedures may be required for correction.[9,12,13] Severe complications are reported in 1 to 10% and intraoperative death, in 0.2

to 5.7%. The overall mortality rate within 30 days of surgery ranges from 2.1 to 10% of cases.[10-13]

The effectiveness of the tools used for extraction and the risk factors associated with the occurrence of catastrophic complications are not well established in the literature.[1,2,10-14] The low rate of utilization and complications, combined with the diversity of approaches and tools available for extraction, make comparison difficult. In the national setting, the lack of incorporation of specific lead extraction technology in the Brazilian Unified Health System (SUS) explains its limited use, as well as the absence of reliable data resulting from lead extraction in Brazil.

The purpose of this study was to assess the effectiveness and the safety of pacemaker and implantable defibrillator lead extraction, aiming at determining the procedures' success rate, the rate of surgical complications, surgical death rate and total mortality within 30 days after hospital discharge, as well as the risk factors for unfavorable outcomes.

Methods

Study design and setting

This is a prospective observational study with data derived from clinical practice. The data were collected at two distinct moments: (1) on index hospital admission, i.e., the episode of hospital care related to the lead extraction procedure; (2) thirty days after hospital discharge.

This study was performed in a high-complexity cardiology hospital, and was approved by the institution's Research Ethics Committee.

Study Population

From January 2014 to April 2020, all the patients submitted to lead extraction were consecutively included, regardless of surgical indication and the technique used. Individuals who were submitted to lead extraction due to orthotopic cardiac transplantation were excluded.

Study outcomes

The primary outcomes of the study were the procedure effectiveness, expressed by the clinical procedural success, and its safety, expressed by the combined rate of major complications and intraoperative mortality.

The definitions of European guidelines were used.[8] In this study, clinical procedural success was defined as the removal of all targeted leads and material or a retention of <4 cm of the lead, as long as the extraction was not performed for the treatment of CIED infections. On the other hand, procedural failure was defined as the retention of more than 4 cm of lead material; the retention of lead material of any size in patients with CIED infection; or the development of any permanently disabling complication or procedural-related death.

The secondary outcomes were: risk factors for major intraoperative complications and death within 30 days after discharge.

Study phases

Preoperative evaluation

Patients with indication for lead extraction and who fulfilled the study eligibility criteria underwent routine preoperative evaluation, including clinical evaluation, laboratory and imaging tests.

Following the institution's routine protocol, the patients were submitted to chest X-ray, to determine lead position; two-sided digital venography to investigate the venous territory and, when there was the diagnosis of CIED infection, transesophageal echocardiogram.

Surgical Procedure

The procedures were performed under general anesthesia with orotracheal intubation, full monitoring, including transesophageal echocardiogram.

The surgeries were grouped according to the lead access route: (1) Epicardial leads, extracted by open surgery; (2) Transvenous leads, extracted using preferably transvenous techniques.

Lead removal using the venous entry site approach

Leads that allowed for extravascular handling were removed using a sequential approach, which was initiated with a simple direct traction and moved towards transvenous extraction, with the use of specific tools, if direct traction was not successful.

- Removal by simple traction: an attempt to remove the leads with no specific extraction tools was made in all cases. To achieve this purpose, a standard stylet was passed through the lumen of the lead to be removed, with firm, continuous traction, in order to separate the lead from the myocardium and venous system. In case this approachwas not successful, the following step was the use of extraction devices.

- Transvenous extraction: the extraction procedure was initiated with the use of a locking stylet. The intravascular dissection was performed with the extraction tools available for the case (laser-powered sheath, mechanical sheath or rotational mechanical sheath). The purpose of the dissection was to guide the sheath until the lead placement site in the myocardium in order to perform the counter-traction.

Lead removal through intravascular capture

In cases where the lead was not accessible for extravascular manipulation (free-floating leads), intravascular capture was performed through femoral or jugular access. After intravascular capture, the lead tip was removed by simple traction or counter-traction, depending on the necessity of each case.

Change in Surgical Strategy

In the cases where the first-choice extraction tool cannot be advanced over the lead, a change in strategy may be necessary, including the use of another extraction tools, intravascular capture or open surgery.

CIED reimplantation

In the patients who were not diagnosed with CIED infection, the placement of the new device was performed during the same surgical procedure. When CIED infection was present, the new implantation was always performed in a separate surgery, after the infection was controlled.

Postoperative assessment and clinical follow-up

At discharge, immediate postoperative data were collected, prioritizing the investigation of perioperative complications.

In accordance with normal routine, all patients were evaluated in the outpatient setting, 30 days after discharge. This evaluation prioritized the investigation of complications resulting from the procedure, the need for readmission or surgical reintervention.

Electronic data collection and management

To ensure database quality, a previously standadized infraestructure was adopted,[15] which included: (1) Data management planning; (2) Definition of data element terminology; (3) Development of electronic forms using the REDCap platform;[16] (4) Parameterization of specific functions of the REDCap; (5) Data collection team training; (6) Dynamic monitoring of database quality; (7) Integration of the REDCap system with the Business Intelligence tool, to create interactive dynamic dashboards, allowing for real-time result view, in a cloud technology environment. To favor the study's reproducibility and publishing of anonymized and de-identified data in real time, we opted for the Open Source platform (Shinydashboard, RStudio) (Figure1).

Variables studied and statistical analysis

The following were analyzed as independent variables for outcomes: demographic data, baseline clinical data, characteristics of the removed CIED, type of extraction and use of specific extraction tolls.

A univariate analysis was used to investigate the risk factors associated with the outcomes, adopting a level of significance of 5%. The multivariate logistic regression model was used with the stepwise method of variable selection for the investigation of independent risk factors, using as inclusion criteria the associations with a p-value ≤ 0.10 in the univariate analysis.

Results

Baseline characteristics

During the study period, we included 365 patients who had undergone one to three lead extraction procedures until treatment conclusion. There was a prevalence of male individuals (55.6%), and the average age was of 59.8 ± 19.3 years, with a median of 63.0 years (Table 1).

Most individuals were oligosymptomatic for heart failure (86.0%), with absence of structural cardiac disease in 39.1% of them. The devices previously implanted were pacemakers in 57.8% and implantable cardioverter-defibrillators (ICD) in 33.1% of the cases.

The main reason for the procedure was lead dysfunction, in 218 (59.7%) patients. CIED infection, with or without intracardiac vegetations, was the cause for removal in 104 (28.5%) of the cases.

Surgical Characteristics

A total of 378 lead extraction procedures were performed in 365 patients. In 9 (2.5%) cases more than one procedure was required. A total of 634 leads, 521 pacemakers and 113 ICDs were removed. The mean lead dwelling time was 7.5 ± 6.6 years with a maximum of 39 years (Table 2).

Open surgery for epicardial lead extraction was performed in 17(4.6%) patients. Surgery with Cardiopulmonary Bypass (CPB) was required as first approach in 6 (1.6%) and, after as a second approach in 7 (1.9%) cases. In all procedures performed through venous entry, the simple traction was attempted, which was successful in 140 (38.4%) patients. In the other patients, transvenous extraction was performed. A locking stylet was used in 183 cases, laser-powered sheath in 80 (21.9%), mechanical sheath in 77 (21.1%) and rotational mechanical sheath in 23 (6.3%) patients.

A change in strategy was required in the same surgical procedure in 12 (3.3%) patients and, as a separate procedure, in 9 (2.5%). The change in strategy demanded the use of another type of dissection tool in 6 (1.6%), intravascular capture in 5 (1.4%), or open surgery with CPB in 7 (1.9%) cases.

Study Primary Outcomes

Procedure Effectiveness

Procedural success rate was of 96.7% (CI 95%= 94.5 – 98.5%), with complete procedural success in 329 (90.1%, CI 95%= 87.1 – 93.2%) patients and clinical procedural success in 24 (6.6%, CI 95%= 4.1 – 9.1%).

Procedural failure rate was of 3.2% (CI 95%= 1.5 – 5.1%). Failure was due to the retention of a fragment >4cm in 3 (0.8%) patients without infection, retention of any fragment in 7 (1.9%) patients with CIED infection and major complication that required surgical repair in 2 (0.5%) patients.

Procedure Safety

The composite outcome of major complications and intraoperative death occurred in 15 (4.1%, CI 95%= 2.1 – 6.1) patients. Intraoperative death occurred in only 1 (0.3%) case due to avulsion of cardiac structures, causing hemorrhagic shock. Only 2 (0.5%) patients had more than one major complication simultaneously. Minor intraoperative complications were observed in 10 (2.7%) patients, but in only one case there were concomitant minor complications (Table 3).

Postoperative events

The patients' median hospital length of stay was 9 days, ranging from 1 to 169 days. The main reason for long hospital stay was the prolonged antibiotic therapy required by patients with CIED infection. After discharge, 13 (3.6%) patients had complications and 8 (2.2%) were submitted to new surgery (Table 4).

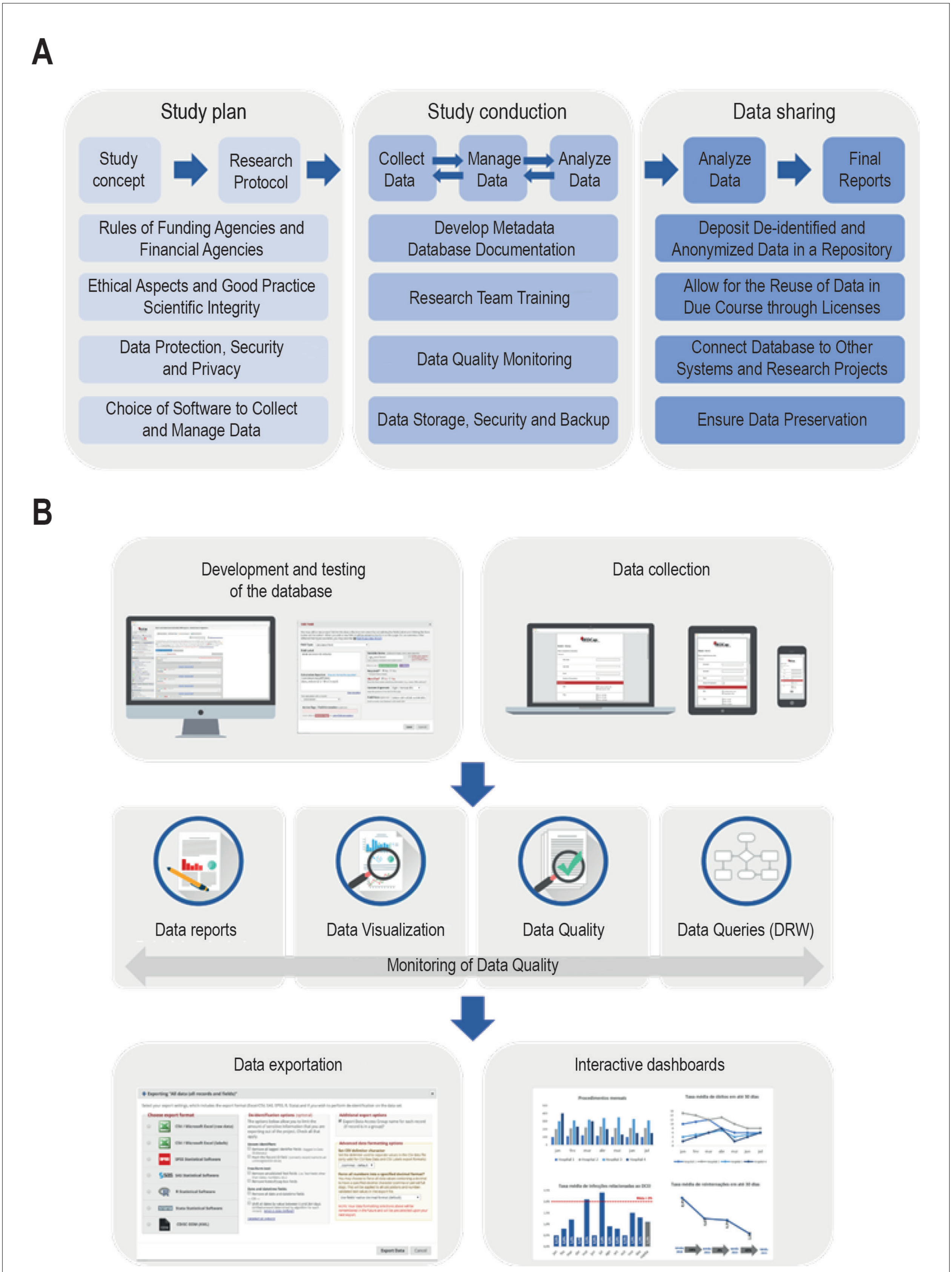

Figura 1 – *Electronic data capture and study data management. A – Data management steps. B – REDCap's functionalities used in the study.*

Table 1 – Demographic and clinical baseline data

Baseline Characteristics	
Males, n (%)	203 (55.6)
Age (years). mean ± SD (variation)	59.8 ± 19.3 (0.8 - 98.0)
Caucasian. n (%)	306 (83.8)
Functional Class (NYHA). n (%)	
I – II	314 (86.0)
III - IV	51 (14.0)
Structural heart disease. n (%)	
Conduction and rhythm disorders (without structural heart disease)	153 (41.9)
Chagas' Disease	68 (18.6)
Ischemic cardiomyopathy	46 (12.6)
Non-ischemic cardiomyopathy	86 (23.6)
Congenital cardiac defect	12 (3.3)
Comorbidities. n (%)	
Hypertension	186 (51.0)
Diabetes	60 (16.4)
Atrial Fibbrilation	70 (19.2)
Heart Failure	140 (38.4)
Chronic kidney failure	43 (11.8)
Stroke	33 (9.0)
Neoplasia under current or recent treatment	9 (2.5)
Left ventricular ejection fraction. mean ± SD (variation)	49.1 ± 16.3 (15- 82.0)
Type of CIED in use. n (%)	
Unicameral PM	41 (11.2)
Dual chamber PM	170 (46.6)
Unicameral ICD	33 (9.0)
Dual chamber ICD	64 (17.5)
CRT-PM	24 (6.6)
CRT-ICD	33 (9.0)
Indication for lead extraction. n (%)	
Infection treatment	104 (28.5)
Multiples abandoned leads	207 (56.7)
Obtaining venous access	22 (6.0)
Lead dislodgement	26 (7.1)
Treatment of thromboembolic complications	3 (0.8)
Other conditions	3 (0.8)
Main diagnosis. n (%)	
Pulse generator pocket infection	57 (15.6)
Intravascular infection without vegetation	10 (2.7)
Intravascular infection with vegetation	37 (10.1)
Lead Dysfunction	218 (59.7)
Indication of upgrade procedure	35 (9.6)
Others	8 (2.2)

ICD: Implantable Cardioverter-Defibrillator; SD: standard deviation; PM: pacemaker; NYHA: New York Heart Association; CRT: cardiac resynchronization therapy; CIED: Cardiac implantable electronic device.

Table 2 – Lead Extraction Procedure Data

Surgical Characteristics	
Procedure duration (minutes). mean ± SD (variation)	147.9 ± 82.0 (20 - 635)
Total number of leads extracted per patient. n (%)	
One	197 (54.0)
Two	125 (34.2)
Three	32 (8.8)
Four	11 (3.0)
Lead dwelling time (years). mean ± SD (variation)	7.5 ± 6.6 (0 – 39)
Lead implantation site. n (%)	
Atrial	221 (34.9)
Right ventricle (pacemaker)	258 (40.7)
Right ventricle (ICD)	113 (17.8)
Coronary sinus	42 (6.6)
Main Surgical Technique. n (%)	
Simple traction	140 (38.4)
Simple traction with dilation	22 (6.0)
Transvenous lead extraction by a venous entry site approach	180 (49.3)
Thoracotomy without cardiopulmonary bypass	17 (4.7)
Thoracotomy with cardiopulmonary bypass	6 (1.6)
Specific Extraction Tools. n (%)	
Locking stylet	183 (50.1)
Mechanical sheath	77 (21.1)
Rotational mechanical sheath	23 (6.3)
Laser-powered sheath	80 (21.9)
Change in Surgical Strategy. n (%)	
Simple traction removal to transvenous extraction	2 (0.5)
Simple traction removal to open surgery	2 (0.5)
Change in the type of intravascular dissection tool	6 (1.6)
Venous entry site extraction approach to intravascular capture	5 (1.4)
Venous entry site extraction approach to open surgery	5 (1.4)
Multiple	1 (0.3)

ICD: implantable cardioverter defibrillator; SD: standard deviation.

The total mortality was of 34 (9.3%) cases: 1 (0.3%) intraoperative death, 29 (7.9%) in the in-hospital postoperative period and 4 (1.1%) after discharge. The most frequent cause of mortality was CIED infection, in 20 (5.5%) cases, followed by cardiovascular-related causes in 6 (1.6%), extraction procedure complications in 5 (1.4%) and non-cardiovascular causes in 3 (0.8%) patients.

Risk factors for major intraoperative complications and mortality

According with the univariate analysis, the lead dwelling time (p= 0.015) and change in surgical strategy (p=0.016) were associated with higher occurrence of major intraoperative complications.

Age (p= 0.004), functional class (p<0.001), heart failure (p= 0.003), renal failure (p<0.001), CIED-related infection (p<0.001), total number of removed leads (p<0.001), type of lead removed (p=0.029), total number of procedures (p<0.001), procedure results (p=0.002), change in surgical strategy (p= 0.005) and major intraoperative complications (p<0.001) were all factors associated with total mortality within 30 days (Table 5).

Using multivariate analysis, it was possible to identify that lead dwelling time ≥ 7 years and change in surgical strategy as independent predictor factors for the occurrence of major intraoperative complications. Functional classes III-IV, chronic kidney failure, CIED infection, number of procedures performed and major intraoperative complications were independent factors for total mortality within 30 days (Table 6).

Table 3 – Major and minor intraoperative lead extraction-related complications

Intraoperative complications	
Major complications. n (%)	
Death	1 (0.3)
Cardiorespiratory arrest	6 (1.6)
Unstable arrhythmia	5 (1.4)
Cardiac tamponade	3 (0.8)
Avulsion of cardiac structures	2 (0.5)
Unstable bleeding	3 (0.8)
Minor complications. n (%)	
Hemothorax requiring drainage	2 (0.5)
Pneumothorax requiring drainage	2 (0.5)
Minimal pneumothorax.	1 (0.3)
Pericardial effusion	4 (1.1)
Unstable bleeding	4 (1.1)
Lead dislodgement	2 (0.5)

Table 4 – Postoperative events after lead extraction

Postoperative events	
Length of hospital stay (days). mean ± SD (variation)	17.4 ± 21.6 (1- 169)
In-hospital major complications	
Death	29 (7.9)
Cardiorespiratory arrest	3 (0.8)
Unstable arrhythmia	1 (0.3)
Cardiac tamponade	1 (0.3)
Pulmonary embolism	2 (0.5)
Unstable bleeding	2 (0.5)
Sepsis	13 (3.6)
In-hospital minor complications	
Hemothorax requiring drainage	1 (0.3)
Pneumothorax requiring drainage	2 (0.5)
Pocket hematoma	6 (1.6)
Lead dislodgement	2 (0.5)
Complications within 30 days after **discharge**	
Death	4 (1.1)
Readmission	33 (9.0)
Device-related reoperation	8 (2.2)
CIED-related infection	1 (0.3)
Lead dysfunction	3 (0.8)
Pulmonary embolism	2 (0.5)
Deep vein thrombosis of the upper extremity	7 (1.9)

SD: standard deviation; CIED: Cardiac implantable electronic device.

Table 5 – Risk factors for major intraoperative complications and total mortality within 30 days

Characteristics	Complications (absent) (n= 350)	Complications (presente) (n= 15)	p-value	Death (absent) (n= 331)	Death (present) (n= 34)	p-value
Male sex. n (%)	197 (56.3)	9 (60.0)	0.214	185 (55.9)	18 (52.9)	0.741
Age (years). mean ± SD	59.9 ± 19.2	57.7 ± 22.5	0.670	58.8 ± 19.4	69.0 ± 15.9	0.004
Functional Class (NYHA). n (%)						
I – II	303 (86.6)	11 (73.4)	0.142	292 (88.2)	22 (64.7)	
III – IV	47 (13.4)	4 (26.6)		39 (11.8)	12 (35.3)	<0.001
Cardiac Disease. n (%)						
Conduction and rhythm disorders	147 (42.0)	6 (40.0)		142 (42.9)	11 (32.3)	
Ischemic cardiomyopathy	46 (13.1)	0	0.258	42 (12.7)	4 (11.8)	0.420
Non-Ischemic cardiomyopathy	157 (44.9)	9 (60.0)		147 (44.4)	19 (55.9)	
Comorbidities. n (%)						
Diabetes (absent)	290 (82.9)	15 (100)		278 (84.0)	27 (79.4)	
Diabetes (present)	60 (17.1)	0	0.145	53 (16.0)	7 (20.6)	0.493
Heart failure (absent)	217 (62.0)	8 (53.3)		212 (64.1)	13 (38.2)	
Heart failure (present)	133 (38.0)	7 (46.7)	0.499	119 (35.9)	21 (61.8)	0.003
Chronic kidney failure (absent)	307 (87.7)	15 (100)		299 (90.3)	23 (67.6)	
Chronic kidney failure (present)	43 (12.3)	0	0.233	32 (9.7)	11 (32.4)	<0.001
CIED type. n (%)						
Unicameral	71 (20.3)	3 (20.0)		66 (19.9)	8 (23.5)	
Dual chamber	225 (64.3)	9 (60.0)	0.862	216 (65.3)	18 (53.0)	0.296
Cardiac resynchronization therapy	54 (15.4)	3 (20.0)		49 (14.8)	8 (23.5)	
Indication for extraction. n (%)						
Non-infectious causes	250 (71.4)	11 (73.3)		253 (76.4)	8 (23.5)	
CIED infection	100 (28.6)	4 (26.7)	1.000	78 (23.6)	26 (76.5)	<0.001
Number of leads removed. n (%)						
1 - 2	310 (88.6)	12 (80.0)		301 (90.9)	21 (61.8)	
3 - 4	40 (11.4)	3 (20.0)	0.400	30 (9.1)	13 (38.2)	<0.001
Lead dwelling time. n (%)	7.3 ± 6.6	11.2 ± 6.7	0.015	7.1 ± 6.2	10.1 ± 9.5	0.142
Lead type. n (%)						
Pacemaker	252 (72.0)	12 (80.0)		234 (70.7)	30 (8.2)	
ICD	98 (28.0)	3 (20.0)	0.768	97 (29.3)	4 (11.8)	0.029
Surgical technique. n (%)						
Simple traction with or without dilation	159 (45.4)	3 (20.0)		148 (44.7)	14 (41.2)	
Transvenous extraction	169 (48.3)	11 (73.3)	0.140	164 (49.6)	16 (47.1)	0.386
Open surgery	22 (6.3)	1 (6.7)		19 (5.7)	4 (11.7)	
Change in surgical strategy. n (%)						
No	339 (96.8)	12 (80.0)		322 (97.3)	29 (85.3)	
Yes	11 (3.2)	3 (30.0)	0.016	9 (2.7)	5 (14.7)	0.005
Number of procedures performed. n (%)						
One	342 (97.7)	14 (93.3)		328 (99.1)	28 (82.4)	
Two	5 (1.4)	1 (6.7)	0.317	3 (0.9)	3 (8.8)	<0.001
Three	3 (0.9)	0		0	3 (8.8)	
Procedure results. n (%)						
Successful	340 (97.1)	13 (86.7)		324 (97.9)	29 (85.3)	
Failure	10 (2.9)	2 (13.3)	0.082	7 (2.1)	5 (14.7)	0.002
Major intraoperative complications. n (%)						
Absent	-	-		323 (97.6)	27 (79.4)	
Present	-	-		8 (2.4)	7 (20.6)	<0.001

SD: standard deviation; CIED: Cardiac implantable electronic device.

Table 6 – Independent predictors of intraoperative major complications and total mortality

Independent predictors	Odds ratio	CI 95%		p-value
Intraoperative major complications				
Lead dwelling time ≥ 7 years	3.78	1.02	13.95	0.046
Change in surgical strategy	5.30	1.26	22.22	0.023
Mortalility				
Functional Class (NYHA) III - IV	6.98	2.45	19.86	<0.001
Chronic Kidney Failure	5.75	1.98	16.67	0.001
CIED infection	13.30	4.45	39.69	<0.001
Total number of procedures	77.32	8.64	692.19	<0.001
Major intraoperative complications	38.84	7.83	192.77	<0.001
ICD lead extraction	0.22	0.06	0.81	0.023

CIED: Cardiac implantable electronic device.

Discussion

This study is the first registry in Latin America designed to assess, prospectively, systematized data of lead extraction procedures in real clinical practice setting. Therefore, this sample composed of 634 removed leads from 365 patients, followed during 30 days after discharge, is representative of patients of all ages, with different structural cardiomyopathies and comorbidities, as well as all types of CIED and leads.

The finding that CIED infection was not the main indication for lead extraction differs from most studies, in which more than half of the population suffers from infection.[3,7,11,12] The high prevalence of non-infected individuals was essential for the achievement of the study objectives, since they are younger patients, with long lead implant duration. These characteristics increased the representativeness of complications associated with the procedure itself and its impact on mortality, at some extent minimizing the effects of infection, comorbidities and other characteristics inherent to the patient.

The development of specific tools for transvenous extraction has been essential to ensure greater patient safety. The comparison of safety and effectiveness of these devices, however, is problematic, because many of them are used as backup solutions for difficult cases or for correcting complications.[8,12-14] In this study, the main types of tools available for transvenous extraction were used. The lack of incorporation of transvenous extraction by the SUS, however, prevented an adequate comparison between the several technologies available, since the choice of device was defined by its availability for each case. Despite this bias, a locking stylet was used in 50.1% of the cases, laser-powered sheaths in 21.9%, mechanical sheaths in 21.1%, and rotational mechanical sheaths in 6.3% of patients.

Thus, safety and effectiveness of lead extraction, the study primary outcomes, could be robustly assessed. The success rate of 96.7%, as well as the major complication rate of 4.1% were comparable to those of international services, with a large volume of extractions.[7,12,14,17,18] The total mortality rate of 9.3% was mainly a result of patient-related causes and, in only 1.4%, due to extraction-related complications.

The risk of catastrophic complications has been the main obstacle for the indication of lead extraction in optional cases. This fact has motivated the search for predictors of severe complications and scores for the identification of more difficult cases.[18-21] The risk factor analysis for major intraoperative complications performed in this study corroborated the importance of time of implantation as a predictor of intraoperative complications. In addition, it indicates that the need to change the strategy during the procedure has also been associated with this type of problem. This knowledge can provide valuable contributions for intraoperative decision-making, giving the surgery team the possibility of interrupting the procedure in cases where the extraction is optional or moving into an open technique with CPB in cases of infection, before a catastrophic complication occurs.

The high total mortality within 30 days after lead extraction procedures is a reason of concern, and may even justify the construction of nomograms to predict the risk of death.[18] Non-modifiable risk factors, inherent to the patient, have been the main causes of death, such as: advanced age, chronic kidney failure or the CIED infection itself.[18] This study confirmed that the presence of renal failure, the advanced functional class for heart failure and the presence of CIED infection are independent mortality predictors within 30 days. Procedure related factors, such as the need of another procedure for the extraction and the occurrence of major intraoperative complications were also mortality predictors. The identification of the presence of ICD lead as a protective factor called our attention, because it contradicts what has been shown in the literature. The detailed observation of the study population, however, explained this findind: ICD patients were, in general, 10 years younger, with lower rates of device infection, which may have been a confounding factor.

Although the study sample is quite representative, it reflects the care practices of a single hospital, considered a reference center in transvenous lead extraction. Therefore, the results may have been influenced by the surgical staff experience level and by the specific infrastructure available for this type of procedure.

Due to the lack of incorporation of transvenous extraction using special techniques in the list of procedures performed in our public health system, this study was not designed to compare the results of the different extraction techniques, since the choice of the extraction tool was determined by its availability for each case. This type of comparison will be made in future researches carried out at our institution in partnership with centers of other locations in Brazil.

Conclusions

Our study showed that lead extraction is an effective and safe treatment, with 1.4% complications directly associated with the procedure. The expressive mortality rate, of 9.3% during the study observation, was a result, mainly, of prior infectious complications, related with the indication for the extraction procedure itself. Risk factors inherent to the patient and to the surgical procedure were identified, which will allow for the establishment of preventive strategies in the patients at a higher risk of presenting unfavorable events.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Costa R, Silva KR; Acquisition of data: Costa R, Silva KR, Crevelari ES, Nascimento WTJ, Nagumo MM; Critical revision of the manuscript for intellectual content: Costa R, Silva KR, Crevelari ES, Nascimento WTJ, Nagumo MM, Martinelli Filho M, Jatene FB.

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.

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Relationship between Pulse Wave Velocity and Cardiovascular Biomarkers in Patients with Risk Factors

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Abstract

Background: **The relationship between pulse wave velocity (PWV) and biomarkers of structural changes of the left ventricle and carotid arteries remains poorly understood.**

Objective: **To investigate the relationship between PWV and these biomarkers.**

Methods: **This was an analytical, retrospective, cross-sectional study. Medical records of patients with diabetes mellitus, dyslipidemia, and pre-hypertension or hypertension, who underwent central blood pressure (CBP) measurement using Mobil-O-Graph®, and carotid doppler or echocardiography three months before and after the CBPM were analyzed. Statistical analysis was performed using Pearson or Spearman correlation, linear bivariate and multiple regression analysis, and the t test (independent) or Mann-Whitney test. A p <0.05 indicated statistical significance.**

Results: **Medical records of 355 patients were analyzed, mean age 56.1 (±14.8) years, 51% male. PWV was correlated with intima-media thickness (IMT) of carotids (r=0.310) and left ventricular septal thickness (r=0.191), left ventricular posterior wall thickness (r=0.215), and left atrial diameter (r=0.181). IMT was associated with PWV adjusted by age and peripheral systolic pressure (p=0.0004); IMT greater than 1 mm increased the chance of having PWV above 10 m/s by 3.94 times. PWV was significantly higher in individuals with left ventricular hypertrophy (p=0.0001), IMT > 1 mm (p=0.006), carotid plaque (p=0.0001), stenosis ≥ 50% (p=0.003), and target-organ damage (p=0.0001).**

Conclusion: **PWV was correlated with IMT and echocardiographic parameters, and independently associated with IMT. This association was stronger in individuals with left ventricular hypertrophy, increased IMT, carotid plaque, stenosis ≥ 50%, and target organ damage. (Arq Bras Cardiol. 2020; 115(6):1125-1132)**

Keywords: **Cardiovasclar Diseases/mortality; Blood Pressure; Risk Factors; Hypertension; Left Ventricle Dysfunction; Diabetes Mellitus.**

Introduction

The high prevalence and mortality of cardiovascular diseases (CVD) highlights the urgent need to implement tools to better stratify cardiovascular risks, to identify patients at high risk, and to diagnose and treat CVD in early stages. One of these tools are cardiovascular biomarkers, which can detect CVD in a subclinical phase with good accuracy, thereby improving the prevention of events and the epidemiological scenario.[1,2]

Some of the main biomarkers related to vascular structure and function are intima-media thickness (IMT), the presence of carotid plaques, pulse wave velocity (PWV), and the ankle-brachial index (ABI).[2] In addition, other cardiovascular biomarkers are used to identify target-organ damage (TOD), such as left ventricular hypertrophy, elevated serum creatinine levels, increased albumin excretion, and reduced glomerular filtration rate.[3,4]

PWV, a vascular damage biomarker used to assess arterial stiffness, is considered a strong and independent marker of TOD and adverse events.[5] PWV is also a predictor of all-cause mortality, indicating the patient's actual risk.[6] Each one meter per second rise in PWV leads to an increases by 14% in the risk of adverse events and by 15% in the cardiovascular risk and all-cause mortality.[6] Among its advantages, PWV is non-invasive, easily performed, relatively inexpensive, and widely validated method[2] with clearly established reference values.[7,8] Despite this evidence, PWV remains underused in clinical

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practice, and few studies have analyzed its relationship with other biomarkers, specially using oscilometric method. Thus, the objective of this study was to investigate the relationship between PWV and other biomarkers of cardiovascular structural changes in patients with cardiovascular risk factors.

Methods

Participants

From September 2012 to March 2017, 660 central blood pressure (CBP) measurements were performed. Among these evaluations, 131 patients performed the examination two times or more, for a total of 169 repeated evaluations. Therefore, the study population consisted of 491 patients that underwent CBP measurement to restratify patients considered as low or intermediate cardiovascular risk.

The sample was calculated considering a 5% error and a 95% confidence level, indicating a minimum sample of 216 patients. Finally, the study sample consisted of 355 Brazilian patients referred to cardiology clinic for CBP measurements (Figure 1).

Study Design and Procedures

This analytical, retrospective, cross-sectional study was performed by analysis of medical records and test reports. Data were first collected from the medical records contained in the institutional archives. The following exclusion criteria were applied: age younger than 18 years; absence of the following diagnoses: diabetes mellitus (DM), dyslipidemia (DLP), pre-hypertension (PH) or hypertension (HT); absence of a carotid Doppler or an echocardiography in the three months before and after CBP measurement (Figure 1).

Then, the diagnoses of all patients were retrieved from the medical records; when the diagnoses were not available, the diagnostic criteria were used – fasting blood glucose levels > 125 mg/dL or use of hypoglycemic drugs for DM; triglyceride levels > 150 mg/dL and low-density lipoprotein (LDL) > 100 mg/dL and/or high-density lipoprotein (HDL) < 40 mg/dL and/or current use of statins were considered dyslipidemic. Individuals with peripheral systolic blood pressure (SBP) ranging from 121 to 139 mmHg and DBP ranging from 81 to 89 mmHg, obtained during CPB measurement procedures, were classified as pre-hypertensive and those with blood pressure equal to or higher than 140/90 mmHg were classified as hypertensive.[4]

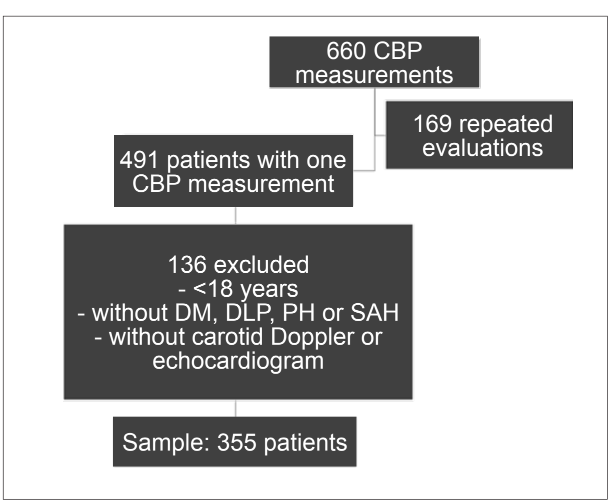

Figure 1 – *Study sample selection flowchart. CBPM, central blood pressure measurement; DM: diabetes mellitus; DLP: dyslipidemia; PH: pre-hypertension; HT: hypertension.*

Data on the following other variables were collected from the medical records: sex (female or male), tobacco smoking (yes or no) and marital status (with partner or without partner). In addition to the results of imaging tests, results of carotid Doppler and/or echocardiogram studies conducted in the three months before or after the CBP examination were analyzed. When those studies were performed more than once in this period, results of the last test before the CBP measurement was considered for analysis.

Central Blood Pressure Measurement

CBP was measured non-invasively using the validated oscilometric Mobil-O-Graph NG (IEM, Stolberg, Germany) with inbuilt ARCSolver algorithm.[10] All the CBPM procedures were performed by the same person, always between 1 p.m and 2 p.m. The measurements were made using triple pulse wave analysis and calibration MAD-c2 (mean arterial diastolic blood pressure).[9,10]

Chronological age was calculated as the difference between the date of birth and the date of the CBP measurement. Weight (kg) and height (m) were used for body mass index calculation (using Quetelet formula)[11] and its subsequent classification.[12] Peripheral SBP (SBPp), peripheral DBP (DBPp), central SBP (SBPc), augmentation index (AIx), and PWV were also analyzed.[13] All patients were instructed not to smoke or drink coffee before the test.

Carotid Doppler and Echocardiogram

Imaging examinations were performed at different imaging centers, determined by patient's choice. Those performed at the cardiology clinic where data collection was performed, were conducted using the Philips HD 11 ultrasound machine.

The carotid Doppler was performed following the American[14] and European[15] consensus guidelines, and the highest values obtained from the left and right common carotid arteries were considered for statistical analysis purposes.

Echocardiographic parameters were assessed by two-dimensional transthoracic echocardiography,[16] measuring the left ventricular septal thickness (LVST), the left ventricular posterior wall thickness (LVPWT), and the left atrial diameter (LAD).

Target-organ Damage

The identification of TOD was based on the presence of increased IMT,[17] atheroma plaques in the carotid Doppler,[3,4] left ventricular hypertrophy (LVH) in the echocardiogram,[18] and increased arterial stiffness identified by a PWV higher than 10 m/s[3,4] (Figure 2).

Imaging test	Sex / Age group	Reference values
Echocardiography[17]	Women	LVST > 0.9 mm LVPWT > 0.9 mm LAD > 38 mm
	Men	LVST > 1.0 mm LVPWT > 1.0 mm LAD > 40 mm
Carotid Doppler	Men or Women	IMT > 1 mm[16]
		Atheroma plaques[3,4]
Central blood pressure measurement	Men or Women	PWV > 10 m/s[3,4]

Figure 2 – *Examinations and reference values considered indicative of target organ damage. LAD: left atrial diameter; IMT: intima-media thickness; LVPWT: left ventricular posterior wall thickness; LVST: left ventricular septal thickness; PWV: pulse wave velocity.*

Statistical Analysis

Data were collected and scanned in duplicate by two researchers, using Epidata software, version 3.1. After assessing and correcting inconsistencies, the data were exported to the Statistical Package for Social Science (SPSS), version 18.0. The Kolmogorov-Smirnov test was applied, and a descriptive data analysis was performed. Statistical analysis was performed based on data distribution, using parametric and non-parametrical tests. Numeric data were described as mean and standard deviation or median and interquartile range, depending on data distribution. Categorical variables were presented with absolute and relative frequencies. The Pearson product-moment correlation or Spearman's rank-order correlation were used to assess the correlation of PWV with the results of the carotid Doppler and the echocardiogram. Correlations were classified in weak ($0 < r < 0.30$), moderate ($0.30 \leq r < 0.60$), strong ($0.60 \leq r < 0.90$) and very strong ($0.90 \leq r < 1$).[19]

The association between PWV and the other biomarkers (IMT, LVST, LVPWT, LAD) was assessed by linear bivariate regression analysis and those variables with p<0,020 were used in multiple regression analysis. All assumptions were met for the application of linear regression analysis. PWV was compared by IMT size, with the presence or not of LVH, with the presence or not of plaque, with plaque size, and with the presence or not of TOD using the *t* test for independent samples or Mann-Whitney test. Values of p<0.05 were considered statistically significant.

Ethical Aspects

The study was conducted in accordance with the 466/12 resolution of the Brazilian National Council of Health and was approved by the Ethics Committee of the Hospital das Clínicas da Universidade Federal de Goiás (UFG), under approval number 1.500.463.

Results

In total, 355 individuals with a mean age of 56.1 (±14.8) years participated in this study. Most of them had dyslipidemia and/or arterial hypertension, 148 (41.7%) were overweight and 130 (36.6%) were obese (Table 1).

A moderate and positive correlation was found between PWV and IMT; and positive and weak correlations were identified between PWV and LVST, and between LVPWT and LAD (Table 2).

IMT was associated with PWV adjusted by age and peripheral systolic pressure (p=0.0004), such that IMT greater than 1 mm increased by 3.94 the chance of having PWV above 10 m/s (Tables 3 and 4).

PWV was significantly higher in individuals with LVH, higher IMT, in those with carotid plaque, in those with stenosis equal to or greater than 50%, and in those with TOD (Table 5).

Discussion

In the present study, PWV was correlated with all biomarkers evaluated, and associated with IMT even when

Table 1 – Sample characterization (n=355)

Variables	Mean (SD) / Median (25%-75%) / n (%)
Age	56.1 (±14.8)
BMI	28.7 (±4.9)
SBPc	113 (107-123)
AIx	21.5 (±13.4)
PWV	8.2 (±2)
Sex	
Male	181 (51%)
Female	174 (49%)
Marital status	
With partner	251 (70.7%)
Without partner	102 (28.7%)
CVRF	
Overweight	148 (41.7%)
Obesity	130 (36.6%)
Tobacco smoking	12 (3.4%)
Diagnosis	
Dyslipidemia	306 (86.2%)
Arterial hypertension	283 (79.7%)
Diabetes mellitus	65 (18.3%)
Pre-hypertension	47 (13.2%)

AIx: augmentation index; BMI: body mass index; CVRF: cardiovascular risk factors; PWV: pulse wave velocity; SBPc: central systolic blood pressure.

Table 2 – Correlation of pulse wave velocity with cardiovascular biomarkers

		IMT (n=178)	LVST (n=313)	LVPWT (n=312)	LAD (n=312)
PWV	r	0.310†	0.191†	0.215†	0.181‡
	p	<0.001*	0.001*	<0.001*	0.001*

p < 0.05. †Spearman's rank-order correlation; ‡Pearson product-moment correlation. IMT: intima-media thickness; LAD: left atrial diameter; LVPWT: left ventricular posterior wall thickness; LVST: left ventricular septal thickness; PWV: pulse wave velocity.

Table 3 – Linear bivariate regression analysis of pulse wave velocity with the cardiovascular biomarkers

Variables	OR	95%CI (OR)	p
LVST	2.49	1.38 – 4.49	0.003*
IMT	3.94	1.53 – 10.15	0.004*
LVPWT	2.34	1.29 – 4.22	0.005*
LAD	2.55	1.18 – 5.49	0.017*

*Linear bivariate regression analysis. CI: confidence interval; IMT: intima-media thickness; LAD: left atrial diameter; LVPWT: left ventricular posterior wall thickness; LVST: left ventricular septal thickness; OR, odds ratio; * p < 0.05.*

adjusted for age and peripheral systolic pressure. The chance of having PWV above 10 m/s increases by 3.94 times in the presence of IMT greater than 1 mm. PWV have had a linear increment with the presence and size of atheroma plaque and with the presence of TOD. These findings are in accordance with previously published studies,[2,20,21] and reinforce the value of this biomarker and its ability to identify early cardiovascular damage, in addition to its excellent cost-effectiveness.

The correlation of PWV with echocardiographic parameters observed in the present study may be explained by the fact that arterial stiffness increases the SBP, and, consequently, the reflected wave returns early and arrives in systole instead of diastole, increasing the post-load of the left ventricle. This increased workload imposed on the myocardium promotes cardiac myocyte hypertrophy, resulting in ventricular hypertrophy.[22-24]

LVH, which may be identified by an increase in left ventricular wall thickness on echocardiogram, is correlated with PWV, and PWV values are significantly higher in individuals with LVH.[22,23] The increase in the load imposed on the left ventricle is one of the main causes of cardiovascular events related to CBP.[25]

Many studies show not only a correlation[26-28] but also an association between arterial stiffness and LVH.[22,23,29-32] Therefore, increased arterial stiffness may be used as a

Table 4 – Multiple regression analysis of pulse wave velocity with the cardiovascular biomarkers

Variables	Adjusted OR	95%CI (OR)	p	Adjusted OR*	95%CI (OR)	p
LVST	1.64	0.59-4.5	0.340	-	-	-
IMT	3.94	1.53- 10.15	0.004	6.86	1.78-26.45	<0.001
LVPWT	1.69	0.64-4.49	0.294	-	-	-
LAD	1.34	0.27-6.80	0.705	-	-	-

*Multiple regression analysis. CI: confidence interval; IMT: intima-media thickness; LAD: left atrial diameter; LVPWT: left ventricular posterior wall thickness; LVST: left ventricular septal thickness; OR, odds ratio; * p < 0.05.*

Table 5 – Comparison of pulse wave velocity according to carotid Doppler variables and presence or not of target organ damage

Variable	Group	n	PWV	CI	p
LVH†	No	212	7.6	7.55 - 8.03	<0.0001*
	Yes	105	9.1	8.74 – 9.53	
IMT‡	≤ 1 mm	152	8.07	7.79 - 8.35	0.006
	> 1 mm	26	9.12	8.32 - 9.90	
Presence of plaque‡	No	82	7.44	7.14 - 7.75	<0.0001*
	Yes	172	9.09	8.83 - 9.35	
Plaque size‡	< 50%	146	8.92	8.64 - 9.20	0.003
	≥ 50%	25	10.0	9.42 - 10.63	
Target organ damage,‡**	No	118	6.9	6.62 - 7.12	<0.0001*
	Yes	237	8.9	8.69 - 9.17	

*CI: confidence interval; IMT: intima-media thickness; LVH: left ventricular hypertrophy; PWV: pulse wave velocity. *p < 0.05. † Mann-Whitney test. ‡ t-test for independent samples. ** IMT>1mm, presence of plaque, LVH or PWV > 10 m/s.*

predictor of LVH, contributing to the prevention and diagnosis of this condition.[23]

In our study, PWV was not independently associated with LVST, LVPWT, or LAD, perhaps because the association analysis was not performed between hypertrophy itself and PWV, as in the studies cited, but rather between echocardiographic parameters and PWV. Furthermore, one of the studies cited[22] used electrocardiographic and not echocardiographic findings, and most studies performed this association analysis based on the left ventricular mass index.[23,28,30,32]

The relationship between the increases in arterial stiffness and the increases in IMT can be explained by the pathophysiology of arterial stiffness, which encompasses changes in the extracellular matrix of the middle layer (tunica media), including elastin breakdown, collagen deposition, and reticulation.[24,33] Those morphological changes are also related to vascular aging.[34]

Increased IMT is also associated with the presence of risk factors for arteriosclerosis; and age, arterial blood pressure, serum lipids, and fasting blood glucose levels are all independent predictors of carotid atherosclerosis.[35] Increased IMT is one of the first subclinical manifestations of arteriosclerosis.[36] The presence of multiple cardiovascular risk factors is independently associated with increases in IMT and decreases in arterial compliance.[37]

The correlation[38] and association of IMT with PWV was also previously reported in an elderly population.[38,39]

The assessment of IMT and PWV can improve cardiovascular risk reclassification, and these biomarkers may be used to identify subclinical TOD.[40] The combination of these biomarkers increases the predictive power of cardiovascular events among elderly people, providing additional and important clinical information.[41]

Significantly higher PWV values were also identified in individuals with stenosis equal to or greater than 50% in the present study. Higher PWV values were also significantly associated with the presence of carotid plaques.[36] Furthermore, decreased carotid elasticity is associated with the presence of plaques and the risk of stroke.[42]

The combined assessment of IMT and the presence of plaques improves the prediction of cardiovascular risk, and the quantitative evaluation of plaques further increases the predictive sensitivity.[43] Moreover, femoral carotid PWV and the number of atheroma plaques are significantly and independently associated with cardiovascular death and can improve the identification of individuals at high cardiovascular risk.[44]

In addition to the associations between PWV and biomarkers, the significant difference in PWV found between study subjects with and without TOD highlights the capacity of PWV to early identify the damage. Arterial stiffness is an independent predictor of mortality for both diabetics and the general population, and it is related to TOD development and progression.[45]

Arterial stiffness, assessed by PWV, is independently associated with the presence of subclinical TOD, including coronary artery calcification, reduced ankle-brachial index (peripheral arterial disease), and white matter hyperintensity (cerebral arterial disease).[46]

When TOD is present and is not identified, many patients are wrongly classified as medium-to-low risk when they are actually at high cardiovascular risk.[47]

Diagnostic tools must be improved and established for the early identification of increased risk, to prevent the onset of TOD and its complications. The appropriate identification of low-risk individuals is equally as important to avoid unnecessary treatments and their concomitant side effects.[48] The use of vascular biomarkers is a cost-effective, value-added method of improving the identification of individuals at high cardiovascular risk, thereby facilitating the prevention of CVD.[44]

The limitations of this study are as follows: when diagnosis of diabetes mellitus, dyslipidemia, and arterial hypertension was not available in the medical records, the diagnosis was made during the study, on an ad hoc basis, which may have under- or overestimated the frequencies of those diseases. Some exposure variables were missing from the medical records. In addition, we cannot ensure that all patients underwent carotid Doppler and echocardiography at the same clinic and with the same evaluator. Hypertrophy could not be detected by the ventricular mass index, since this information was not available in the medical records.

The medical records and diagnostic criteria were reviewed with scientific rigor, and the data were reviewed by two researchers and subsequently crosschecked. All these procedures should suffice to validate the findings.

The present study highlights the importance of using PWV for the early detection of arterial stiffness and TOD, focusing on increases in IMT, the presence of carotid plaques, and LVH. Overall, the use of PWV may optimize the stratification of cardiovascular risk to facilitate early intervention and prevent CVD and its complications.

Conclusions

PWV was significantly correlated with IMT and echocardiographic parameters and was associated with IMT. Furthermore, an IMT greater than 1 mm increased the chance of having PWV above 10 m/s by 3.94 times. PWV was significantly higher in individuals with LVH, IMT greater than 1 mm, in those with stenosis equal to or greater than 50%, and in those with TOD.

Author Contributions

Conception and design of the research: Fagundes RR, Vitorino PVO, Barroso WKS; Acquisition of data: Fagundes RR, Lelis ES; Analysis and interpretation of the data: Fagundes RR, Vitorino PVO, Lelis ES, Cunha PMGM, Barroso WKS; Statistical analysis and Writing of the manuscript: Fagundes RR, Vitorino PVO; Critical revision of the manuscript for intellectual content: Fagundes RR, Vitorino PVO, Lelis ES, Jardim PCBV, Souza ALL, Jardim TSV, Cunha PMGM, Barroso WKS.

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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Parameters of Central Hemodynamics as New Biomarkers of Cardiovascular Risk

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Short Editorial related to the article: Relationship between Pulse Wave Velocity and Cardiovascular Biomarkers in Patients with Risk Factors.

Historically, the importance of the arterial pulse wave was already observed by the Egyptians and the Chinese, before Christ. The knowledge of peripheral hemodynamics showed great progress after the introduction of non-invasive blood pressure (BP) measurement using the sphygmomanometer about 120 years ago and, to date, brachial BP represents an excellent predictor of cardiovascular morbidity and mortality.[1] However, changes in macro and microcirculation cannot be completely observed only by peripheral BP measurement. Thus, structural and functional vascular changes can be better assessed by central hemodynamic parameters, represented by central BP, augmentation index and pulse wave velocity (PWV),[2,3] with OPV being the gold standard in the assessment of arterial stiffness.[4] The reference prognostic value of central hemodynamics was clinically demonstrated by the CAFE study (Conduit Artery Function Evaluation Study), which showed that a greater reduction in central BP compared to peripheral BP resulted in a greater reduction in cardiovascular events.[5]

In turn, other studies associated the role of PWV with the presence of cardiovascular and cerebrovascular lesions, so this topic was included in the European guidelines for hypertension in 2007.[6] PWV was first used as a clinical index of arterial elasticity in 1922, but its determination too long to be applied to clinical practice because its registration and calculation were difficult to obtain. Aortic stiffness, measured by carotid-femoral PWV, has been the most used in epidemiological studies. Obtaining PWV in the carotid-femoral segment is simple, non-invasive, reproducible, widely accepted and clinically relevant, as it includes the aorta, an important segment in relation to the pathophysiological effects of arterial stiffness. Currently, PWV can be considered a biomarker of cardiovascular risk[7] and is a predictor of cardiovascular events and mortality.[8,9]

The concept of organic lesion markers has been introduced in the past decades. A biomarker is a variable measure that presents itself as a substance found in a biological sample or can be evaluated by imaging tests. A biomarker can reflect the pathophysiology of the disease, predict future events or indicate the presence of subclinical or clinical disease. A biomarker can also be measured to assess the response to the treatment established. Occasionally, a marker can function as an etiological or risk factor.[10]

BP is recognized as a universal biomarker for systemic arterial hypertension (SAH). BP measurement defines the condition of hypertension, guides the therapeutic approach and assesses responses to the treatment established. Additional biomarkers offer the possibility of reclassifying individuals, especially in the intermediate risk categories, with a greater or lesser risk of target organ damage than that estimated by BP alone. Thus, providing information regardless of BP and other classic risk factors is one of the basic requirements for a biomarker that can serve as an instrument for restructuring risk, as proposed in the article presented in this edition. Fagundes et al. investigated the relationship between biomarkers of subclinical lesions based on the relationship between PWV and biomarkers of left ventricular hypertrophy (interventricular septum thickness and left ventricular posterior wall thickness, and left atrial diameter) and a vascular marker [carotid intima-media thickness (cIMT)]. They demonstrated that PWV correlated with cIMT and with the echocardiographic parameters above, showing an independent association with cIMT, that is, cIMT above 1 mm increased by about 4 times the chance of PWV greater than 10 m/s, a cutoff point above which the risk of cardiovascular events increases.[11]

Besides, the use of other parameters of central hemodynamics, such as central BP, is able to detect different SAH phenotypes with brachial BP and to classify cardiovascular risk more reliably. Chuang et al.,[12] showed, in an adult population, four distinct BP phenotypes based on the measurements of peripheral pressure and central BP, that is, concordant brachial and central normotension, isolated brachial hypertension, isolated central hypertension and concordant brachial and central hypertension. They also demonstrated that the concordant increase of the two pressures led to a greater risk of coronary artery disease in 10 years compared to the increase of only one of the evaluated pressures. The study also showed that the detection of SAH by the conventional method alone underestimated the real prevalence of hypertension, compared to the combined use of the two forms of BP assessment.[12] In another study with elderly aged 65, combined brachial and central hypertension was significantly associated with cardiac (left ventricular hypertrophy and diastolic dysfunction), vascular (PWV) and renal (albumin/creatinine ratio) compared to isolated peripheral and central measures.[13]

Keywords

Hypertension; Blood Pressure; Hemodynamic; Risk Factors; Pulse Wave Analysis; Vascular Diseases/prevention and control.

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Short Editorial

Thus, peripheral BP remains the best biomarker in the management of patients with SAH; however, it provides incomplete information about the pathogenesis and involvement of target organs, and may not represent the best means of assessing the therapeutic response established. New modalities of biomarkers, represented by the parameters of central hemodynamics, will help to individualize preventive and therapeutic strategies in individuals with hypertension. BP will not be replaced by other biomarkers, but it can be supplemented by markers that provide additional information.[14]

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Original Article

Effect of Heroin on Electrocardiographic Parameters

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Abstract

Background: **Heroin addiction is currently a significant health problem, and information on the electrocardiographic effects of heroin is limited.**

Objetivo: **The aim of the present study is to investigate effects of heroin addiction on electrocardiographic parameters.**

Methods: **A total of 136 individuals, including 66 individuals who smoke heroin as the study group and 70 healthy individuals with no drug addiction as the control group, were included in the study. Individuals who inject heroin were excluded. Electrocardiographic (ECG) evaluation of those using heroin was performed and compared with those of the control group. In addition, pre-treatment and post-treatment ECG of the heroin group were compared. A p-value of <0.05 was accepted as statistically significant.**

Results: **Heart rate (77.2±12.8 *versus* 71.4±11.2; p=0.02) were found to be higher in the heroin group compared to the control group. QT (341.50±25.80 *versus* 379.11±45.23; p=0.01), QTc intervals (385.12±29.11 *versus* 411.3±51.70; p<0.01), and T peak to end time (Tpe) (65.41±10.82 *versus* 73.3±10.13; p<0.01) were significantly shorter in the heroin group. No difference was observed between the groups with regard to Tpe/QT and Tpe/QTc ratios. In the subgroup analysis of the heroin group, QT (356.81±37.49 *versus* 381.18±40.03; p<0.01) and QTc (382.06±26.41 *versus* 396.06±29.80; p<0.01) intervals were significantly shorter in the pre-treatment period.**

Conclusion: **Heroin addiction significantly affects the QT, QTc, and Tpe time intervals. The arrhythmia effects of these parameters are well known. More attention to the electrocardiographic parameters of these individuals should be given. (Arq Bras Cardiol. 2020; 115(6):1135-1141)**

Keywords: **Heroin; Heroin Dependence; Narcotics/toxicity; Long Qt Syndrome; Arrhythmias, Cardiac/adverse effects; Pulmonary Edema; Renal Insufficiency; Leukoencephalopaties.**

Introduction

Heroin, which is a central nervous system depressant (diacetylmorphine), is a semi-synthetic opiate. Heroin is a highly abused opioid, and heroin addiction incurs a significant detriment to society worldwide. The prevalence of heroin use has increased in recent years. Mortality among heroin users varies between 1 and 3%, and the most effective treatment method of heroin addiction is opioid replacement therapy.[1,2] Its main adverse effect is respiratory distress, which can lead to death. With loss of tolerance, heroin overdose can be lethal after a period of abstinence. The other various complications of heroin addiction, such as pulmonary edema,[3] shock,[4] myocardial damage, acute renal failure,[5] rhabdomyolysis,[6] and leukoencephalopathy[7] have been described in the literature. Besides that, heroin has proved to be effective on vagal modulation and autonomic regulation.[8] However, our knowledge of the cardiac effects of heroin addiction is limited, which is an important public health problem of this extent. There are also some studies in the literature showing the relation between heroin, myocardial toxicity, and arrhythmias.[9,10] Therefore, understanding heroin dependent ECG changes is essential. The aim of the present study is to investigate effects of heroin addiction on electrocardiographic parameters.

Methods

After approval by the Ethics Committee, a total of 136 individuals were included in the study, which included 66 patients who use heroin via smoking and undergoing therapy in the Alcohol and Drug Addiction Treatment and Training Center, between 2014 and 2017, as the study group; and 70 healthy individuals with no drug addiction other than smoking as the control group. Control group was selected consecutively from the patients visiting the cardiology clinic. ECG evaluation of those using heroin was performed and compared to those of the control group. In addition, pre-treatment and post-treatment ECG of the heroin group was evaluated. The clinical and demographic characteristics of patients, status and duration of heroin addiction were collected from patients and their files in the hospital. Only those with heroin use via smoking were included in the study. Electrocardiography (ECG) records of patients were obtained with Schiller Cardiovit AT-102 plus, using the standard 12 derivation (10 mm/mV calibration and

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25 mm/s sliding rate) at first admission to the hospital. Only the patients on heroin which was taken within 12 hours of the ECG records obtained were included the study. ECG measurements of QT and Tpe intervals were performed manually by two expert cardiologists, using a magnifying glass to decrease measurement errors. Leads 2 and V5 were selected for measuring QT and Tpe intervals, respectively. The average of the three beats in each ECG leads was calculated. QT interval is calculated as the interval from the beginning of the QRS to the end of the T wave. Tpe interval is defined as the interval from the peak of T wave to the end of T wave. QTc intervals were calculated using the Bazett formula. Complete blood count (CBC) and biochemical tests were performed using a Beckman Coulter LH-750 and a Beckman Coulter L × 20, respectively; the results of each patient were recorded. Echocardiographic evaluations of all patients were made at the first admission to the hospital. All participants underwent 2D and Doppler echocardiographic evaluation (VIVID 3, General Electric, USA) and the left ventricular ejection fraction was calculated using modified Simpson rules. Those who used heroin via the intravenous route, alcohol-dependent, those with coronary artery diseases, cardiac failure, cardiac valve disorders, known arrhythmias, hypertension, congenital cardiac diseases, diabetes, hepatic or renal failure, chronic obstructive pulmonary disease, endocrine diseases, metabolic or electrolyte disorders, acute or chronic infections, or patients that took medications which can affect QT and QTc intervals were excluded from the study.

Statistical Analysis

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) programs. Data compliance with the normal distribution was tested using the Kolmogorov-Smirnov test. The normally distributed numeric variables were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. For the comparisons between the heroin and the control groups, unpaired student's t test was used. Chi-square and Fisher's exact tests were carried out to compare categorical variables. For the comparisons of both the pre-treatment and post-treatment periods, McNemar's test and t-test paired samples were used. A *p*-value of <0.05 was accepted as statistically significant.

Results

The distribution of the study population (n=136, mean age 30.40±9.58) was as following: 66 (48.52%) Heroin (+) and 70 (51.47%) Heroin (-). Females corresponded to 8.82% of the study population. There was no significant difference in the distribution of mean age between groups. In the heroin group, the mean duration of heroin use was five years. Statistically, there are not significant differences between the groups, related to the gender, smoking, left ventricular ejection fraction, and cerebrovascular disease. No difference was determined in the other demographic and laboratory characteristics between both groups (Table 1).

Comparison of the electrocardiographic findings between the groups revealed that there was no statistically difference between the groups in terms of PR period, nonspecific ST segment-T wave changes, QRS and R wave peak time durations. In heroin (+) group, QT (341.50±25.80 *versus* 379.11±45.23, p<0.01) and QTc (385.12±29.11 *versus* 411.3±51.70, p<0.01) intervals were significantly shorter than heroin (-) group. T-peak to T-end time was significantly shorter in the heroin (+) group, compared to the heroin (-) group (65.41±10.82 *versus* 73.3±10.13, p<0.01). No significant difference was observed between both groups in terms of Tpe/QT and Tpe/QTc ratios (Table 2).

A total of 16 patients completed the treatment successfully. In the subgroup analysis of this group, QT (356.81±37.49 *versus* 381.18±40.03, p<0.01) and QTc (382.06±26.41 *versus*

Table 1 – Groups' Baseline Characteristics and Laboratory Findings

Variables	Heroin (+) (n= 66)	Heroin (-) (n= 70)	p-value
Baseline characteristics			
Age (years old), mean (SD)	30.2±10.1	30.6±9.1	0.808
Gender (female), n (%)	3(4.5%)	9(12.8%)	0.087
Current Smoker, n (%)	35(53.0%)	31(44.2%)	0.307
Coronary Artery disease, n (%)	0	0	-
Hypertension, n (%)	0	0	-
Diabetes Mellitus, n (%)	0	0	-
Cerebrovascular Disease, n (%)	1(1.5%)	2(2.8%)	0.594
Left ventricular ejection fraction (%)	59.8±2.9	60.4±9.4	0.620
Laboratory Findings			
Sodium (mmol/dl; SD)	139.48±4.81	140.37±5.20	0.302
Potassium (mmol/dl; SD)	4.32±0.51	4.45±0.65	0.198
Calcium (mg/dl; SD)	9.45±0.82	9.53±0.93	0.596
Magnesium (mg/dl; SD)	1.99±0.30	2.02±0.26	0.533
Creatinine (mg/dl; SD)	0.77±0.22	0.72±0.23	0.197
HDL-C (mg/dl; SD)	37.61±8.45	38.89±10.53	0.437
LDL-C (mg/dl; SD)	137.74±39.81	125.66±45.14	0.101
Triglyceride (mg/dl; SD)	155.42±96.50	163.44±85.55	0.608
WBC (x10^3 /µL; SD)	6.89±4.03	7.12±4.35	0.750
Hemoglobin (g/dL; SD)	14.31±4.38	14.53±2.74	0.724
Hematocrit, n (%;SD)	42.53±4.11	42.88±5.43	0.673
Platelets (x10^3 /µL; SD)	253.75±68.32	261.16±77.14	0.555
RDW%	15.23±2.06	13.88±1.78	0.001
TSH(uIU/mL)	2.12±1.77	2.16±1.98	0.896

** Independent Samples T-Test, chi-square Test, Fisher's Exact Test *p<0.05 statistically significant. Continues variables are reported mean ± SD). Categorical variables are reported n (%). HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; WBC: White Blood Cell; RDW: Red Cell Distribution Width; TSH: Thyroid Stimulating Hormone.*

Table 2 – ECG Findings of the Groups

ECG Findings	Heroin (+) (n= 66)	Heroin (-) (n= 70)	p-value
Heart Rate, beat/min	77.25±12.84	71.43±11.22	0.02
PR, msc	147.83±29.49	151.12±33.19	0.54
Nonspecific ST segment-T wave changes, n (%)	8(12.1%)	4(5.7%)	0.18
QRS, msc	98.82±19.53	100.50±19.87	0.49
QT, msc	341.50±25.80	379.11±45.23	<0.01
QTc, msc	385.12±29.11	411.3±51.70	<0.01
Tpe, msc	65.41±10.82	73.3±10.13	<0.01
R wave peak time, msc	32.18±8.16	34.22±9.32	0.17
Tpe/QT	0.19±0.03	0.2±0.03	0.70
Tpe/QTc	0.17±0.03	0.18±0.03	0.15

**Independent Samples T-Test, Chi-square Test, Fisher's Exact Test; Continues variables are reported as mean ± SD). Categorical variables are reported as n (%); p<0.05 statistically significant.*

Table 3 – ECG findings of treated patients

Variables	Before Treatment (n= 16)	After Treatment (n= 16)	p-value
Heart Rate, beat/min	79.06±9.08	74.81±8.37	0.02
PR, msc	148.75±18.65	150.01±19.15	0.13
Nonspecific ST segment-T wave changes, n (%)	3(18.7)	3(18.7)	1.00
QRS, msc	98.08±10.58	98.68±8.80	0.46
QT, msc	356.81±37.49	381.18±40.03	<0.01
QTc, msc	382.06±26.41	396.06±29.80	<0.01
Tpe, msc	64.75±8.10	66.37±9.68	0.28
R wave peak time, msc	33.06±4.80	33.93±5.10	0.42
Tpe/QT	0.18±0.02	0.17±0.02	0.18
Tpe/QTc	0.17±0.02	0.18±0.02	0.23

** McNemar's test, paired samples t-test. Continues variables are reported as mean ± SD, and categorical variables are reported as n (%); p<0.05 statistically significant.*

396.06±29.80, p<0.01) intervals were significantly shorter in the pre-treatment period. No difference was determined in the other electrocardiographic parameters between both the pre-treatment and posttreatment periods (Table 3).

Discussion

Today, heroin addiction is a significant health problem. However, despite that, information on the electrocardiographic effects of heroin is limited. To the best of our knowledge, the present study is the first in literature about heroin-dependent electrocardiographic changes. In this study, we showed that heroin addiction significantly affects QT, QTc, and Tpe time intervals.

Heroin addiction is responsible for cardiac events. The effect of heroin use on cardiac functions has been previously investigated in some studies. Heroin use was shown to significantly increase the rate of mitral and tricuspid valve abnormalities.[11] Demirkıran et al.[12] demonstrated that synthetic cannabinoids negatively affected the left ventricular function, whereas heroin did not.[12] Heroin use does not seem to have any effects on the left ventricular functions according to the results of these studies; on the other hand, atrial and myocardial irregularities with histopathological sampling[13] and interstitial myocardial leukocyte count, T lymphocyte and macrophage counts were observed to promote a five-fold increase in myocardial samples.[14] The cardiac effects of heroin are not limited to myotoxic effects. Pavlidis et al.[15] reported that myocardial infarction could be observed, even though rarely, in which the common mechanism is unknown.[15] Orlando et al.[16] reported a subclinical reduction in the ejection fraction of the left ventricle in 20 heroin-dependent individuals.[16] However, these studies do not provide any information about the effect of heroin addiction on electrocardiographic parameters. Furthermore, in studies investigating the mechanisms of heroin-related arrhythmias and subsequent sudden deaths, heroin use did not only lead to myocardial infiltration, but it also led to fibromuscular dysplasia in the sinus node, atrioventricular node and transmission pathways, and to fat infiltration; they concluded that this may be the cause of arrhythmia related to sudden death in heroin-dependent individuals.[9,10] Therefore, revealing heroin-dependent ECG changes has become even more important.

In one of the first studies on the electrocardiographic effects of heroin dependence, Glauser et al.[17] showed that the most common findings were nonspecific ST-T changes in 17 patients; sinus tachycardia, in 11 patients.[17] However, electrocardiographic parameters such as QT, QTc, Tpe time, and QSR durations have not been examined in this study. In a case report, authors showed that heroin overdose is a possible cause of Brugada phenocopy.[18] Although some studies have been performed on mice and dogs, there is not much literature information about electrocardiograms in humans. In the present study, heroin addiction was shown to significantly decrease QT, QTc, and Tpe time intervals. The short QT syndrome, such as QT prolongation, is also well known for its association to severe cardiac arrhythmias and sudden cardiac death.[19-21] In addition, the Tpe interval has been proposed as a non-invasive marker of arrhythmic risk. T-peak to T-end interval on the electrocardiogram (ECG) is a measure of myocardial dispersion of repolarization. Increasing evidence suggests that Tpe interval may predict arrhythmia susceptibility in patients with various cardiovascular diseases.[22] Marjamaa et al.[23] concluded that the minor allele of common variant rs7219669 is associated to Tpe interval shortening in two independent study populations, thus being a candidate to modulate arrhythmia susceptibility at population level.[23] In the present study, heroin use was found to have a significant effect on these important parameters. Heroin users show reduced cardiac vagal modulation, and methadone therapy raised vagal activity directly in individuals who had recently relapsed into heroin use.[8] In addition to the increased myocardium inflammatory findings, we also believe that this decrease in vagal activity may be responsible for ECG changes. Most studies on heroin addiction and ECG are about methadone. Methadone is used in the treatment of heroin addiction, and one of its most important known effects is the prolongation of QT and QTc durations.[24,25] Methadone is an inhibitor of the cardiac ion channel KCNH226 and causes QT prolongation in a dose-dependent manner.[26] On the other hand, it can increase vagal activity and prolong QT duration.[8] After the present study, we believe that a part of methadone's effects may be related to the neutralization of the heroin effect. Our study demonstrated that heroin addiction significantly changed QT, QTc, and Tpe intervals independent from the effect of adulterants and methadone. In addition to heroin dependent individuals, methadone is also known to prolong QT. However, in heroin user group, this result should be taken into consideration when discussing the QT prolonging effect of methadone in those who depend on heroin. Although the effect of heroin on potassium channels is unknown, the effect on vagal activity has been shown.[8] With these results, even though it is not responsible for all QT prolongation mechanism, we think that neutralizing heroin effects significantly contributes to QT prolongation. With the present study, we cannot explain exactly whether QT prolongation is the direct effect of methadone or the result of the neutralization of the heroin effect in previous studies. In terms of bringing a new point of view, it is an important subject in guiding the other studies. On the other hand, methadone is a complete opioid agonist, and overdose deaths are a major problem. Buprenorphine, a partial opioid agonist, has become an increasingly popular option in clinical practice in our country and all over the world. Buprenorphine is probably the safer agent due to its unique pharmacological action and has been declared a new dawn for treating heroin dependence with less abuse potential and low overdose risk.[27] Therapeutic doses of buprenorphine were shown to have no effects on QT and QTc duration,[28,29] and buprenorphine in commonly used doses is a suitable alternative to methadone, with regard to the risk of QTc prolongation.[30] Therefore, individuals from the present study were treated with buprenorphine instead of methadone. Buprenorphine had no significant effects on QT and QTc durations, which was one of our study advantages. Seen that, we observed the effects of heroin on ECG more clearly. When we look at the treatment subgroup, there is a significant change in QT and QTc durations because of heroin discontinuation. If these individuals were treated with methadone, understanding whether this effect was due to heroin or methadone would be very difficult. Unfortunately, like in other countries, the most important disadvantage in this subgroup is the proportion of patients who can complete medical heroin-addiction treatment, which is insufficient in our study.[31] Most patients could not complete the treatment, and that is why the number of individuals in the study subgroup decreased significantly. Although there was a significant change in QT and QTc in the post-treatment group, there was only a numerical increase in Tpe duration, and this increase did not reach statistical significance. We assume this is due to insufficient number of individuals who have completed the treatment. However, studies with a larger number of participants are needed to make a definite decision on this issue.

Heroin has an extremely short half-life in blood (less than five minutes), and is immediately converted to the active metabolite 6-acetylmorphine (6-AM), which is further metabolized to morphine.[32] In urine, active metabolite 6-AM can be detected for a longer period, possibly up to 12 hours.[33] Therefore, patients who had used heroin only in the last 12 hours were included in the present study. On the other hand, when heroin is used via the intravenous route, it is administered together with additional chemical substances, named as adulterants (acetaminophen, caffeine, diphenhydramine, methorphan, alprazolam, quetiapine, chloroquine, diltiazem, cocaine, procaine, lidocaine, quinine/quinidine, phenacetine, and thiamine), and the potential cardiac effects of these substances complicate the evaluation of heroin electrocardiographic effects.[34] Thus, in order to investigate the cardiac effects of only heroin, we excluded those who used heroin by intravenous injection. The present study demonstrated that heroin use significantly decreased the QT, QTc and Tpe intervals independent from the effect of adulterants.

Study limitations

Our study had some limitations: the single-center design and the relatively lower number of individuals are the most important ones.

Conclusion

Heroin use is a serious public health issue, which significantly affects the QT, QTc, and Tpe time intervals. The arrhythmia effects of these parameters are well known, and we should be more alert to the electrocardiographic parameters of these individuals. Given that the present knowledge on the effects of heroin use on cardiac functions is limited, studying the matter is imperative for its contribution to the literature. Nonetheless, further studies with larger sample sizes are needed for a consensus and clear results.

Author Contributions

Conception and design of the research: Yildirim E, Selcuk M, Saylik F, Deniz O; Acquisition of data: Selcuk M, Saylik F, Mutluer FO, Deniz O; Analysis and interpretation of the data: Yildirim E, Deniz O; Statistical analysis: Yildirim E, Saylik F, Mutluer FO; Writing of the manuscript: Yildirim E, Selcuk M; Critical revision of the manuscript for intellectual content: Yildirim E, Selcuk M, Mutluer FO.

Potential Conflict of Interest

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Study Association

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

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Heroin by Dreser x Eroica by Beethoven

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Short Editorial related to the article: Effect of Heroin on Electrocardiographic Parameters

As a Classical Music lover, I go to the São Paulo Concert Hall frequently. On my way to get there it's necessary to drive through an area with high density of addicts on streets, known as Crackland. In that moment I get to see closely the important negative social effects and damage of addiction in its users. Now I meet this issue in a different way, reading the paper: "Heroin and Electrocardiography- Effect of Heroin on Electrocardiography parameters"[1] that adds an incremental knowledge in the medical literature about heroin cardiac effects and searches for signals of when this occurs.

The authors of "Heroin and Electrocardiography- Effect of Heroin on Electrocardiography parameters"[1] make it clear that there is little scientific information published in this field. Research in the PubMed shows a 1980 reference called "ECG examinations 115 heroin addicts"[2] with no access to the abstract or the full-text contents. Very little was found about this specific topic since then. How can this be explained considering addiction has since then increased in alarming scale? Is there lack of interest by researchers in this area? Are there little financial resources for researchers? Logistical difficulties for studies in this field? Lack of interest in this social group?

The magnitude of the numbers is striking. Data from the "World Drug Report" published in 2019 by "The United Nations Office on Drugs and Crime (UNODC) reveals that 35 million people had some kind of disorder as a consequence of substance abuse and only one person in each seven received treatment.

Addiction leads to rampant use with risk of death. In the case of heroin, the risk of death is about 1-3% among the addicts and it is most frequently related to respiratory depression[3,4] although myocardial injury and arrhythmia can occur and may probably be underdiagnosed.[5,6]

The authors of "Heroin and Electrocardiography- Effect of Heroin on Electrocardiography parameters"[1] show an occurrence of abnormalities in the ventricular repolarization of heroin users, specifically decreased QT and QTc interval plus Tpe measure. These abnormalities were found in electrocardiograms performed in up to 12 hours after the use of heroin, the time of action of its active metabolit 6-acethilmorphine. These electrocardiograms abnormalities can be signalizing the predisposition to arrhythmic events in this group leading to therapeutic actions concerning to the rhythm disorders and the specific risks.

As the heroin dependence is high and its abstinence is unbearable, the therapeutic choice has always been the replacement by other less damaging opioids. In this way, methadone has been used as a substitute with less harmful effects than heroin. This fact has made it difficult to differentiate cardiac effects caused exclusively by heroin. It is also important to mention that the most frequent way of heroin use is intravenous and that many times it is mixed with adulterants which have cardiac effects. There are therefore multiple reasons why the exclusive cardiac actions of heroin were mostly unknown until now. The authors of "Heroin and Electrocardiography- Effect of Heroin on Electrocardiography parameters"[1] succeeded in isolating the heroin exclusive actions in ventricular repolarization electrocardiographic parameters by including in the study patients under treatment for addiction who were using buprenorphine, that is a partial agonist opioid that doesn't change the parameters of repolarization in the electrocardiogram. In this manner, they could compare the electrocardiogram of 16 patients in the use of heroin before and after they stopped the drug and they were able to find an increase of duration of QT and QTc after discontinuing the addiction. It is important to say that only 16 from 66 (24,24%) patients followed the therapy until the end, showing the low adherence to the treatment.

The authors of "Heroin and Electrocardiography- Effect of Heroin on Electrocardiography parameters"[1] have given us, in an elegant way, a new contribution for the knowledge in this area and they have made it clear that other studies will be necessary to clarify this issue completely.

In the field of Classical Music, this year we are celebrating 250 years of Ludwig Van Beethoven's birthday. He composed the famous "Eroica Symphony" in 1804. In 1895, a German researcher named Heinrich Dreser working for the pharmaceutic industry Friedrich Bayer & Co became interested in the potential therapeutic benefits of the diacetylmorphine and called it the "heroic drug". In 1898, the drug was launched in the market and it was called Heroin. This commercial name was adopted until 1924[7] when it was finally prohibited. And about Beethoven, we still keep on listening to his music until today.

Keywords

Street Drugs; Heroin; Cocaine; Pharmacology; Electrocardiography/methods; Analgesics Opioid/ therapeutic use.

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Original Article

Coronary Calcium Score and Stratification of Coronary Artery Disease Risk in Patients with Atherosclerotic and Non-Atherosclerotic Ischemic Stroke

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Abstract

Background: Ischemic Stroke (IS) and Coronary Artery Disease (CAD) frequently coexist and share atherosclerotic disease risk factors. According to the American Heart Association, IS subtypes may be considered CAD risk equivalents, but the evidence for non-atherosclerotic IS is uncertain. Additionally, the Coronary Calcium Score (CCS) is an accurate marker to address CAD risk; however, CCS distribution between IS subtypes is not well characterized.

Objectives: To compare the CCS between atherosclerotic and non-atherosclerotic IS groups; and to determine which covariates were associated with high CCS in IS.

Methods: This cross-sectional design included all patients with IS, 45 to 70 years of age at the time of the stroke, consecutively admitted to a rehabilitation hospital between August 2014 and December 2016, without prevalent CAD. All patients underwent CT scanning for CCS measurement. CCS≥100 was considered a high risk for CAD, with a significance level of $p<0.05$.

Results: From the 244 studied patients (mean age 58.4±6.8 years; 49% female), 164 (67%) had non-atherosclerotic etiology. The proportions of CCS≥100 were similar between the atherosclerotic and the non-atherosclerotic groups (33% [n=26] x 29% [n=47]; p= 0.54). Among all IS patients, only age ≥60 years was independently associated with CCS≥100 (OR 3.5; 95%CI 1.7-7.1), accounting for hypertension, dyslipidemia, diabetes, sedentarism, and family history of CAD.

Conclusion: Atherosclerotic IS did not present a greater risk of CAD when compared to non-atherosclerotic IS according to CCS. Only age ≥60 years, but not etiology, was independently associated with CCS≥100.

Keywords: Stroke; Coronary Artery Disease; Calcium Signaling; Dyslipidemias; Hypertension; Diabetes Mellitus.

Introduction

Ischemic Stroke (IS) and Coronary Artery Disease (CAD) are the leading causes of mortality worldwide.[1] The estimated simultaneous prevalence of both diseases could be as high as 70%, with any degree of CAD.[2] Additionally, the absolute risk of myocardial infarction is 2.2% per year in patients who had IS or transient ischemic attack,[3] and the risk of fatal cardiac events is approximately twice the risk of recurrent fatal stroke at 5 years after surviving stroke.[4]

This close relationship between IS and CAD may be explained by similar pathophysiology and risk factors for atherosclerosis in both diseases, like systemic arterial hypertension, dyslipidemia, and smoking, which share preventive and therapeutic goals. According to the American Heart Association and the American Stroke Association, IS subtypes may be considered CAD risk equivalents, but the evidence for non-atherosclerotic IS is uncertain.[5]

Large artery atherosclerosis is a frequent IS etiology, ranging from 9% to 24% of overall IS cases, alternating with cardioembolic and small vessel disease subtypes as the most prevalent IS causes,[6,7] depending on the cohort characteristics and risk factor distribution.[8,9] However, it is not well established whether non-atherosclerotic subtypes of IS are under the same level of CAD risk as atherosclerotic IS. Additionally, undiagnosed coronary atherosclerosis in IS patients varies in prevalence and severity. Angiographic coronary stenosis of greater than 50% is present in 26% of the patients with IS and no known history of CAD.[10] Alternatively, using the coronary calcium score (CCS) as a non-invasive risk stratification strategy, the prevalence of CAD in IS can be as high as 70%, in whom approximately one quarter are under a very high risk (CCS>400).[11]

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Therefore, this study aimed to cross-sectionally compare the CCS between atherosclerotic and non-atherosclerotic IS, as a marker of CAD risk. In addition, this study determined which covariates were associated with high CCS in IS, other then etiology. We therefore hypothesized that coronary calcium would be higher in atherosclerotic IS than in IS from other etiologies, serving as a valuable screening tool for risk stratification in IS.

Methods

This cross-sectional design included all patients with a diagnosis of IS, 45 to 70 years of age, at the time of the neurologic event, admitted consecutively at Brasília Unit of the Sarah Network of Rehabilitation Hospitals between August 2014 and December 2016. Patients with previous diagnosis of CAD were excluded, given that our target population was at-risk individuals and not with established disease. All patients signed the informed consent form prior to study enrollment. This study was approved by the institution's Ethics Committee.

IS was confirmed by clinical evaluation and an image method. Stroke etiology was classified by two independent neurologists, using a computerized system based on the Stop Stroke Study Causative Classification System (SSS-CCS) Trial of ORG 10172 in Acute Stroke Treatment (TOAST) available on line.[12,13] Disagreements were resolved by a third independent neurologist. For this analysis, all non-atherosclerotic etiologies were adjudicated in one group for logistic regression.

Etiological investigation included transthoracic echocardiography, chest radiograph, EKG, neuroimaging (MRI or CT), non-invasive intracranial vascular studies (magnetic resonance angiography, computed tomography angiography, and transcranial Doppler). If necessary, transesophageal echocardiography and 24-hour Holter monitoring were performed. Other exams were also requested upon clinical evaluation, such as complete blood count, renal function, screening for endemic diseases (HIV, syphilis, and Chagas' disease). In selected patients, thrombophilia (antithrombin III, protein C and S deficiency, search for antiphospholipid syndrome, prothrombin and factor V of Leiden mutations and homocysteine levels) was also investigated.

Coronary calcium score

All patients underwent CCS determination. A prospective axial image of the heart was acquired using multidetector computed tomography cuts of 3mm, synchronized with the EKG. Three models of CT scanners were used: Siemens Sensation 64, Siemens Perspective 128, and Siemens Definition. The images were analyzed in the Siemens Syngo Calcium Scoring software and the radiologists were blinded to the stroke etiology. Semiautomatic analysis of calcified plaques was performed with electronic identified images with more than 3 adjacent pixels with density greater than 130 Hounsfield Units.[14] High risk was defined as a CCS≥100, considered as a prognostically validated cut-off.[15–17] As a sensitivity analysis, the distribution of the lowest risk, defined as a CCS=0 between both IS groups, was also compared.

Characterization of the studied variables

Study variable were defined as follows:

Systemic Arterial hypertension: systolic arterial pressure more than 140 mmHg, diastolic arterial pressure more than 90 mmHg; use of antihypertensive drug.

Dyslipidemia: LDL more than 160 mg/dL or use of lipid-lowering agent.

Diabetes mellitus: fasting blood glucose more than 126 mg/dL or use of hypoglycemic agent and/or insulin.

Sedentary life style: less than 150 minutes of moderate exercise per week.

Obesity: body mass index more than 30 kg/m^2

Family history of premature CAD: first degree relatives with a diagnosis of CAD of < 50 years old in men and of < 65 years old in women.

Smoking: self-reported current use of cigarettes for at least one year or cessation of smoking for less than five years.

Modified Rankin Scale: used to measure the degree of disability or dependence in one's daily activities. This was calculated by one neurologist upon rehabilitation program admission.[18]

10 year atherosclerosis cardiovascular disease (ASCVD) estimation risk: the pooled cohort equations was used to estimate the risk of coronary events in 10 years, classified as: low risk (<5%), borderline risk (5-7.4%), intermediate risk (7.5-19.9%), high risk (≥ 20%).[19]

Statistical analysis

Categorical variables are presented as count with proportion or as continuous variables as mean ± SD or median (25-75th percentile). Kolmogorov-Smirnov normality test was used to verify the distribution. To address the main objective, atherosclerotic and non-atherosclerotic groups were compared using the chi-square test for categorical variables, and the independent samples *t* test or Mann-Whitney U test, as appropriate, for continuous variables.

To address our secondary objective, a multivariate logistic regression model was used to investigate the covariates associated with a higher CAD risk, represented as a CCS≥100. The dependent variable was CCS dichotomized between ≥100 and <100. The candidate covariates to be tested as independents in the final model were considered on the basis of clinical evidence, information available in the literature and univariate analysis; in this case, the decision criterion was a p-value < 0.20. Thus, the final multivariate model included age >60years, hypertension, dyslipidemia, diabetes, sedentarism, and family history of premature CAD. The overall accepted level of significance was p < 0.05. Analyses were conducted in SPSS 20.

Results

From a total of 269 eligible patients, 25 did not attend further evaluations, resulting in a final sample of 244 patients for analysis. No silent myocardial infarction was suspected after enrollment according to patient medical history, EKG, and echocardiography. The atherosclerotic group frequency was 33% (n=80), without a significant age difference compared to the non-atherosclerotic group (Table 1), who were also admitted slightly later. Gender distribution between groups was also similar (49% of female gender for both). Considering the main cardiovascular risk factors, no difference was found in the hypertension, dyslipidemia, diabetes, sedentarism, and obesity rates. On the other hand, the rates of smoking and family history of premature CAD were higher in the atherosclerotic group. Although the ASCVD score was higher for atherosclerotic IS, the median ASCVD for each group was >7.5% and <20%; therefore, both were classified as an intermediate risk. A greater median CCS was observed in atherosclerotic IS patients; however, with no statistical difference when compared to non-atherosclerotic IS patients.

To define the etiology, 87% of the patients underwent magnetic resonance imaging and 13% only a computed tomography. Neurologists disagreed in seven cases (3%), requiring the evaluation of a third neurologist. Atherosclerotic IS etiology was the most prevalent, followed by 74 (30%) due to cardio-aortic embolism, 37 (15%) caused by small artery occlusion, 14 (6%) due to other causes, and 39 (16%) of undetermined causes. As a group, there were 164 (67%) non-atherosclerotic cases. Among the 80 cases of atherosclerotic etiology, 18 (23%) were due to intracranial atherosclerosis. Atherosclerotic and non-atherosclerotic IS showed similar proportions of patients with CCS ≥ 100. Similarly, those with CCS zero also had equivalent proportions between groups (Figure 1).

As dichotomized IS etiology did not discriminate CCS ≥ 100, other potential contributors were analyzed. Considering clinically defined variables and those statistically different in the univariate analysis (table 2), 6 variables entered the final adjusted model: age (dichotomized in ≥60 and <60 years old), hypertension, dyslipidemia, smoking, diabetes, and family history of premature CAD. Accounting for all those covariates, only age ≥60 years remained independently associated with CCS ≥100 (Table 3).

Discussion

Our results showed that one third of stroke patients presented atherosclerotic etiology, closely followed by cardio-aortic embolism. We found that the coronary calcium score was similarly distributed between atherosclerotic and non-atherosclerotic IS, given no clinical or statistical differences were observed in the Agatston score or in the proportion of patients within a higher CAD risk, estimated by a CCS≥100. Among other potential contributors, only current smoking and family history of premature CAD could differentiate those with atherosclerotic IS when compared to non-atherosclerotic etiology– with approximately twice higher frequency for both characteristics in atherosclerotic IS.

Although ASCVD estimated risk was greater in the atherosclerotic IS group, as compared to the non-atherosclerotic IS group, both were classified in the intermediate risk stratum. Considering that the ASCVD equation potentially overestimates the risk, CCS could potentially improve the individual risk stratification.[20]

Differently from our hypothesis, the risk according to CCS strata was similar between atherosclerotic and non-atherosclerotic IS. The proportion (approximately one third) of patients with a high CAD risk (CCS≥100) was similar for both groups. Interestingly, this finding was also true amongst patients with the lowest CAD risk (CCS zero), similarly distributed between the IS groups. Given that CCS categories did not distinguish IS etiologies, we tried to identify other potential contributors associated with CCS≥100. After accounting for clinically relevant covariates, only patients with 60 years or more had a higher likelihood of having a CCS ≥ 100 (OR 3.52; 95% CI 1.72-7.18). Age is a well-known risk factor for CAD, and its association with increasing CCS is in agreement with other authors who have demonstrated it in larger cohorts.[21–23]

CCS is a well-defined marker of CAD, which accurately reveals - with a low dose of radiation - an atherosclerotic burden in coronary arteries,[24] and has a robust prognostic value.[25] An absolute increase in CCS is proportional to coronary event rates.[25,26] Given some variation in the absolute CCS score, considering different cohorts, and a non-normal distribution, classifying patients within strata improves generalizability and clinical application.[17,27] Therefore, CCS≥100 Agatston units are associated with a significantly higher CAD risk,[15] while CCS of zero predicts a very low long term risk of CAD.[26] As we showed, CCS keeps its ability to assess individual cardiovascular risk in stroke patients regardless of whether the IS etiology is atherosclerotic or not.

Regarding the shared clinical characteristics between IS and CAD, we expected that the atherosclerotic IS group would have a greater risk of CAD. However, our hypothesis was not confirmed. The similar CAD risk profile between the atherosclerotic and non-atherosclerotic IS groups can be attributed to a very high frequency – in both etiological groups – of traditional risk factors for atherosclerotic vascular diseases: ≥70% for arterial hypertension, dyslipidemia, and sedentary lifestyle. Moreover, the smoking and diabetes rates in our sample (32% and 28%, respectively) were higher than the prevalence observed in the Brazilian population: 15% for smoking and 9% for diabetes.[28] These findings and the relatively low mean age in this study, may reflect the poor control of modifiable risk factors indistinctively present in stroke survivors, irrespective of the etiology.

Emphasizing the close relationship between CAD and IS, Rivera et al. showed that, in autopsy studies, coronary plaques were present in 72% of patients with fatal stroke, in whom approximately 27% showed evidence of silent myocardial infarction. Interestingly, coronary atherosclerosis and myocardial infarction were prevalent regardless of the stroke subtypes.[29]

The relationship between extracranial atherosclerosis and CAD is well established.[30] However, this association with intracranial atherosclerosis is controversial[31] and seems to be less frequently associated with IS,[32] at least in the Brazilian population. Intracranial atherosclerosis is known to be more prevalent in the Asian population,[32] but it was described to be as high as 50% among male African Americans as well.[33] We observed intracranial

Table 1 – Clinical characteristics of the Study Sample

	Overall (n= 244)	Non-atherosclerotic (n= 164; 67%)	Atherosclerotic (n= 80; 33%)	p-value
Age, years; mean±SD	58.4 ± 6.8	57.8 ± 6.7	59.5 ± 7.0	0.078
Time since stroke, months*; median [25-75th percentile]	5.0[3.0-9.0]	5.0 [2.5-8.0]	6.0 [4.0-10.5]	0.019
Female, n(%)	120 (49.2)	81 (49.4)	39 (48.8)	0.925
Hypertension, n(%)	177 (72.5)	119 (72.6)	58 (72.5)	0.992
Dyslipidemia, n(%)	183 (74.9)	123 (75.0)	60 (74.7)	0.833
Smoking, n(%)	77 (31.7)	37 (22.7)	40 (50.0)	<0.001
Diabetes, n(%)	69 (28.3)	49 (29.9)	20 (25.0)	0.427
Sedentary lifestyle, n(%)	170 (70.0)	113 (69.0)	57 (71.6)	0.691
Obesity, n(%)	46 (18.9)	28 (17.1)	18 (22.5)	0.309
Rankin scale	3.3±0.9	3.3±0.9	3.3±0.9	0.486
Family history of premature CAD, n(%)	37 (15.2)	18 (11.3)	19 (23.6)	0.016
Current 10-year ASCVD risk; median [25-75th percentile]	9.1 [4.8-15]	8.4 [3.7-13.9]	10.3 [6.2-18.1]	0.013
Coronary calcium score; median [25-75th percentile]	9.0 [0.0-129.7]	4.0 [0.0-128.8]	24.6 [(0.0-132.4]	0.510

*CAD: coronary artery disease; ASCVD: atherosclerotic cardiovascular disease risk. *Months from index stroke to enrollment in the study.*

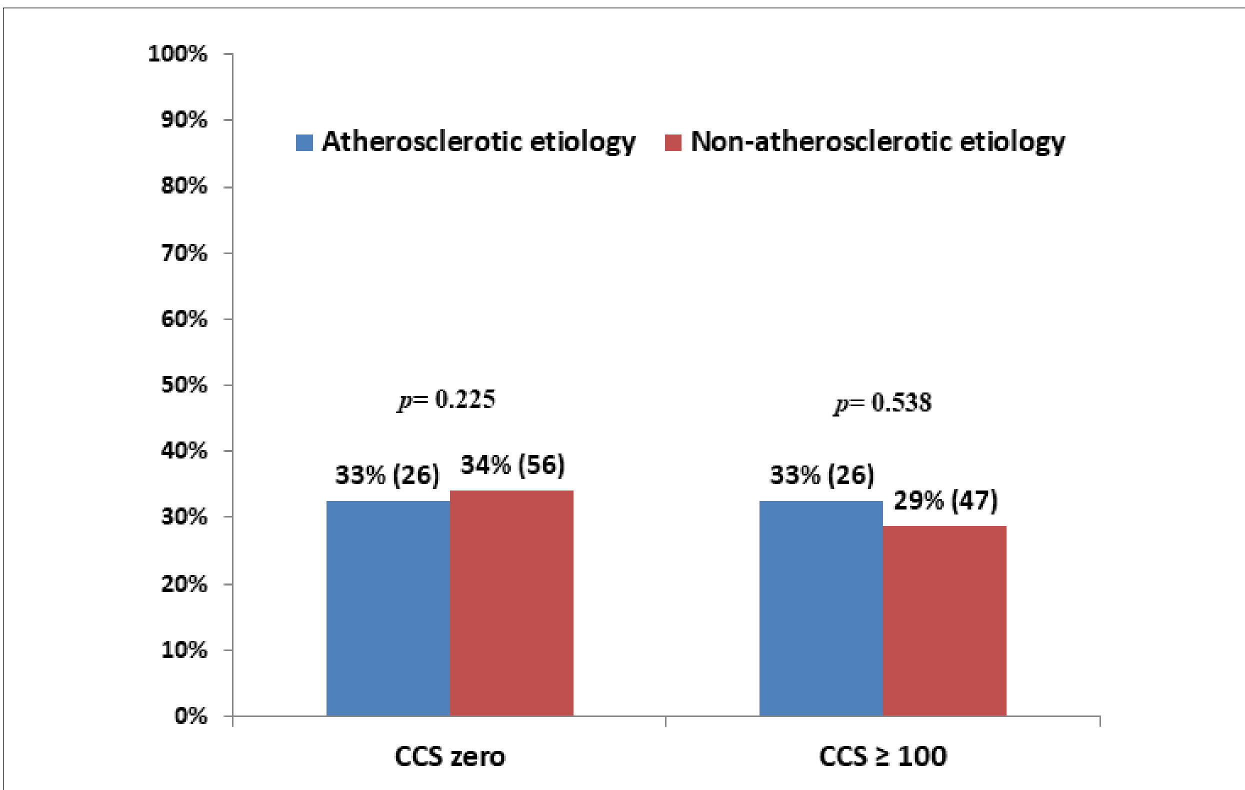

Figure 1 – *Prevalence of coronary calcium score (CCS) categories in atherosclerotic and non-atherosclerotic groups.*

Table 2 – Clinical and demographic characteristics from the overall ischemic stroke patients, by the higher coronary calcium score (CCS) cut-off point

	CCS ≥ 100	CCS < 100	p
	n = 72	n = 172	
Sex (female)	32 (44)	88 (51)	0.338
Age ≥60 years	54 (75)	60 (35)	< 0.001
Arterial hypertension	64 (89)	113(66)	< 0.001
Smoking	25(36)	52 (32)	0.492
Diabetes	28 (39)	41 (24)	0.017
Dyslipidemia	62 (86)	120 (71)	0.008
Sedentary lifestyle	51 (78)	100 (66)	0.72
Obesity	15 (21)	31 (18)	0.644
Family history of premature CAD	14 (23)	20 (12)	0.049

Values are n (%). CAD: coronary artery disease.

Table 3 – Measures of association between clinical covariates and higher risk CCS (≥ 100), in final adjusted multivariate model, from the overall ischemic stroke patients.

Variable	OR	95% CI	p
Age ≥ 60 years	3.52	1.72 - 7.18	0.001
Arterial hypertension	2.35	0.8 - 6.88	0.12
Dyslipidemia	1.67	0.7 - 3.98	0.244
Diabetes mellitus	1.15	0.57 - 2.33	0.692
Sedentary lifestyle	1.46	0.68 - 3.14	0.331
Family history of premature CAD	1.69	0.73 - 3.88	0.219

CAD: coronary artery disease.

atherosclerosis in 23% of atherosclerotic IS cases. In our study, we used the SSS-CCS algorithm, which includes intracranial and extracranial atherosclerotic disease in the same atherosclerotic etiologic group; therefore, it could have been less restrictive, but also less discriminative for the association we aimed to define.

The low frequency of cryptogenic stroke can be attributed to the high quality of investigation and the use of SSS-CCS algorithm that standardized the etiologic classification, also leading to a low rate of disagreement among neurologists. Even with the exclusion of patients with prior CAD, the rate of 30% of stroke caused by cardio-aortic embolism is in part due to the presence of 11% of patients with Chagas' cardiomyopathy. Chagas's disease is a common clinical condition in Latin America, whose main mechanisms for stroke are embolism due to the presence of left ventricular apex aneurysm, severe systolic dysfunction, and atrial fibrillation.[34]

Our study has several limitations. First, considering that our facility is a rehabilitation center, admittance criteria may somehow bias overall IS frequency estimation. Some patients with delayed admittance may have a limited diagnostic precision of IS etiology. Patients with lacunar stroke were less prevalent than in the literature, which could likely be explained by frequently lower rehabilitation demands in this subgroup. In contrast, patients with severe neurologic limitations with a narrow rehabilitation potential are less frequently admitted, and for similar reasons, clinically unstable patients (treating an ongoing infection; with surgical demands; with decompensated endocrine-metabolic conditions) were not admitted for rehabilitation purposes. Although this could have included less severe coronary atherosclerosis, this was a common inclusion criterion for both groups. Second, this is a single center study and the sample size is relatively small, but CCS≥100 prevalence among IS survivors is consistent with other authors' reports (30-45%).[35,36] Third, we expected a CCS≥100 proportion of 15 percentage points lower in the non-atherosclerotic IS group based on an arbitrary clinical observation, which is in agreement with our hypothesis; however, upon concluding the study, a 4 percentage points difference was observed (Figure 1), which could have limited the power to detect between group differences regarding our main question.

The strength of this work is providing information on CAD risk according to CCS in stroke survivors from a Brazilian population and particularly in the non-atherosclerotic IS group, to which evidence is scarcer. According to the American Heart Association and American Stroke Association, the atherosclerotic IS population should be considered a high risk group for CAD, where preventive strategies should be adequately addressed; however, stroke is more heterogeneous than CAD, particularly within the non-atherosclerotic IS subtypes, where traditional risk factors and associated outcomes are less well determined.[5] Etiologies known not to be associated with a high risk for CAD, such as patent foramen ovale and cervical artery dissection, more frequent in younger patients, can be underrepresented in non-atherosclerotic IS groups, and could have been in our sample as well. Given the lower level of evidence to consider non-atherosclerotic IS as CAD risk equivalent, prognostic validation is still necessary; therefore, generalization should be interpreted cautiously. Data on this gap was provided in this study, showing that CCS can be used to address individual CAD risk in IS, showing similar risk profiles between atherosclerotic and non-atherosclerotic subtypes, at least in our population, given the high frequency of traditional CVD risk factors. It is important to note that even though CCS was not able to discriminate IS etiologies in our analysis, it does improve the individual risk stratification for CAD in the general population,[32] even in high-risk patients,[37] whose applicability seems to be preserved for ischemic stroke patients as well, regardless of etiology.

Conclusions

In the studied population, ischemic stroke of atherosclerotic etiology did not present a greater risk of CAD when compared to non-atherosclerotic ischemic stroke according to CCS. Age equal to or over 60 years was the only variable associated with CCS ≥ 100. In ischemic stroke survivors, CCS should be considered for individual risk stratification for CAD, even in non-atherosclerotic etiologies.

Author contributions

Conception and design of the research: Negrão EM, Hora TF, Montanaro VVA, Ramalho SHR; Acquisition of data: Negrão EM, Hora TF, Montanaro VVA, Martins BJAF; Analysis and interpretation of the data and Writing of the manuscript: Negrão EM, Ramalho SHR; Statistical analysis: Ramalho SHR; Critical revision of the manuscript for intellectual content: Negrão EM, Freitas MCDNB, Marinho PBC, Hora TF, Montanaro VVA, Martins BJAF, Ramalho SHR.

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.

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Coronary Calcium Score. Is There a Difference among Ischemic Stroke Subtypes?

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Short Editorial related to the article: Coronary Calcium Score and Stratification of Coronary Artery Disease Risk in Patients with Atherosclerotic and Non-Atherosclerotic Ischemic Stroke

Ischemic heart disease is an important cause of death in stroke patients during a long-term follow-up.[1,2] Ischemic stroke survivors have a high prevalence of asymptomatic coronary artery disease (CAD).[3] Indeed, half of those with no cardiac history have some degree of coronary atherosclerotic plaques and one-third have more than 50% of coronary stenosis.[4] For the assessment of CAD risk, a non-invasive stratification score based on the extent and density of computed tomography coronary artery calcium (CAC) was proposed by Agatston et al.[5] The measurement of CAC to improve clinical risk prediction for cardiovascular events in selected asymptomatic adults is the recommendation of worldwide guidelines.[6-10] Although there is a strong association between atherosclerosis and subclinical CAD, it is remains uncertain for non-atherosclerotic stroke patients.[1,11]

In this issue of ABC Cardiol, Negrão et al.[12] conducted a cross-sectional study to compare the coronary calcium score (CCS) between atherosclerotic and non-atherosclerotic ischemic stroke patients who were admitted at Rehabilitation Hospital. Of 244 evaluated patients, 80 (33%) were included in the atherosclerotic etiology group. The non-atherosclerotic group was represented by the remaining etiologies, such as cardioembolism (30%), small artery occlusion (15%), other causes (6%), and undetermined cause (16%). Although there was no difference in CAD risk between those groups, age ≥60 years was an independent predictor for high CAD risk (OR 3.52; 95%CI 1.72-7.18).[12]

This study provided relevant insights that should be addressed. First, stroke and CAD have a close association, sharing common risk factors.[1,3] Even among young stroke patients, the prevalence of these risks is substantial. A recent published study reported that the three most common risk factors for stroke at a young age were arterial hypertension, lipid disorders and lifestyle-related factors. More than half of the patients had at least two independent risk factors for stroke.[13]

Likewise, the stroke population in the present study showed a relatively young age (58.4 ± 6.8 years), but had a high frequency of risk factors. Second, acute coronary syndrome results mainly from large-vessel atherosclerosis, whereas ischemic stroke patients are a heterogeneous group, including five categories of etiology classification (large-artery atherosclerosis; cardioembolism; small artery occlusion; other determined cause; and undetermined cause).[14] In addition, it is well recognized that there is a variation in CAD risk according to the stroke mechanism. Patients with artery dissection, other nonatherosclerotic arteriopathies, and paradoxical embolism seem to be at low CAD risk. While those with cardioembolic stroke, mainly attributed to atrial fibrillation, may have a higher likelihood of coronary events. As opposed to a large amount of data on extracranial artery atherosclerosis and CAD, insufficient information is available about intracranial atherosclerosis.[11,14] Third, statin therapy may be a confounder in CCS quantification. Since statins can reduce the fibrolipid plaques and promote micro-calcification, it might also lead to an increase in CCS.[15] Finally, as the authors pointed out, there was a possible selection bias, excluding either patients with quite severe limitation or low recovery demand. Therefore, these results should be interpreted taking into account these limitations and the cohort characteristic, before jumping to broad generalization.

Overall, it was not a surprise that the CCS itself was unable to distinguish stroke etiology. Most interestingly, atherosclerotic and non-atherosclerotic stroke patients showed similar proportions for CAD risk. Large studies with longer follow-up periods should be undertaken to determine the CCS value for individual CAD risk stratification in ischemic stroke patients regardless of the etiology. Risk prediction tools are critical for intervention strategies, aiming to prevent major coronary events in stroke patients.

Keywords

Stroke; Coronary Artery Disease; Calcium Score; Myocardial Ischemia; Atherosclerosis.

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Original Article

Standardizing Radiation Exposure during Cardiac Catheterization in Children with Congenital Heart Disease: Data from a Multicenter Brazilian Registry

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Abstract

Background: **In recent years the increasing number of interventional procedures has resulted in growing concerns regarding radiation exposure for patients and staff. The evaluation of radiation exposure in children is difficult due to the great variability in body weight. Therefore, reference levels of radiation are not well defined for this population.**

Objectives: **To study and validate the ratio of dose-area product (DAP) to patient weight as a reference measurement of radiation for hemodynamic congenital heart disease procedures in children.**

Methods: **This observational multicenter study uses data obtained from a Brazilian registry of cardiac catheterization for congenital heart disease from March 2013 to June 2014. Inclusion criteria were all patients aged <18 years old undergoing hemodynamic procedures for congenital heart disease, with recorded DAP doses. P-value < 0.05 was considered as statistically significant.**

Results: **This study evaluated 429 patients with median age and weight of 50 (10, 103) months and 15 (7, 28) kg, respectively. Median DAP was 742.2 (288.8, 1,791.5) μGy.m2. There was a good correlation between DAP and weight-fluoroscopic time product(rs=0.66). No statistically significant difference was observed in DAP/weight ratio between therapeutic and diagnostic procedures. There was a wide variation in the DAP/weight ratio among the therapeutic procedures (p<0.001).**

Conclusions: **The DAP/weight ratio is the simplest and most applicable measurement to evaluate radiation exposure in a pediatric population. Although there is limited literature available, the doses obtained in the present study were similar to those previously found. Ongoing research is important to evaluate the impact of strategies to reduce radiation exposure in this population (Arq Bras Cardiol. 2020; 115(6):1154-1161)**

Keywords: **Diagnostic,Imaging/methods; Radiation Exposure Pathways; Heart Defects, Congenital; Cardiac Catheterization/ methods; Child**

Introduction

Over the last 20 years, cardiac catheterization has not only been used as a diagnostic examination for congenital heart diseases, but has also played an important role in palliative and definitive treatments of more than 50% of patients with congenital heart diseases.[1] During this period, the complexity, duration, and number of percutaneous procedures have increased, along with a consequent increase in the exposure of patients to ionizing radiation.[2-4]

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Children are highly sensitive to ionizing radiation, due to their higher proportion of actively dividing cells and the large fraction of exposed body area.[2] Thus, there is a great concern about the cumulative effects, particularly the high risk of malignancy caused by long-term chromosomal damage, with reports demonstrating that children are up to ten times more susceptible to the development of cancer by radiation exposure than adults.[5,6] In addition, the effective radiation dose is higher for children, resulting in a higher radiation dose for surrounding organs when an area of interest is being assessed.

There are limited studies on radiation doses emitted during interventions in children with congenital heart disease.[3,7] To achieve a reduction in the radiation dose, it is essential to establish reference doses that allow comparisons between procedures.[4] However, it is difficult to evaluate the radiation exposure in a pediatric population due to the differences in the complexity of procedures, age and weight of the patients, as well as in the types of equipment used.[8] Moreover, the calculation of the estimated effective radiation dose is complex. Currently, the total radiation dose (total air kerma) and total dose-area product (DAP; air kerma-area product), which is a better estimator of stochastic (long-term radiation effects and risk of malignancy) and cumulative effects of exposure, are used as indicators of a cumulative radiation dose to the skin.

Recently, Chida et al.[2] and Kobayashi et al.[8] observed a correlation between DAP and weight as a reference radiation dose in children. They concluded that the radiation dose tends to vary proportionally to patient size. In this context, the present study aims to evaluate the DAP/weight ratio as a reference for radiation exposure in pediatric cardiac catheterization procedures performed in Brazil.

Materials and Methods

Study Design and Population

This is a cross-sectional observational study in which patients aged <18 years old and participating in the Congenital Heart Disease Intervention and Angiography (CHAIN) registry, a Brazilian registry of cardiac catheterization for congenital heart disease, were evaluated after undergoing a diagnostic or interventional procedure between March 5th, 2013 and June 30th, 2014.

The CHAIN registry is a national multicenter prospective study, coordinated by the Teaching and Research Institute of *Hospital do Coração*, together with the Ministry of Health and the Brazilian Society of Hemodynamics and Interventional Cardiology. The main objective was to gather prospective data and create a national registry of catheterization of patients with congenital heart diseases, as well as to propose a comprehensive analysis of the current status and devise effective action measures for public health in Brazil.

Patients who underwent electrophysiological procedures or those in whom vascular access was achieved using hybrid procedures were excluded from the study. Patients who underwent more than one catheterization on different dates were considered as distinct patients in each procedure and were included in the overall statistics as well as in the group of each specific procedure. Patients who underwent more than one intervention using the same procedure were classified according to the most complex procedure.

Analyzed Variables

Demographic characteristics of patients, such as age, gender, weight, body surface, type of heart disease, and residual lesions, were obtained from the CHAIN registry, in addition to data regarding the hemodynamic procedure performed, including fluoroscopic time and radiation exposure dose. DAP, which represents the radiation dose measured in the air in relation to the distance from the X-ray tube multiplied by the X-ray beam area at this distance, was expressed in μGy.m^2. Radiation measurements expressed in units of Gy.cm^2, cGy.cm^2, and mGy.cm^2 were converted and recorded in μGy.m^2. Moreover, the DAP/weight ratio (μGy.m^2/kg) was analyzed among the catheterization categories for possible comparisons and standardization of radiation doses. Procedures lacking data related to radiation dose, or radiation dose recorded in different units, were excluded from the study.

Therapeutic catheterization procedures were divided into 10 categories. Radiation exposure was evaluated after the patients were categorized into age (<1 year; 1–4 years; 5–9 years; 10–14 years, and ≥15 years) and weight (up to7 kg; up to15 kg; up to 28 kg; >28 kg) subgroups. Data regarding DAP, DAP/weight ratio, age, weight, fluoroscopic time, and weight–fluoroscopic time product were not normally distributed, and were, therefore, described as medians (interquartile range).

Statistical Analysis

All data were analyzed using SPSS (IBM, SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp).

The Kolmogorov Smirnov method was the statistical test used to verify the normality of the data. Continuous variables did not present normal distribution after the Kolmogorov-Smirnov test was applied. Non-normally distributed quantitative variables are presented as medians (interquartile range). Categorical variables are presented as absolute frequencies (n). Associations between continuous variables were evaluated using the Spearman correlation coefficient test (r_s). The relationship between non-parametric continuous quantitative and two categorical variables were assessed using the Mann-Whitney U test. The relationship between non-parametric continuous quantitative and more than two categorical variables was assessed using the Kruskal-Wallis test. P-value < 0.05 was considered as statistically significant.

Results

A total of 1,311 patients aged <18 years old from 16 participating centers participating in the CHAIN study were included in the analysis. Among those, 206 patients had no records on radiation doses and were excluded. Of the remaining 1,026 patients with recorded radiation doses, 597 were excluded as their doses were not recorded as DAP. This resulted in a total of 429 participating patients (56.4% male) from six centers. After these exclusion criteria were applied, three out of the six centers contributed 90% of patient data.

Demographic data and the characteristics of the population and procedure groups are described in Table 1.

The median DAP in the studied population was 742.2 (288.8, 1,791.5) μGy.m^2. Interventional procedures had higher median DAP than diagnostic ones: 751 (315, 2,095) *versus* 715 (230, 1,535) μGy.m^2, respectively. No differences were observed in the DAP/weight ratio between diagnostic and therapeutic procedures: 57 (23, 110) *versus* 57 (30, 139) respectively.

DAP was found to have a good correlation with the weight–fluoroscopic time product (r_s = 0.66), and this correlation pattern was also observed when diagnostic and therapeutic procedures were separately analyzed (r_s = 0.56 and r_s = 0.72, respectively) (Figures 1 and 2). Patients categorized into weight subgroups demonstrated higher radiation doses (DAP) in

Table 1 – Demographic data and characteristics of the procedures

		Diagnostic procedures	Interventional procedures	p
Patients	429	151	278	
Age (months)	50.1 (10; 102.9)	38.8 (13.6; 104.5)	53 (9.2; 102.6)	0.892
Weight (kg)	15 (7.2; 28)	12 (7.2; 27)	16 (7.1; 29.5)	0.466
Procedure time (min)	40 (27.5; 57)	35 (25; 50)	45 (30; 60)	0.000
Fluoroscopic time (min)	9 (5; 15)	8 (4; 13)	9 (5.7; 16)	0.003
Weight x fluoroscopic time (kg.min)	114 (54.5; 250)	90 (45; 224)	128 (60; 277)	0.006
DAP (uGy. m^2)	742 (288.8; 1,791.8)	715.2 (230; 1,534.9)	751.5 (315.4; 2,095.2)	0.14
DAP/weight (uGy.m^2/kg)	57.2 (28; 124.9)	57 (23.3; 110.5)	57 (30.5; 139.5)	0.137

Results are described in medians and interquartile range (25^{th}, 75^{th} percentile). DAP: dose-area product. Statistical significance when p ≤ 0.05.

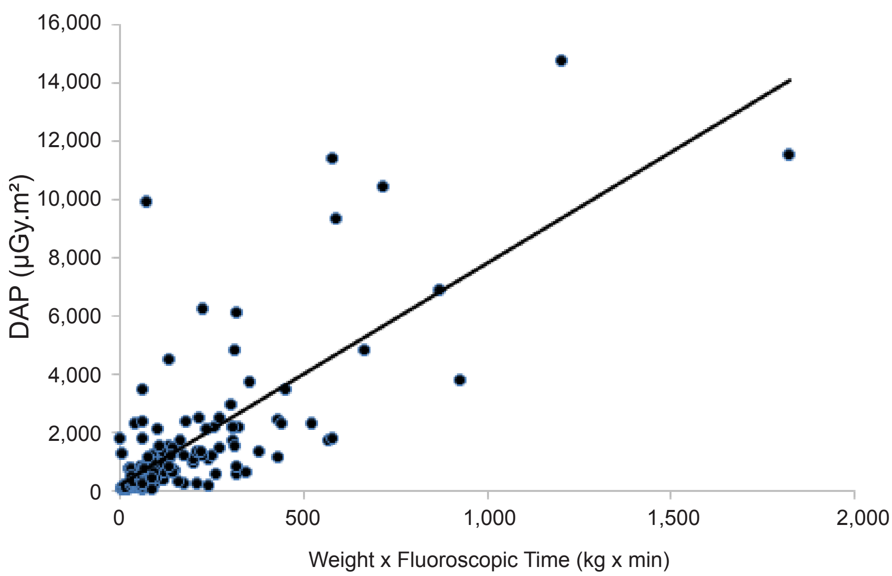

Figure 1 – *Scatterplot shows relationship between dose–area product (DAP) and weight– fluoroscopic time product in pediatric patients who underwent diagnostic cardiac catheterization (r = 0.75).*

therapeutic than in diagnostic procedures (p= 0.001). When patients were categorized into age subgroups, a significant difference in radiation doses was observed between diagnostic and therapeutic procedures, but only in patients aged >15 years (p=0.004; Table 2).

Table 3 highlights the different procedures, fluoroscopic times, and corresponding DAP/weight ratios. The highest DAP/weight ratios were observed for percutaneous pulmonary valve implantation (Melody), closure of ventricular septal defects (VSD), and balloon or stent angioplasty in the right ventricular outflow tract (RVOT) or pulmonary artery (PA), with means of 273.8, 169.2, and 155.9, respectively. In addition, there was a significant difference between intervention procedure subgroups and DAP/weight ratios (p<0.001).

Discussion

In recent years, the complexity and number of transcatheter procedures have increased.[4] Thus, methods to protect patients and staff from cumulative exposure to ionizing radiation and its potential effects are important and, therefore, establishing reference data is crucial.[8] Currently, the major limitations for setting reference values with interventional procedures for congenital heart diseases are the lack of standardization of dosage and measurement units,[9] as well as the existence of a wide variety of procedures and complexities, weight and age variations, types of equipment and medical abilities. All these factors contribute to a great heterogeneity, which makes comparisons difficult.[4,8] The Food and Drug Administration and the World Health Organization recommend recording

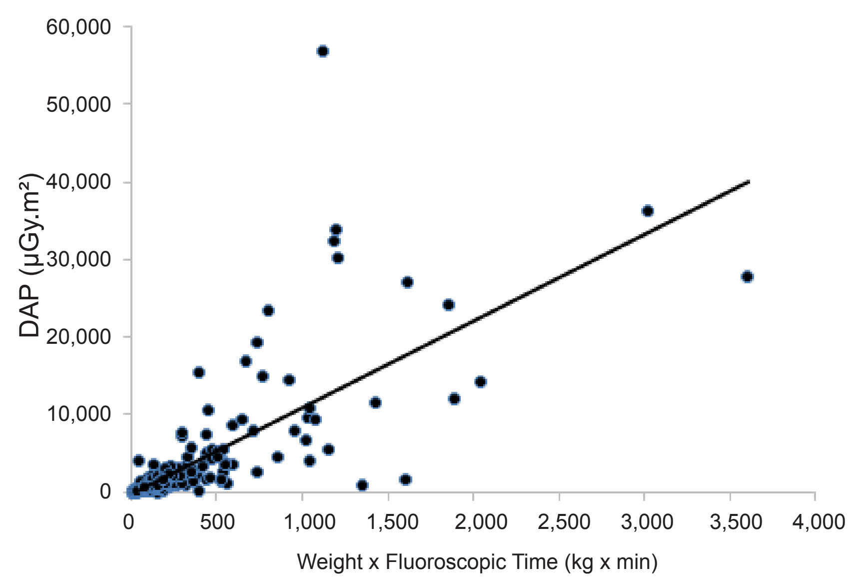

Figure 2 – *Scatterplot shows relationship between dose–area product (DAP) and weight– fluoroscopic time product in pediatric patients who underwent diagnostic cardiac catheterization (r = 0.75).*

Table 2 – Dose-area product (DAP; uGy.m²) of diagnostic and therapeutic catheterizations stratified by age groups

	Type of Catheterization		
Age group	**Diagnostic**	**Therapeutic**	**p**
< 1 year	n= 36 303.8 (172; 754)	n=78 250.7 (138.6; 570.7)	0.25
1-4 years	n= 50 524.8 (194.3; 1,038.7)	n=73 602.7 (409.5; 1,329.3)	0.06
5-9 years	n=75 1,340 (428.9; 2,175.9)	n=71 1,189.7 (491.7; 2,125.4)	0.82
10-14 years	n= 119 1,739.6 (773.7; 4,524.5)	n=38 2,765 (1,385.3; 8,399.4)	0.08
> 15 years	n= 11 2,182.2 (295.1; 3,735.7)	n= 18 11,723.5 (5,493.5; 28,357.2)	0.004

DAP values described in medians and interquartile ranges (25th, 75th percentile). n: absolute number of patients. Statistical significance when p ≤ 0.05.

DAP and calculating effective doses for all patients undergoing procedures utilizing radiation.[10] Based on this proposal, a total of 429 patients aged <18 years and registered in the CHAIN study were evaluated in the present study. Although relatively smaller than the number of patients reported in previous studies,[4,7,8,11,12] the results from the present analysis reveal the potential of using the DAP/weight ratio as a reference for comparison.

The absence of a statistical difference in DAP between diagnostic and therapeutic procedures in the present study can be explained by recent advances in low-complexity interventional procedures, such as the percutaneous closure of atrial septal defects (ASD), patent foramen ovale (PFO), and patent arterial duct (PDA), in addition to pulmonary valvuloplasty, which use relatively low radiation doses. Furthermore, diagnostic procedures often involve patients with complex cardiac diseases without a defined diagnosis, requiring high fluoroscopy times.

During the analysis of diagnostic and therapeutic catheterization, it was observed that DAP increased as age increased. When the two procedures were compared with age subgroups, no statistical differences were observed, except in the group aged >15 years, in which the radiation dose was significantly higher in therapeutic procedures, similar to that reported by Ubedaet al.,[13] This was likely a result of a higher number of complex procedures, such as percutaneous valve implantation and angioplasty in older patients.

Table 3 – Fluoroscopic time and normalized dose–area product indexed to body weight(DAP/weight; uGy.m²/kg) stratified by procedure types

	Patients	%	Fluoroscopy time	DAP/weight (uGy.m²/kg)
Diagnostic	151	37.3	8 (4; 13)	57.2 (23; 110.5)
Pulmonary valvuloplasty	44	10.9	10 (7; 15)	51.8 (35; 93)
Aortic valvuloplasty	20	4.9	9 (7; 13)	59.8 (29.1; 125.9)
PDA occlusion	56	13.8	6 (5; 9)	41.9 (27.6; 71.4)
ASD/PFO device closure	52	12.8	5 (4; 7.7)	25.5 (13.5; 36.2)
VSD device closure	6	1.5	20 (10; 44)	170 (71.4; 513.4)
RVOT/PA angioplasty or stent	35	8.6	17 (11; 27)	155.9 (75.9; 224.5)
Aortic angioplasty/ Aortic stent	32	7.9	11 (6; 16.7)	98.2 (42; 206.6)
PDA Stent	6	1.5	9 (8.5; 15.5)	77.2 (58; 126.6)
Melody valve implant	3	0.7	36 (p25 = 34)	273.8 (p25 = 41.9)

Fluoroscopy time and DAP values described in medians and interquartile ranges (25th, 75th percentile). n: absolute number of patients. Statistical significance when p ≤ 0.05. PDA: patent arterial duct; ASD: atrial septal defect; PFO: patent foramen ovale; VSD: ventricular septal defect; RVOT: right ventricular outflow tract; PA: pulmonary artery.

The main interventional procedures analyzed in the present study had dose medians comparable to those reported in recent studies[3-8,11,13,14] (Table 3), particularly when values were compared using the DAP/weight ratio, which standardizes increasing values of DAP related to weight differences in the same procedure. The variation of the DAP/weight ratio between the different types of interventional catheterization was statistically significant, as demonstrated in other studies.[2,8,11,12,14] The highest doses of radiation were observed in percutaneous pulmonary valve implantations (Melody), closures of VSD, and balloon or stent angioplasties in RVOT or PA, as reported previously.[8,11] The medians of the DAP/weight ratio in pulmonary valvuloplasties, closures of VSD, and balloon or stent angioplasties of RVOT or PA were similar to those obtained by Kobayashi and Borik et al.,[8,11]

In many procedures in the present study, DAP medians were lower than those observed in previous studies.[3,4,15] Glatz et al.,[15] evaluated 2,265 patients in a single-center study and obtained a median DAP significantly higher than in most procedures studied, including adults and patients who weighed >65 kg (maximum, 128 kg). In contrast, the CHAIN study presented a median weight of 21 kg. The only procedure reported by Glatz et al. with a lower dose than those of the present study was the balloon/stent aortoplasty (DAP of 484 *versus* 1,904 μGy.m², respectively). Ghelani et al. published a study conducted from 2009 to 2011 with 2,713 patients in which the DAP of some interventional procedures was evaluated. The reported DAP medians were higher than those of other studies, including the CHAIN study. These results can also be partially justified by the inclusion of patients aged >15 years and adults, representing approximately 20% of the evaluated population. However, in this study, DAP/Kg was not evaluated. All these data corroborate the concept that the use of the DAP/weight ratio is a rational measure to standardize the evaluation of radiation dose in a heterogeneous pediatric population. In accordance with this line of thought, Cevallos and the C3PO group recently published new benchmarks for radiation dosage in the pediatric population. Differently from the previous study by the same group[4], they assessed DAP/Kg stratified by age groups and procedure types, which allows for comparison with the current literature.[12] This study was performed after radiation quality improvements (QI) efforts in the different centers involved. Interestingly, the mean doses found by our group in the present were very similar to those reported by Cevallos et al. after a QI program (Table 4).

The main limitation of the present study was the lack of data from some participating centers, probably due to the absence of standardization of the collected data. As a consequence, the studied sample was smaller and possibly less heterogeneous. At the same time, this corroborates the hypothesis of a lack of standardization of radiation exposure measurements in pediatric populations and demonstrates that a number of Brazilian centers do not yet properly report the radiation dose used in their procedures. This reinforces the need for awareness of institutions with regard to an appropriate control and a well-developed quality assurance program for radiation safety. Moreover, in some analyses, the number of patients evaluated was small and thus a statistical analysis was not possible, for example, percutaneous pulmonary valve implantation. Nevertheless, the radiation doses these patients received were similar to those cited in the literature.

Conclusions

Radiation dose increases with patient age and the complexity of the procedure. In the present study, the radiation doses observed were similar to those from other reported studies. The radiation doses in these procedures should serve as a benchmark for other institutions for appropriate control of radiation exposure of patients and staff.

The DAP/weight ratio appears to be the most useful and applicable measurement of radiation for the establishment of a reference dose for the pediatric population, given that it allows the elimination of age categories and encompasses

Table 4 – Comparison of our data stratified by procedures type procedures radiation data (CHAIN) with previously published radiation dose databases

Procedures	Manica, 2018 (CHAIN)		Cevallos, 2017 (C3PO)		Borik, 2015		Kobayashi, 2014 (CCISC)		Onnasch, 2007	
	n	[a] DAP/w	n	[b] DAP/w	n	[a] DAP/w	n	[c] DAP/w	n	[c] DAP/w
Pulmonary valvuloplasty	44	51.8 (34-92)	258	53 (104-335)	286	28 (1-345)	342	56 (152)	-	-
Aortic valvuloplasty	20	59.8 (29-126)	136	99 (165-383)	138	42 (8-211)	138	80 (127)	-	-
PDA occlusion	56	41.9 (27-71)	443	37 (72-217)	266	18 (4-251)	467	42 (71)	165	34.5 (37)
ASD/PFO device closure	52	25.5 (13-36)	295	34 (64-199)	345	21 (2-367)	568	41 (71)	259 / 21	41.9 (50)/ 23 (30)
VSD device closure	6	169.2 (71-513)	-	-	-	-	-	-	32	130 (175)
RVOT/PA angioplasty or stent	35	155.9 (76-224)	-	-	366	102 (8-910)	427	132 (222)	-	-
Aortic angioplasty	32	98.2 (42-206)	288	90 (165-384)	120	43 (7-447)	182	66 (107)	-	-
Aortic stent					52	80 (13-448)	112	90 (159)	-	-
PDA Stent	6	77.2 (58-126)	-	-	-	-	-	-	-	-
Melody valve implant	3	273.8	199	257 (400-671)	38	191 (60-935)	88	186 (299)	-	-

DAP/w: DAP indexed by body weight. DAP values described in medians and interquartile ranges: [a] (25th, 75th percentile); [b] (75th, 95th percentile); [c](75th percentile). Aortic angioplasty and stenting are grouped together in CHAIN and C3PO.
n: absolute number of patients; DAP: dose–area product; PDA: patent arterial duct; ASD: atrial septal defect; FO: foramen ovale; VSD: ventricular septal defect; RVOT: right ventricular outflow tract; PA: pulmonary artery; CHAIN: Brazilian registry of Congenital HeArt disease INtervention and angiography; C3PO: Congenital Cardiac Catheterization Project on Outcomes; CCISC: Congenital Cardiovascular Interventional Study Consortium.

the broad spectrum of body sizes. As such, new studies using the DAP/weight ratio are important for the development of reference doses in hemodynamic procedures and for the evaluation of strategies aiming to reduce radiation exposure of patients and staff.

Author Contributions

Conception and design of the research: Manica J, Ribeiro M, Pedra C, Rossi R; Acquisition of data: Manica J, Duarte V, Ribeiro M, Pedra C, Rossi R; Analysis and interpretation of the data: Manica J, Duarte V; Statistical analysis: Duarte V, Petraco R; Writing of the manuscript: Manica J, Duarte V, Hartley A, Petraco R; Critical revision of the manuscript for intellectual content: Petraco R, Pedra C, Rossi R.

Potential Conflict of Interest

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

Sources of Funding

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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 2.919.655. 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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The Importance of Benchmark Radiation

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Short Editorial related to the article: Standardizing Radiation Exposure during Cardiac Catheterization in Children with Congenital Heart Disease: Data from a Multicenter Brazilian Registry

Everyone knows the importance of benchmark to evaluate processor speed in a computer. We can also have some inputs from the computer itself, as it goes slowly or when it is not able to open a new program. Therefore, we must pursue the best and the fastest processors to solve the problem. The company responsible for making those computer chips is also the one that creates new processor benchmarks, and we need that information for every decision we make when buying or upgrade a computer.

Benchmark is present in several situations, whenever we need to compare how we are working. And when a new proposal arrives, what would be the best practices.

When we work in the catheterization laboratory, we must know how far the radiation goes in order to offer safe patient management, and more importantly, if we change a protocol, we have to make a reasonable choice for it.

For many years, our goal in the catheterization laboratory was to achieve a perfect image and build a complete diagnosis of the heart defect in order to refer the patient to surgery. That was another century, and another way of thinking about Pediatric Cardiology and how to treat congenital heart diseases. Other diagnostic tools were beginning to be used, such as the echocardiogram and tomography. At that time, radiation concerns were minor! In the laboratory, “new machines” (nowadays only suitable for history) were forced to put many images in a roll film to achieve what was “hidden” in the small child’s heart. Just like Marie Curie discovering radium and many years later dying from the consequences of her great work, we simply employed radiation without “seeing” what was beyond that.

The global average annual effective dose of radiation (considering the susceptibility to harm different organs) per person is about 2.4 mSv (Sievert) and ranges from 1 to more than 10 mSv depending on where people live (about 6 mSv in the U.S.). The majority (80%) comes from natural sources. Medical exposure accounts for 98 percent of the radiation exposure from all artificial sources and is the second largest contributor to the population exposure worldwide.[1]

Keywords

Cardiac Catheterization/methods; Heart Defects Congenital; Radiation Exposure; Child.

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In Pediatric Cardiology, this can be more important. Conventional radiographs in children with heart disease represents 92% of examinations, whereas cardiac catheterization represents 1,5%. But catheterization exams contributed with 60% of cumulative exposure and, if added to computed tomography, they accounted for 81% of cumulative exposure.[2] The risk associated with radiation exposure is particularly relevant for children with more complex heart diseases, who often receive repetitive imaging with high-exposure modalities.[2]

Today, as we have other tools to explore the heart, like the echocardiogram, tomography or magnetic resonance imaging, we can anticipate the most important information we need. The catheterization laboratory is now mainly dedicated to therapeutic procedures. That is why those who deal with congenital heart diseases must have a complete knowledge of each patient disease to be studied or treated. We should never be a “hole closer” of atrial septal defects or ventricular septal defects.

Many articles from several important medical centers have drawn attention to the problem of radiation in catheterization, and how to bring it down to a lower level. Children are especially vulnerable to radiation, as pointed out by the article by Manica et al.[3] They have a greater skin surface and generally a bigger area exposed to radiation in exams. In most medical centers in our country that work with congenital heart disease and catheterizations exams, radiation is not adequately measured and controlled.

The article by Manica et al.[3] is a very important study, and it emphasizes the need of a simple and useful measurement for controlling radiation in the laboratory. The effective dose of radiation is a variable of complex calculation and it is absolutely not practical. On the other hand, DAP (Dose Area Product) is automatically visible by the machine and, as pointed out by Kobayashi et al.[4] and suggested in this article, DAP/m^2 can be used in children as a good benchmark to be applied in the same laboratory to compare different periods with radiation level modifications — and for every laboratory to know whether the protocols being used are adequate or not. The authors also demonstrate a very important detail that the practitioner sees every day at work: diagnostic exams can be more time consuming than therapeutics,[3] release a greater amount of radiation on the patient and on the staff involved afterwards.

As we have expected, the “weight-fluoroscopic product” had a good correlation with DAP. So even if you know nothing about DAP, you must be cautious about how long you “put your foot” on the fluoroscopic image, and more importantly, you must be sure to use a low frame rate and a dose as low as possible. As pointed out by Borik et al.,[5] simple modifications can represent a significant dose reduction, as the fluoroscopy frame rate of 7,5 frames/second, using the "air gap technique"[6] and a minimal magnification, with the detector placed as far as possible from children.

In another recent radiation exposure-controlled study by Hill et al.,[7] they confirm that simple and essential modifications must be used in everyday practice. Data presented by Borik et al.[5] and Cevallos et al.[8] include many patients studied and organized practical tables with the most common procedures and the respective DAP/kg.

In our current practice, more exams with 3D rotational angiography are done and constitute an essential method. They provide a real-time roadmap for anatomy-guided procedures and more precise diagnosis in some circumstances. However, the amount of radiation could be high if protocols are not implemented. Minderhoud et al.[9] demonstrated that a simple protocol modification can reduce the exposure of the entire catheterization exam.

Therefore, the work of Manica et al.[3] adds a very important tool to control radiation in our everyday practice: the DAP/kg. As a simple and effective benchmark for radiation in the catheterization of congenital heart disease, it should be included in every laboratory report.

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Inequalities in Mortality Rates from Malformations of Circulatory System Between Brazilian Macroregions in Individuals Younger Than 20 Years

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Abstract

Background: **Deaths from malformations of the circulatory system (MCS) have a major impact on mortality reduction. given that most cases are avoidable with correct diagnosis and treatment.**

Objectives: **To describe the distribution of mortality from MCS by sex. age. and macroregion in Brazil. in individuals under the age of 20. between 2000 and 2015.**

Methods: **A descriptive study of mortality rates and proportional mortality (PM) from MCS. other congenital malformations (OCM). circulatory system disease (CSD). ill-defined causes (IDC). and external causes (EC) in Brazil.**

Results: **There were 1.367.355 deaths from all causes in individuals younger than 20. 55.0% under 1 year of age. A total of 144.057 deaths were caused by congenital malformations. 39% of them by MCS. In both sexes. the annual mortality from MCS was 5.3/100.000. PM from MCS was 4.2%. CSD 2.2%. IDC 6.2% and EC 24.9%. Unspecified MCS showed the highest PM rates in both sexes and age groups. especially in the north and northeast regions (60%). Deaths from malformations occurred 5.7 times more frequently during the first year of life than in other ages (MCS: 5.0; OCM: 6.4).**

Conclusions: **MCS was the leading cause of death among all malformations. being twice as important as CSD. mainly under 1 year of age. The frequency of misdiagnosis of MCS as cause of death was high in all ages and both sexes. especially in the north and northeast regions. These findings highlight the need for the development of public health strategies focused on correct diagnosis and early treatment of congenital cardiopathies. leading to a reduction in mortality. (Arq Bras Cardiol. 2020; 115(6):1164-1173)**

Keywords: **Cardiovascular Diseases; Epidemiology; Infant Mortality; Children; Heart Defects Congenital; Public Health Service; Infant Newborn/treatment.**

Introduction

In the year 2000. 10.65 million of all-cause deaths were recorded in people under the age of 20 worldwide. In 2015. this number declined to 6.65 million. as the mortality rate decreased from 443.76 per 100.000 inhabitants to 269.38 during this period.[1] This reduction has been attributed to improvements in access to healthcare and education and to a decline in poverty and fertility.[2-4] In addition to this decline in the global mortality rate. there have been changes in the causes of death – while the main cause of deaths was once infectious diseases. perinatal causes. such as prematurity and malformations. have become the most common causes. especially in countries with higher economic development.[2.5]

Of all deaths due to congenital malformations. malformations of the circulatory system (MCS) are more likely to impact on mortality reduction. given that mortality can be avoided with correct diagnosis and treatment.[6.7] In 2015. MCS accounted for 43% of deaths from congenital malformations in people younger than 20 years. Of children who are born with congenital heart disease without receiving medical intervention. 14% do not survive the first month of life and 30% do not survive the first year.[8.9]

At the same time that mortality in people under 20 years of age has declined in Brazil in recent decades. the relative importance of congenital malformations has increased. rising from the fourth leading cause of death in 2000 to the third in 2015 accounting for 40% of the total of these deaths in the latter year.[9.10]

Mortality from MCS generally occurs in children under 1 year of age and between ages 1 and 4. given that MCS are often incompatible with life and highly dependent on adequate medical and hospital support.[11] The knowledge of demographic characteristics of patients who died from MCS would help in the improvement of healthcare and mortality

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reduction. The objective of this study was to describe the distribution of mortality from MCS by sex. age group. and region in people under age 20 during the period between 2000 and 2015.

Materials and Methods

This was a descriptive study of mortality rates (number of deaths per 100.000) and proportional mortality (PM) due to MCS. other congenital malformations (OCM). circulatory system disease (CSD). ill-defined causes (IDC). and external causes (EC) in people under age 20 in Brazil. between 2000 and 2015. Information regarding deaths was obtained from the website of the Department of Informatics of the Brazilian Unified Health System (DATASUS) (http://tabnet.datasus.gov.br/cgi/sim/dados/cid10_indice.htmdados).[12] Data set consisted of the compilation of all death certificates registered in each year between 2000 and 2015. by geoeconomic microregion of Brazil. The cause of death codes used were those defined by the World Health Organization (WHO)'s International Statistical Classification of Diseases and Related Health Problems. 10th revision (CID-10).[13]

Information about the populations was obtained from the Brazilian Institute for Geography and Statistics (IBGE) website (https://www.ibge.gov.br/apps/populacao/projecao).[14] where projections based on censuses are available from the year 2000 to the year 2060 by Brazilian macroregion. sex. age group. and overall totals. Data between 2000 and 2015 were used in the study. considering both sexes. all Brazilian macroregions. and the following age groups: 0-4. 5-9. 10-14. and 15-19 years.[15] The study period was determined based on the availability of population information. which became consistently available on the IBGE website from the year 2000 on.

Information about deaths was obtained for each geo-economic macroregion. both sexes. and all age groups under 20 (under 1 year of age. 1 to 4 years. 5 to 9 years. 10 to 14 years. and 15 to 19 years) defined by the WHO.[15] Thus. the mortality rate in the 1-4 age group was calculated using an approximation. subtracting the number of live births by sex and region from the total population age 0-4 years. Mortality rates in children under the age of 1 year are the same as infant mortality. given that the denominator was the number of live births. Information regarding live births by sex and region for the period 2000-2015 was obtained from the DATASUS website.[16]

Deaths caused by diseases of the ICD-10 chapter XVII were divided into MCS and OCM.[13] Deaths from MCS were classified into the following categories: malformations of cardiac connections (Q20). cardiac septa (Q21). pulmonary and tricuspid valves (Q22). aortic and mitral valves (Q23). others (Q24. except Q24.9 and unspecified Q24.9). great arteries (Q25). and other vessels (Q26-Q28). CSD correspond to ICD-10 chapter IX. IDC correspond to chapter XVIII and EC correspond to ICD-10 chapters XIX and XX.

PM. defined as the ratio between deaths due to a specific cause and deaths due to all causes. was calculated in two ways: total PM (PMt). whose denominators included all causes of death. and endogenous proportional mortality (PMe). whose denominators exclude external causes. Mortality rates (per 100.000) were estimated using the ratio between deaths due to a specific cause and the estimated populations. PMt and mortality rates were estimated by sex. age group. and macroregion for the period 2000-2015. while PMe was obtained on an annual basis. by sex. age group. and macroregion.

The Microsoft Office Excel[17] and Stata® version 14[18] were used for calculations.

This study was carried out in accordance with ethical standards and was approved by the Research Ethics Committee of the Clementino Fraga Filho University Hospital. which belongs to the Federal University of Rio de Janeiro.

Results

In Brazil. from 2000 to 2015. there were 1.367.355 deaths due to all causes in people under age 20. of which 845.481 were male and 521.874 were female. The rate of deaths under 1 year of age fell from 61.41% in 2000 to 51.22% in 2015. The relative frequency of death was higher for males in all age groups. with a frequency 3.8 times higher in the 15-19 group. Mean annual all-cause mortality was 126 per 100.000 inhabitants in both sexes; of these deaths. 61.7% occurred in males.

A total 144.057 deaths from congenital malformation of an organ or system were registered. 85.8% of them in children under 1 year of age. with a similar distribution between the sexes. Of these deaths. 57.892 (39.05) were caused by MCS. Mortality from malformation during the first year of life was 5.7 times higher than all other age groups. with MCS 5.0 times more common and OCM 6.4 times more common. Annual mortality from MCS was 5.3 deaths per 100.000 inhabitants in people under age 20 in both sexes. 5.0 in females and 5.6 in males. PM from MCS was 4.2% in people under age 20 in both sexes. 5.1% in females and 3.7% in males.

In people younger than 20. CSD was the cause of 29.904 deaths in Brazil. 13.198 of which in females and 16.706 in males. PM from CSD was 2.2% in both sexes. 2.5% in females and 2.0% in males. In children under 1 year of age. the risk of death from CSD was 14.7 per 100.000 live births; this number declined in subsequent age groups. reaching 3.9 per 100.000 inhabitants in the 15-19 group. On the other hand. PM increased from 1.4% in children under age 1 to 3.5% in the 15-19 age group.

In Brazil. 85.458 deaths were attributed to IDC. which corresponds to 6.2% of all deaths in people under age 20. Of these deaths. 35.518 occurred in females and 49.940 in males. The risk of death from IDC in both sexes in children under 1 year of age was 95.04 per 100.000 live births; this number declined in subsequent age groups. reaching 5.09 per 100.000 inhabitants in the 15-19 group. On the other hand. PM increased from 6% in children under age 1 to 10.8% in the 1-4 age group. with a progressive decline in the other age groups.

There were 340.974 deaths from EC. 274.627 (80.5%) of which occurred in males and 66.347 (20%) in females. In Brazil. deaths from EC in people under age 20 increased progressively in each age group. in both sexes; this was. however.

more pronounced in males. Compared with the under one-year-old group. PM in the 15-19 age group was 31 times greater in males and 18.5 greater in females.

Results of PM and mortality rates by cause of death. age group. sex. and region are shown in Tables 1 to 6. In the south and central-west regions of Brazil. the risk of death from MCS was almost twice as high as in the north and northeast regions in children under 1 year of age; the risk declined progressively with age group.

PMe from MCS (which did not include EC) increased 1.5-fold in children under 1 year of age in both sexes in the south. southeast. and central-west regions from 2000 to 2015. This number increased 2.6-fold in the north region and 3.2-fold in the northeast region. Results are described regardless of sex since no differences were found between men and women. In other age groups. variations over time were small. with a few isolated peaks. due to low death frequencies. In children under 1 year of age. there was a 4.6% difference in PMe between the south and the northeast regions in the year 2000; this number declined to 2.8% in 2015. Similarly. in the 15-19 group. PMe between the south and the northeast regions fell from 1.7% in 2000 to 0.6% in 2015 (Figure 1). In general. the differences in PMe between regions decreased in all age groups. especially in the last years observed.

Regarding MCS. in all regions and regardless of sex and age. the highest PM occurred without a precise diagnosis. denominated unspecified according to the ICD-10. In the north and northeast regions. more than 60% of deaths from MCS were not specifically classified (Q24.9). The second most frequent category of MCS was malformation of cardiac septa. in all geographic regions. independent of sex and age; this was most pronounced in the southeast region. with a frequency of 13% (Figure 2).

Discussion

In Brazil. between 2000 and 2015. over half (55%) of deaths in people under 20 were concentrated in children under 1 year of age. This demonstrates the extent to which this age group is vulnerable. We observed a similar distribution pattern of mortality from MCS with respect to age group and sex in different regions of Brazil. The same applies to other causes of death. However. the relative importance of large groups of causes of death varied in different manners with age. regardless of sex. In people under 20. malformations. MCS. and OMC decreased in importance as age increased. In contrast. mortality from CSD showed an opposite pattern. EC showed a "J" curve and IDC showed little variation. peaking in the 1-4 age group.

Even though the risk of all-cause mortality was higher in males. the relative importance of death from malformations and CSD was higher in females on account of the higher prevalence of EC among males. which increased with age. This observation is in agreement with previous studies;[19] relatively high mortality from EC in men has been reported in different locations around the world.[1.4.10.20] This may be attributed to men's greater exposure to risk factors. such as accidents. alcohol consumption. use of tobacco and other drugs. use of firearms and other weapons. truancy and dropping out. and involvement illicit activities.[21]

The distribution of PM from MCS throughout the regions of Brazil was in accordance with that reported in Latin America. According to the Global Burden of Disease (GBD) study. in 2015. PM from MCS in people under age 20 was 9.7% in Mexico. followed by the Southern Cone (Argentina. Chile. and Uruguay) with 7.8%. Brazil with 6.5%. the Andean Region comprising Bolivia. Ecuador. and Peru with 5.8%. and the Caribbean with 4.4%.[1] Thus. regions with higher indexes of poverty have higher percentages of death from MCS. which may be attributed to a lower diagnostic capacity. given that diagnosis of MCS requires adequate medical and hospital support.[5.6] There is a noticeable difference between the percentage shown in this study and that of the GBD. because the latter compiled complete data from only eight states in Brazil and estimated data for the rest.[3]

Given the progress of PMe over time. it seems that a correction of the low percentage of MCS diagnoses in death occurred in all regions. mainly in the north and northeast regions. especially in children under age 1. when mortality from MCS most commonly occurs. However. the percentages of imprecise anatomical and functional diagnoses of MCS. classified as unspecified. continue to be greater in these regions. In addition. the highest percentages of deaths from IDC were also in the north and northeast regions in children under age 5. Thus. it is necessary to improve diagnostic methods. especially in the poorest regions of the country.

Of all causes of death from MCS. unspecified causes were the most frequent in both sexes and in all age groups and regions. which suggests low levels of access to prenatal and newborn diagnoses. According to the Brazilian Society of Pediatrics. 1-2 of every 1.000 live births have critical congenital heart diseases. but 30% of these cases are discharged from the hospital without a correct diagnosis. and may evolve into shock. hypoxia. or premature death before adequate treatment is provided.[22] Prenatal care and obstetric echocardiography could reduce these deaths by making early diagnosis and referral to specialized treatment centers possible. even before birth.[23]

The decline in some regional differences. indicated by the PMe in the last years of the study period. may be attributed to public health measures for the detection of congenital heart diseases. such as pulse oximetry[23] in newborns with gestational age above 34 weeks. which has been recommended since 2011. and was incorporated into the Brazilian Unified Health System's list of procedures in 2014.[24] Another exam is fetal echocardiography routinely performed in pregnant women aged over 35 or with other risk factors for fetal malformation.[25] In 2004. a "Pact for the Reduction of Maternal and Neonatal Mortality" was signed on the three levels of government in Brazil with the goal of reducing neonatal mortality. The strategies were designed to reduce mortality. with greater emphasis placed on the north and northeast regions.[26]

There was an inverse trend of CSD with MCS. and the importance of CSD increased as age increased. It is worth mentioning that children with MCS who survive the first year of life. even with treated for MCS. may develop complications and sequelae. such as heart failure. arrhythmia. endocarditis. and other CSD. which may lead to death during adolescence.

Table 1 – Proportional mortality and mortality rates in children according to cause of death. sex. and age group in the north region of Brazil. 2000-2015

Causes of death		Male					Female				
		<1 year	1-4 years	5-9 years	10-14 years	15-19 years	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	2,564	282	83	55	51	2,064	286	64	66	39
	PM(%)	*4.9*	*2.7*	*1.5*	*0.9*	*0.2*	*5.06*	*3.3*	*1.6*	*1.6*	*0.6*
	Mort100.000	*100.5*(1)	*2.0*(2)	*0.6*	*0.4*	*0.4*	*85.3*(1)	*2.1*(2)	*0.5*	*0.5*	*0.3*
Other MC	Deaths	4,047	261	67	50	53	3,710	244	60	44	26
	PM(%)	*7.7*	*2.5*	*1.2*	*0.8*	*0.2*	*9.1*	*2.8*	*1.5*	*1.1*	*0.4*
	Mort100.000	*158.7*(1)	*1.8*(2)	*0.5*	*0.4*	*0.4*	*153.4*(1)	*1.8*(2)	*0.4*	*0.3*	*0.2*
DCS	Deaths	496	217	180	307	635	426	233	159	272	457
	PM(%)	*0.9*	*2.1*	*3.3*	*5.0*	*2.9*	1.0	2.66	4.07	*6.54*	*6.6*
	Mort100.000	*19.4*(1)	*1.5*(2)	*1.2*	*2.2*	*4.8*	*17.6*(1)	*1.69*(2)	1.15	*2.03*	*3.6*
Ill-defined	Deaths	4,548	1,845	683	722	1,475	3,452	1,514	499	493	694
	PM(%)	*8.6*	*17.6*	*12.5*	*11.8*	*6.6*	*8.5*	*17.3*	*12.8*	*11.9*	*10.0*
	Mort100.000	*17.3*(1)	*12.8*(2)	*4.8*	*5.2*	*11.1*	*142.7*(1)	*11.0*(2)	*3.6*	*3.7*	*5.4*
External	Deaths	837	2,341	2,133	2,794	16,668	602	1,402	1,180	1,373	2,517
	PM(%)	*1.6*	*22.4*	*38.9*	*45.6*	*75.0*	*1.5*	*16.0*	*30.2*	*33.0*	*36.4*
	Mort100.000	*32.8*(1)	*16.3*(2)	*14.8*	*20.1*	*125.5*	*24.9*(1)	*10.9*(2)	*8.5*	*10.3*	*19.7*
All causes	Deaths	52,729	10,459	5,476	6,130	22,218	40,754	8,750	3,911	4,158	6,914
	PM(%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
	Mort100.000	*2,067.2*(1)	*72.7*(2)	*38.1*	*44.1*	*167.3*	*1,684.9*(1)	*63.5*(2)	*28.4*	*31.1*	*54.0*

MCS: malformations of the circulatory system; Other MC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality;Mort100,000: mortality rate per 100,000 (1) Mortality per 100,000 live births (2) Mortality per 100,000 in the population aged from 0 to 4 years excluding live births

Table 2 – Proportional mortality and mortality rates in children according to cause of death, sex and age group in the northeast region of Brazil, 2000-2015

Causes of death		Male					Female				
		<1 year	1-4 years	5-9 years	10-14 years	15-19 years	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	6,743	822	255	182	193	5,602	937	234	180	157
	PM (%)	*4.5*	*3.4*	*1.8*	*1.0*	*0.2*	*4.9*	*4.6*	*2.3*	*1.6*	*0.8*
	Mort100,000	*93.3*(1)	*2.4*(2)	*0.6*	*0.4*	*0.4*	*81.5*(1)	*2.8*(2)	*0.6*	*0.4*	*0.4*
Other MC	Deaths	11,086	758	256	175	171	9819	770	223	172	151
	PM (%)	*7.5*	*5.7*	*1.9*	*1.0*	*0.2*	*8.6*	*3.7*	*2.2*	*1.6*	*0.8*
	Mort100,000	*153.4*(1)	*2.2*(2)	*0.6*	*0.4*	*0.4*	*143.0*(1)	*2.3*(2)	*0.5*	*0.4*	*0.4*
DCS	Deaths	1,138	721	565	1,005	2,374	986	692	493	845	1,595
	PM (%)	*0.8*	*3.0*	*4.1*	*5.6*	*3.0*	*0.9*	*3.4*	*5.0*	*7.7*	*8.0*
	Mort100,000	*15.7*(1)	*2.1*(2)	*1.3*	*2.3*	*5.6*	*14.4*(1)	*2.1*(2)	*1.2*	*2.0*	*3.8*
Ill-defined	Deaths	12,576	3,403	1,378	1,429	3,357	9,545	2,931	1,071	1,118	1,800
	PM (%)	*8.5*	*14.2*	*10.0*	*7.9*	*4.3*	*8.4*	*14.3*	*10.8*	*10.1*	*9.1*
	Mort100,000	*174.1*(1)	*9.9*(2)	*3.2*	*3.3*	*7.9*	*139.0*(1)	*8.9*(2)	*2.6*	*2.7*	*4.3*
External	Deaths	1,994	4,895	5,245	9,119	62,854	1,372	3,044	2,627	3,380	7,621
	PM (%)	*1.3*	*20.4*	*38.1*	*50.5*	*80.3*	*1.2*	*14.8*	*26.4*	*30.7*	*38.3*
	Mort100,000	*27.6*(1)	*14.3*(2)	*12.3*	*21.1*	*147.4*	*20.0*(1)	*9.2*(2)	*6.4*	*8.1*	*18.3*
All causes	Deaths	148,346	23,957	13,782	18,038	78,248	113,735	20,529	9,949	11,019	19,872
	PM (%)	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*
	Mort100,000	*2053.1*(1)	*70.0*(2)	*32.0*	*42.0*	*183.5*	*1,656.6*(1)	*62.1*(2)	*24.1*	*26.4*	*47.8*

MCS: malformations of the circulatory system; Other MC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality;Mort100,000: mortality rate per 100,000 (1) Mortality per 100,000 live births (2) Mortality per 100,000 in the population aged from 0 to 4 years excluding live births

Table 3 – Proportional mortality and mortality rates in children according to cause of death, sex, and age group in the southeast region of Brazil, 2000-2015

Causes of death		Male					Female				
		<1 year	1-4 years	5-9 years	10-14 years	15-19 years	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	10,534	1,091	250	250	218	9,088	1,101	275	218	183
	PM(%)	*7.1*	*4.7*	*1.8*	*1.2*	*0.2*	*7.8*	*5.7*	*2.6*	*1.7*	*0.7*
	Mort100,000	*110.0*(1)	*2.7*(2)	*0.5*	*0.5*	*0.4*	*99.5*(1)	*2.8*(2)	*0.5*	*0.4*	*0.3*
Other MC	Deaths	15,407	1,252	366	301	290	14,042	1,246	372	288	263
	PM(%)	*10.4*	*5.4*	*2.6*	*1.5*	*0.3*	*12.0*	*6.4*	*3.5*	*2.3*	*1.1*
	Mort100,000	*160.8*(1)	*3.1*(2)	*0.7*	*0.6*	*0.5*	*153.7*(1)	*3.2*(2)	*0.7*	*0.5*	*0.5*
DCS	Deaths	1,537	818	533	980	2,579	1,401	784	534	723	1585
	PM(%)	*1.0*	*3.6*	*3.8*	*4.8*	*2.6*	*1.2*	*4.1*	*5.0*	*5.7*	*6.5*
	Mort100,000	*16.0*(1)	*2.0*(2)	*1.0*	*1.8*	*4.6*	*15.3*(1)	*2.0*(2)	*1.1*	*1.4*	*2.9*
Ill-defined	Deaths	6,054	1,821	720	1,166	3,856	4,441	1,406	650	837	1,610
	PM(%)	*4.1*	*7.9*	*5.1*	*5.7*	*3.9*	*3.8*	*7.3*	*6.1*	*6.6*	*6.6*
	Mort100,000	*63.2*(1)	*4.5*(2)	*1.4*	*2.2*	*6.9*	*48.6*(1)	*3.6*(2)	*1.3*	*1.6*	*3.0*
External	Deaths	4,969	5,237	5,166	10,487	80,167	3,237	3,470	2,897	4,158	10,563
	PM(%)	*3.4*	*22.8*	*36.5*	*51.0*	*80.4*	*2.8*	*17.9*	*27.3*	*32.9*	*43.0*
	Mort100,000	*51.9*(1)	*12.8*(2)	*9.8*	*19.4*	*143.6*	*35.4*(1)	*8.9*(2)	*5.7*	*8.0*	*19.5*
All causes	Deaths	147,871	23,006	14,167	20,571	99,661	116,679	19,333	10,663	12,650	24,550
	PM(%)	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*
	Mort100,000	*1,543.8*(1)	*56.3*(2)	*26.9*	*38.0*	*178.6*	*1,277.4*(1)	*49.4*(2)	*2.1*	*24.2*	*45.3*

MCS: malformations of the circulatory system; Other MC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality;Mort100,000: mortality rates per 100,000 (1) Mortality per 100,000 live births (2) Mortality per 100,000 in the population aged from 0 to 4 years excluding live births

Table 4 – Proportional mortality and mortality rates in children according to cause of death, sex, and age group in the south region of Brazil, 2000-2015

Causes of death		Male					Female				
		<1 year	1-4 years	5-9 years	10-14 years	15-19 years	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	3,869	429	114	94	127	3,147	409	114	80	76
	PM(%)	*8.5*	*5.5*	*2.2*	*1.2*	*0.4*	*8.7*	*6.6*	*3.1*	*1.7*	*0.9*
	Mort100,000	*120.8*(1)	*3.1*(2)	*0.6*	*0.5*	*0.6*	*103.1*(1)	*3.1*(2)	*0.7*	*0.4*	*0.4*
Other MC	Deaths	5,694	590	188	147	141	5,093	495	158	145	116
	PM(%)	*12.5*	*7.6*	*3.7*	*2.0*	*0.4*	*14.1*	*8,0*	*4.3*	*3.1*	*1.3*
	Mort100,000	*177.8*(1)	*4.3*(2)	*1.0*	*0.8*	*0.7*	*167.0*(1)	*3,8*(2)	*0.9*	*0.8*	*0.6*
DCS	Deaths	257	191	123	255	618	233	184	118	197	358
	PM(%)	*0.6*	*2.5*	*2.4*	*3.4*	*2.0*	*0.6*	*2,9*	*3.2*	*4.3*	*4.1*
	Mort100,000	*8.0*(1)	*1.4*(2)	*0.7*	*1.3*	*3.2*	*7.6*(1)	*1,4*(2)	*0.7*	*1.1*	*1.9*
Ill-defined	Deaths	1,802	375	130	210	577	1,388	370	110	163	293
	PM(%)	*4.0*	*4.8*	*2.5*	*2.8*	*1.8*	*3.9*	*5.9*	*3.0*	*3.5*	*3.3*
	Mort100,000	*56.3*(1)	*2.7*(2)	*0.7*	*1.1*	*3.0*	*45.5*(1)	*2.8*(2)	*0.6*	*0.9*	*1.6*
External	Deaths	2,037	2,211	2,265	4,272	25,974	1,532	1,332	1,250	1,825	4,398
	PM(%)	*4.5*	*28.5*	*44.3*	*56.8*	*82.3*	*4.3*	*21.4*	*33.9*	*39.5*	*50.3*
	Mort100,000	*63.6*(1)	*16.0*(2)	*12.5*	*22.5*	*133.1*	*50.2*(1)	*10.1*(2)	*7.2*	*10.0*	*23.4*
All causes	Deaths	45,436	7,749	5,113	7,514	31,541	36,020	6,228	3,692	4,621	8,738
	PM(%)	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*	*100*
	Mort100,000	*1,419.1*(1)	*56.3*(2)	*28.2*	*39.6*	*161.6*	*1,180.9*(1)	*47.3*(2)	*11.2*	*25.4*	*46.5*

MCS: malformations of the circulatory system; Other MC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality;Mort100,000: mortality rates per 100,000 (1) Mortality per 100,000 live births (2) Mortality per 100,000 in the population from 0 to 4 years excluding live births

Table 5 – Proportional mortality and mortality rates in children according to cause of death, sex, and age group in the central-west region of Brazil, 2000-2015

Causes of death		Male					Female				
		<1 year	1-4 years	5-9 years	10-14 years	15-19 years	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	2,434	277	64	44	52	2,115	239	41	49	51
	PM(%)	*8.0*	*4.9*	*1.9*	*1.0*	*0.3*	*8.8*	*5.2*	*1.8*	*1.7*	*1.0*
	Mort100,000	*129.8*(1)	*3.5*(2)	*0.6*	*0.4*	*0.5*	*118.6*(1)	*3.2*(2)	*0.4*	*0.5*	*0.5*
Other MC	Deaths	3,481	272	79	52	53	3,065	254	57	71	44
	PM(%)	*11.4*	*4.8*	*2.3*	*1.1*	*0.3*	*12.7*	*5.5*	*2.5*	*2.5*	*0.8*
	Mort100,000	*185.7*(1)	*3.5*(2)	*0.8*	*0.5*	*0.5*	*171.9*(1)	*3.4*(2)	*0.6*	*0.7*	*0.4*
DCS	Deaths	307	137	92	202	439	234	152	72	160	305
	PM(%)	*1.0*	*2.4*	*2.7*	*4.5*	*2.3*	*1.0*	*3.3*	*3.1*	*5.6*	*5.8*
	Mort100,000	*16.4*(1)	*1.7*(2)	*0.9*	*2.0*	*4.2*	*13.1*(1)	*2.0*(2)	*0.7*	*1.6*	*3.0*
Ill-defined	Deaths	927	248	108	152	378	588	210	78	89	168
	PM(%)	*3.0*	*4.4*	*3.2*	*3.4*	*1.9*	*2.4*	*4.6*	*3.4*	*3.1*	*3.2*
	Mort100,000	*49.4*(1)	*3.2*(2)	*1.1*	*1.5*	*3.7*	*33.0*(1)	*2.8*(2)	*0.8*	*0.9*	*1.7*
External	Deaths	979	1,620	1,575	2,615	16,173	688	1,080	847	1,256	2,696
	PM(%)	*3.2*	*28.5*	*46.8*	*57.8*	*83.6*	*2.9*	*23.5*	*36.8*	*44.1*	51.0
	Mort100,000	*52.2*(1)	*20.7*(2)	*15.8*	*25.9*	*156.5*	*38.6*(1)	*14.4*(2)	*8.9*	*12.9*	*26.7*
All causes	Deaths	30,511	5,683	3,366	4,522	19,348	24,081	4,590	2,303	2,845	5,290
	PM(%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
	Mort100,000	*1,627.5*(1)	*72.5*(2)	*33.8*	*44.8*	*187.2*	*1,350.7*(1)	*61.2*(2)	*24.1*	*29.2*	*52.4*

MCS: malformations of the circulatory system; Other MC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality; Mort100,000: mortality rates per 100,000 (1) Mortality per 100,000 live births (2) Mortality per 100,000 in the population aged from 0 to 4 years excluding live births

Table 6 – Proportional mortality and mortality rates in children according to cause of death, sex, and age group, Brazil, 2000-2015

Causes of death		<20 years	Male						Female					
		Total	Total	<1 year	1-4 years	5-9 years	10-14 years	15-19 years	Total	<1 year	1-4 years	5-9 years	10-14 years	15-19 years
MCS	Deaths	57,892	31,077	26,144	2,901	766	625	641	26,815	22,016	2,972	728	593	506
	PM(%)	*4.2*	*3.7*	*6.2*	*4.1*	*1.8*	*1.1*	*0.3*	*5.1*	*6.6*	*5.0*	*2.4*	*1.7*	*0.8*
	Mort100,000	*5.3*	*5.6*	*107.0*(1)	*2.7*(2)	*0.6*	*0.4*	*0.5*	*5.0*	*94.7*(1)	*2.9*(2)	*0.5*	*0.4*	*0.4*
Other MC	Deaths	86,165	45,237	39,715	3,133	956	725	708	40,928	35,729	3,009	870	720	600
	PM(%)	*6.3*	*5.4*	*9.3*	*4.4*	*2.3*	*1.3*	*0.3*	*7.78*	*10.8*	*5.1*	*2.9*	*2.0*	*0.9*
	Mort100,000	*7.9*	*8.2*	*162.6*(1)	*2.9*(2)	*0.7*	*0.5*	*0.5*	*7.7*	*153.7*(1)	*2.9*(2)	*0.7*	*0.5*	*0.4*
DCS	Deaths	29,904	16,706	3,735	2,084	1,493	2,749	6,645	13,198	3,280	2,045	1,376	2,197	4,300
	PM(%)	*2.2*	*2.0*	*0.9*	*2.9*	*3.6*	*4.8*	*2.6*	*2.54*	*1.0*	*3.4*	*4.5*	*6.2*	*6.6*
	Mort100,000	*2.8*	*3.0*	*15.3*(1)	*1.9*(2)	*1.1*	*2.0*	*4.7*	*2.5*	*14.1*(1)	*2.0*(2)	*1.0*	*1.6*	*3.1*
Ill-defined	Deaths	85,458	49,940	25,907	7,692	3,019	3,679	9,643	35,518	19,414	6,431	2,408	2,700	4,565
	PM(%)	*6.2*	*5.9*	*6.1*	*10.9*	*7.2*	*6.5*	*3.8*	*6.82*	*5.9*	*10.8*	*7.9*	*7.7*	*7.0*
	Mort100,000	*7.9*	*9.0*	*106.0*(1)	*7.0*(2)	*2.2*	*2.6*	*6.8*	*6.7*	*83.5*(1)	*6.2*(2)	*1.8*	*2.0*	*3.3*
External	Deaths	340,974	274,627	10,816	*16,304*	16,384	29,287	201,836	66,347	7,431	10,328	8,801	11,992	27,795
	PM(%)	*24.9*	*32.5*	*2.5*	*23.0*	*39.1*	51.6	*80.4*	*12.75*	*2.2*	*17.4*	*28.8*	*34.0*	*42.5*
	Mort100,000	*31.4*	*49.7*	*44.3*(1)	*15.0*(2)	*11.9*	20.9	*142.5*	*12.5*	*32.0*(1)	*9.9*(2)	*6.6*	*8.9*	*20.2*
All causes	Deaths	1,367,355	845,481	424,932	70,854	41,904	56,775	251,016	521,874	331,269	59,430	30,518	35,293	65,364
	PM(%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	100.0	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
	Mort100,000	*126.0*	*153.0*	*1,739.3*(1)	*65.2*(2)	*30.4*	*40.5*	177.3	*98.0*	*1,424.7*(1)	*57.0*(2)	*23.0*	*26.1*	*47.6*

MCS: malformations of the circulatory system; OtherMC: other congenital malformations excluding MCS; CSD: circulatory system disease; PM(%):proportional mortality;Mort100,000:

Original Article

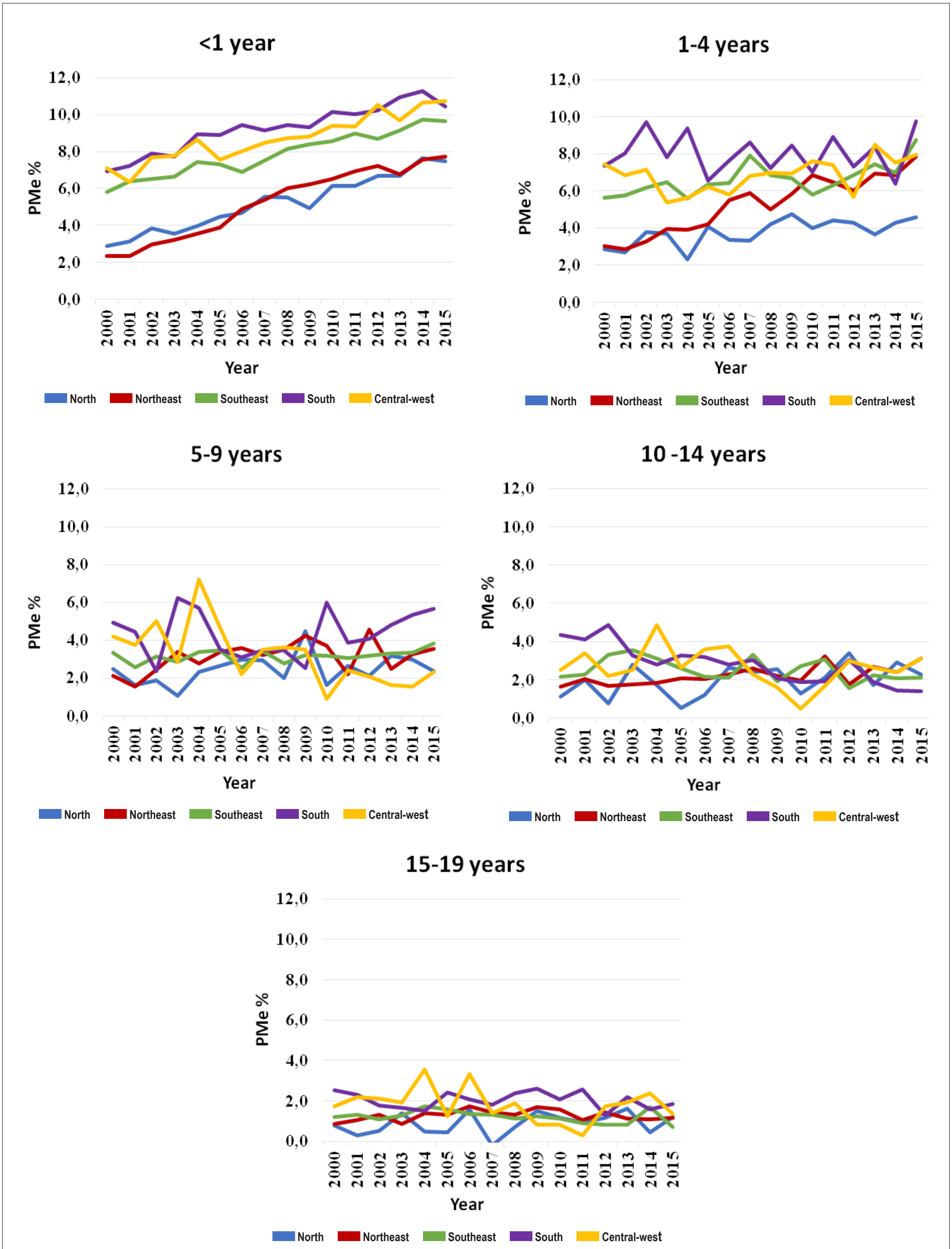

Figura 1 – *Endogenous proportional mortality due to malformations of the circulatory system by age group and macroregion of Brazil. 2000 to 2015; *PMe%= endogenous proportional mortality due to malformations of the circulatory system. excluding external causes*

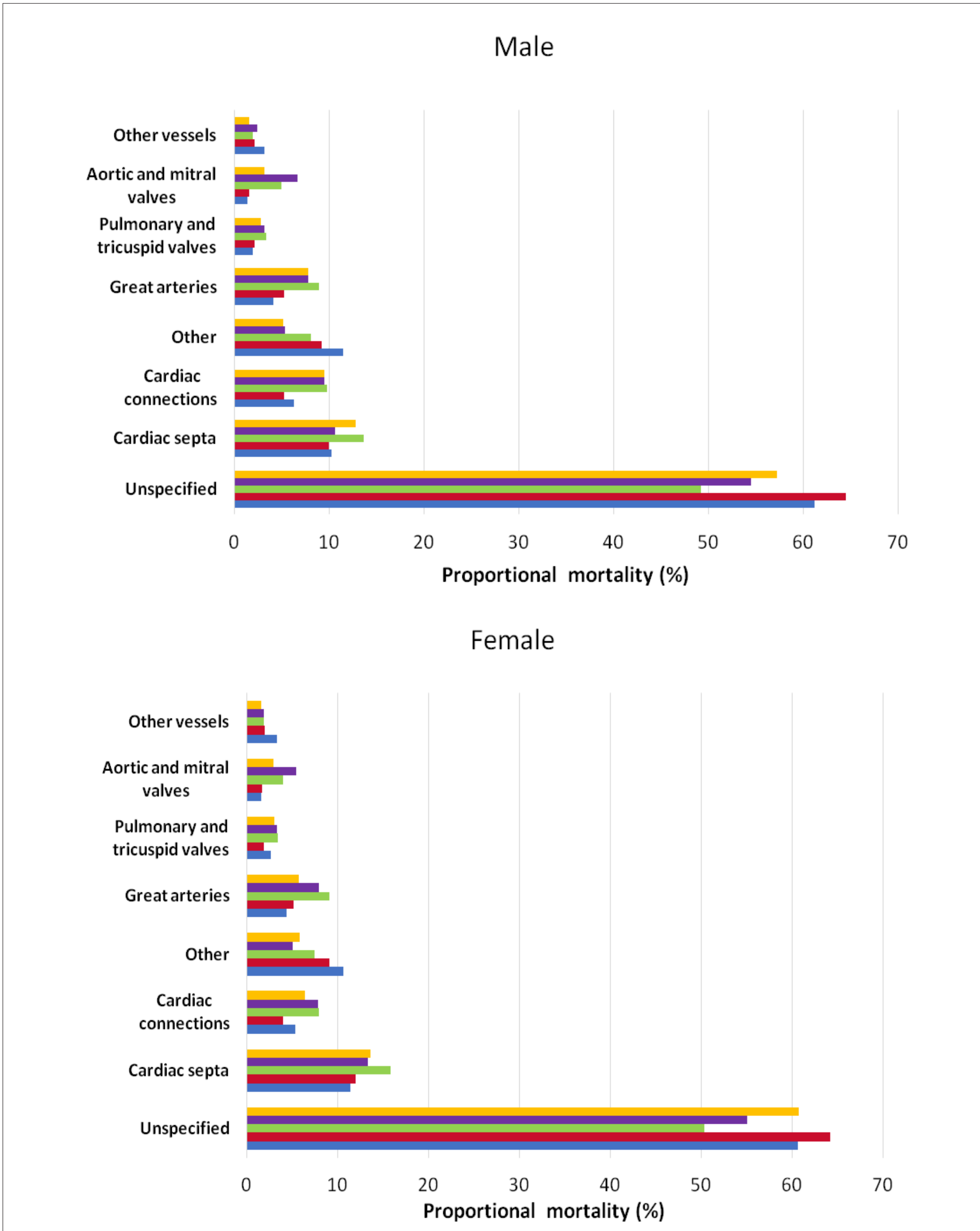

Figure 2 – *Proportional mortality from malformations of the circulatory system in individuals under 20 years. by sex and macroregion of Brazil. 2000 to 2015*

and increase mortality from CSD.[27] The lowest differences in the MCS:CSD ratios were found are in the northeast region. followed by the north region. This may be explained by misdiagnoses of MCS and CSD. since a correct differential diagnosis relies on appropriate. timely diagnostic resources. which are scarcer in these two regions.

One limitation of this study was the age-group division provided by the IBGE. based on population projections. that was adopted in the study. In this categorization. children under 1 year of age was included in the same age group of children under 5 years of age. and hence values of children from ages 1 to 4 were approximated to values slightly lower than the real ones. Thus. the risks measured by the mortality rates per 100.000 in this age group were slightly overestimated. However. this fact did not affect the estimates of PMs. as they do not depend on population estimates. Another limitation is the quality of information on the causes of death provided in death certificates. Data on the time between diagnosis and death were incomplete. and for this reason. it was not possible to determine the influence of the inaccurate diagnosis of MCS on death. Death certificates are. however. the only comprehensive source of data regarding deaths in Brazil as a whole.

Conclusion

In Brazil. from 2000 to 2015. in people under age 20. MCS were the leading cause of death among all malformations. being twice as important as CSD. especially in children under 1 year of age. There were improvements in diagnoses of death from MCS in the final years of the study period. However. in MCS. the frequency of imprecise diagnoses is still elevated in both sexes. in all age groups. and especially in the north and northeast regions of Brazil. Thus. public health strategies must be strengthened. and that greater attention must be given to newborns aiming the correct diagnosis and early treatment of congenital cardiopathies.

Author contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Salim TR. Andrade TM. Klein CH. Oliveira GMM

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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Short Editorial

Mortality in Congenital Heart Disease in Brazil - What do we Know?

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Minieditorial referente ao artigo: Desigualdades nas Taxas de Mortalidade por Malformações do Sistema Circulatório em Crianças Menores de 20 Anos de Idade entre Macrorregiões Brasileiras

Congenital Heart Disease (CHD) comprises any change in the anatomy of the heart and its blood vessels. The incidence of CHD is 8 to 10 per 1,000 live births, that is or one in one hundred births. In Brazil, 28,900 children are born with CHD per year (1% of the total births), of which about 80% (23,800) require cardiac surgery, and half of them, within the first year of life.[1] Congenital malformations represent the second main cause of mortality in children under one year of age. CHD is the most frequent and the one with the highest mortality in the first year of life in Brazil, and the second cause of death in up to 30 days of life.[2] Congenital heart disease manifestations are very variable and may occur soon after birth or appear later in childhood or adolescence.

Brazil is a continental country, where the diversity observed both in the diagnosis and in treatment of congenital heart diseases is very large among the macro-regions. It is a fact that there has been a gradual improvement in diagnosis, after the more active dissemination of the oximetry test, with technological advances and the diffusion of echocardiography throughout the country, even so a low survival rate is still observed in the neonatal period. Lopes et al. demonstrated a lethality of 64.7% for critical congenital heart disease and a 28-day survival rate reduced by almost 70% in these newborns, signaling a great need for investment in assistive technology and trained professionals for this among this population.[3]

There have been some national studies evaluating the trend of mortality from cardiac malformations in Brazil. Braga et al carried out an observational ecological study based on the Mortality Information System (SIM), of which data are managed by the Ministry of Health and are processed by the Information System of the Unified Health System (DATASUS). The authors found a tendency toward a reduction in cases of mortality from congenital heart disease in Brazil during the study, but point out the probable underreporting and underdiagnosis as study limitations, especially in the neonatal period.[4]

Recently in the article entitled "Inequalities in mortality rates due to malformations of the circulatory system in children under 20 years of age among Brazilian macro-regions",[5] the study data were extracted from DATASUS and the Brazilian Institute of Geography (IBGE) and were directly related to the accuracy of the filling-in of death certificates. The codification of the basic cause of death was performed according to the 100th revision of the World Health Organization's Statistical Classification of Diseases and Related Health Problems (ICD 10). There were 1,367,355 deaths from all causes among children under 20 years old, 55% in children under 1 year old. Deaths due to congenital malformations were 144,057, of which 39% were due to malformations of the circulatory system, corresponding to 5.3 / 100,000 inhabitants. Between 2000 and 2015, the main cause of death in children under 20 was circulatory system malformation.

In this study, the South and Midwest regions had almost twice the risk of death from congenital heart malformation than the North and Northeast regions in those under one year of age, with progressive reduction of this risk with an increase in the age group. These data reinforces once again the probable diagnostic scarcity, directly reflecting data notification in death certificates.[5] In this study, the high percentages of inaccurate diagnoses of circulatory system malformations, which were classified as not specified in death certificates, drew attention, mainly in the poorest regions of the country.

Children who were born with congenital heart malformations and could be treated in a timely manner, may develop evolutionary complications, such as heart failure, infectious endocarditis, prosthesis and tube dysfunction, thrombosis, cardiac arrhythmias, ventricular dysfunction, in addition to the need for reoperations or new interventional procedures. These comorbidities and reinterventions can evolve with an unfavorable outcome even in childhood, adolescence or early adulthood, further increasing the rate of mortality from diseases of the circulatory system in patients with congenital heart disease.

Proportional mortality corresponds to the ratio between deaths from specific causes and total deaths. According to data from the Global Burden of Disease, the proportional mortality from congenital heart malformation in children under 20 in 2015, was 6.5% in Brazil, 9.7% in Mexico, 5.8% in Andean America (Bolivia, Ecuador and Peru), 7.8% in Argentina, Chile and Uruguay and 4.4% in the Caribbean.[6]

The neonatal and infant age group up to one year still has a noticeable high rate of inaccurate diagnoses as a cause of death throughout Brazil, but mainly in the North and Northeast regions. This fact reinforces that it is crucial to strengthen public health strategies focused on the diagnosis and early treatment of congenital heart diseases. Some steps have been taken, such as the "pact for the reduction of maternal and neonatal mortality" signed between the three levels of

Keywords

Congenital Heart Disease; Mortality; Oximetry Test; Underdiagnosis; Epidemiology; Public Health Administration.

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attention of the Brazilian federation in 2004; the institution of mandatory oximetry testing in 2014,[7,8] which despite its extreme importance and easy performance, unfortunately is still not a national reality in all maternity hospitals in the country to date.[9]

In 2017, the Brazilian Ministry of Health launched a federal project to expand the care of children with congenital heart disease,[2] aiming to increase the care of these children by 30% per year, which corresponds to more than 3,400 procedures per year, totaling about 12,600 procedures / year, which would have a great impact on the reduction of neonatal mortality. Much needs to be done to minimize the extremely high neonatal mortality in Brazil related to congenital heart disease, from optimizing the early diagnosis of newborns or even prenatal diagnosis to structuring beds in the intensive care unit to treat these newborns, whether through clinical, surgical or hemodynamic intervention.

The association of efforts in all spheres needs to gain volume. The spread of this serious public health problem has to occur broadly for society and the desired support of the private business system in this struggle needs to be strengthened, as is the case in more developed countries. All health professionals involved, physicians, nurses, psychologists, physiotherapists, and nutritionists need to increasingly establish an active partnership with the public health system, so that more hospitals can be trained in all the steps necessary to care for patients with congenital heart disease. Starting with more trained teams, better data notification will occur in such a large country as Brazil, providing us with a more reliable picture of the reality of congenital heart disease in our country. In addition, more diagnoses with consequent early treatments will make all the difference in breaking this great paradigm that is infant mortality from congenital heart disease in our country.

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Outlook and Perspectives in Diagnosis and Treatment of Congenital Heart Diseases in Brazil

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Short Editorial related to the article: Inequalities in Mortality Rates from Malformations of Circulatory System Between Brazilian Macroregions in Individuals Younger Than 20 Years

The 1988 Brazilian Constitution, also called the "Citizen Constitution", established universal access to health when, in its article 196, it stated that this is the right of all citizens and the Government's responsibility. Just over a decade later, the Brazilian Unified Health System (SUS, *Sistema Único de Saúde*) was created, which, in order to respect the principles of universality, integrality and equality established in the Magna Carta, laid down guidelines for decentralization, comprehensive care and popular participation.

Very much inspired at the time on the English health system, SUS is undoubtedly one of the largest public health systems worldwide, responsible for approximately 190 million people, 80% of whom depend exclusively on it to take care of their health, as they do not have access to the private health system. Still, even among those with access to the private system, the use of the public health system is constitutionally guaranteed, without limits or restrictions.

SUS financing is undoubtedly one of the biggest challenges faced during its 20 years of existence, because although the funds are in theory guaranteed by Constitutional Amendment Number 29 and by several other legal provisions, the breadth of its coverage makes it impossible to be constantly updated in coverage and paid amounts. In fact, despite being theoretically a universal and integral system, the consequence of financing difficulties is that the public system offers less comprehensive preventive, diagnostic and therapeutic resources than the private system, which has created a huge gap between the two systems over time. Therefore, it becomes essential to develop clear public health policies to manage these resources and, probably, at some point a broad re-discussion of the role of the public and private systems in serving the population will have to take place.

In this issue, we will have the opportunity to read an important article.[1] In a clear, objective and technical way, it demonstrates with concrete numbers obtained from the official SUS database the importance that congenital heart diseases have in the mortality of individuals younger than 20 years of age, and especially in children under 1 year. The study shows that this universal coverage is not reflected in real life when it comes to this group of diseases.

Keywords

Constitution and Bylaws; Unified Health System; Heart Defects Congenital/diagnostic; Healthcare Financing.

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The incidence of congenital heart disease in the general population is 8 in every 1,000 live births.[2] Using the Brazilian birth rate,[3] we would have approximately 30,000 new births of children with heart disease. In at least half of these newborns, heart disease shows a good evolution, with spontaneous cure or non-severe evolution, to the point that the diagnosis is made only in adulthood.[4] Therefore, still approximately, we would have 15,000 newborns who would annually require some type of treatment, often surgical or through interventional cardiology, and many of them soon after birth or during the first year of life.

Keeping this reasoning in mind, official data indicate the scarce number of high cardiovascular complexity hospitals that provide care to SUS patients in Brazil.[5]

The National Policy for High Complexity Cardiovascular Care (PNACAC, *Política Nacional de Atenção Cardiovascular de Alta Complexidade*) classifies the services according to the type of activity developed and establishes a minimum quantity of annual production: cardiovascular surgeries (180 procedures); interventional cardiology procedures (144); extracardiac endovascular procedures (120); pediatric cardiovascular surgeries (120); vascular surgeries (90); and electrophysiology laboratory procedures (39). This policy, however, is based only on the number of procedures and the established capacity, not taking into account the real need of the different regions in the country. The result is the distortion of the system, with scarce and poorly distributed beds for the care of cardiovascular diseases and, also, a service can be considered of high cardiovascular complexity without the need to encompass all the area activities mentioned above.

The authors' survey,[5] using data from 2014, showed the existence of a little over 3,000 beds in Brazil reserved for High Cardiovascular Complexity in SUS in the 277 hospitals irregularly distributed throughout Brazil. Only 9.6% of them have assistance in pediatric cardiac surgery. Some states, such as Tocantins, do not have a service with pediatric cardiac care. Still, just over 20% of these hospitals in Brazil are public – although most of the private ones are philanthropic (and therefore have tax advantages) – even so we are back to the constant struggle over the underfunding of the Unified Health System. These are children born with complex heart disease, where it is not uncommon to need several interventions throughout life, carried out by multidisciplinary teams and different specialties.

Another problem is the issue of the multidisciplinary team. The evolution of the diagnosis and treatment of congenital heart diseases requires not only specific training, but also that these different specialties act in a complementary, integrated and sometimes simultaneous way. The PNACAC requires a minimum number of surgical procedures to consider the service as high complexity, but it does not do the same for the performance of equally important procedures – many do not have accreditation, equipment or procedures in interventional cardiology and / or electrophysiology for that population concurrently with cardiac surgery service, nor other support activities such as nutrition, complementary exams (computed tomography and MRI) or specialized physiotherapy. New materials and techniques make interventional cardiology today an important and viable alternative not only for the diagnosis, but mainly for the treatment of many congenital heart diseases, which can increase the number of patients that are treated, thus freeing the cardiac surgeon to perform other procedures that the catheterization team cannot do.

Thus, returning to the numbers above, crossing the information on the number of patients with congenital heart disease requiring treatment at birth (or at least in the pediatric age group) with the number of performed surgeries and catheterizations and beds available for this population, we are sure that many of these children do not even have their diagnosis confirmed, and even if they have, they might die without any assistance. Or sometimes they die during transfer to a referral service. The consequence is clear and immediate: they are "invisible" deaths, which appear little in the statistics and in the media and are therefore forgotten and relegated to a secondary level. Among the most important causes of death in Brazil and worldwide are heart diseases.[6] But these deaths, when mentioned, are immediately associated with Acute Myocardial Infarction, not with congenital heart diseases.

In 2017, the Ministry of Health signaled the starting of change when the National Assistance Plan for Children with Congenital Heart Disease (*Plano Nacional de Assistance a Crianças com Cardiopatia Congênita*)[7] was launched, which would integrate actions for access to diagnosis, treatment and rehabilitation of children with heart disease. The initial goal was to increase the number of surgeries performed in the public health system by 30%. The Ordinance, published under number 1,727, took an important step in transferring funding for pediatric cardiac procedures to the Fund for Strategic Actions and Compensation (FAEC, *Fundo de Ações Estratégicas e Compensação*). The immediate result was an 8% increase in the number of pediatric cardiac surgeries a year later.[8]

Considering all these data, it is obvious that there is an urgent need to move forward with the National Assistance Plan for Children with Congenital Heart Disease, now aiming to opening beds and training new specialized services in the diagnosis and treatment of those diseases. Cardiovascular system malformations are an important cause of mortality in newborns and infants and need more attention by the government. It is impossible to talk about a universal health care system when some are more equal than others; when not everyone in need has access to diagnosis nor adequate treatment. And when they are managed to be treated, still SUS does not offer the same possibilities of materials or procedures as the private sector does. These factors, together with an extensive training of specialized professionals and the underfunding of the system, make it clear that only more objective attitudes on the part of the federal, state and municipal governments will change this scenario.

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Recommendations for the Post-Mortem Management of Cardiac Implantable Electronic Devices

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Abstract

The management of cardiac implantable electronic devices after death has become a source of controversy. There are no uniform recommendations for such management in Brazil; practices rely exclusively on institutional protocols and regional custom. When the cadaver is sent for cremation, it is recommended to remove the device due to the risk of explosion and damage to crematorium equipment, in addition to other precautions. Especially in the context of the SARS-CoV-2 pandemic, proper guidance and organization of hospital mortuary facilities and funeral services is essential to minimize the flow of people in contact with bodily fluids from individuals who have died with COVID-19. In this context, the Brazilian Society of Cardiac Arrhythmias has prepared this document with practical guidelines, based on international publications and a recommendation issued by the Brazilian Federal Medical Council.

Keywords

Cardiac Resynchronization Therapy Device/complications; Principle Based Ethics; Autopsy/methods.

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The number of cardiac implantable electronic devices (CIEDs) placed, such as pacemakers, multisite devices, implantable cardioverter-defibrillators, and implantable loop recorder, has increased substantially in recent decades due to major diagnostic and therapeutic advances, as well as to the evident increases achieved in patient longevity (older adults may experience a longer life span as a result of CIED placement). The growing range of clinical situations in which these devices are used has been followed by an increase in complications and other related issues.

One major concern in relation to CIEDs—especially in the elderly population, due to the high mortality rates related to SARS-Cov-2 infection (COVID-19)—is their handling after death:

- Should the CIED be turned off?

- Should the CIED be removed before the patient's burial?

- If the body will be cremated, which precautions should be taken?

- If the decision is made to remove the CIED, who should perform the procedure?

In response to these questions, the Brazilian Society of Cardiac Arrhythmias (SOBRAC) has developed a series of recommendations based on international evidence,[1,2] which we believe to be essential guidance for physicians, hospitals, and funeral services, which are faced with this situation on a daily basis:

1. In cases of sudden death, the CIED should be electronically interrogated whenever the attending physician believes further elucidation of the cause of death is warranted, as the capability of these devices to record and store heart rhythm can be useful for this purpose.

2. In cadaver with CIEDs who will be buried rather than cremated, neither reprogramming nor device removal is necessary.

3. Conversely, cadaver with CIEDs whose remains will be cremated must always undergo device removal due to the risk of explosion and damage to crematorium facilities secondary to overheating (the device is exposed to a temperature of approximately 1300°C for 90 minutes).

4. Implantable cardioverter-defibrillators (ICDs) in cadaver who will be cremated or will undergo autopsy must be disabled by telemetry prior to the start of either of these procedures, so as to prevent inadvertent activation and delivery of a shock to forensic or mortuary professionals during manipulation. Device reprogramming via telemetry should be performed by a physician with expertise in cardiac implantable electronic devices or by a qualified technician. For autopsy, one alternative that can be considered under exceptional circumstances is magnet placement over the ICD generator instead of reprogramming via telemetry. In such cases, the magnet must be kept over the generator even after device removal, since the risk of shock persists until the ICD is disabled by reprogramming.

5. According to a guidance letter issued by the Federal Medical Council (see Appendix) on May 5, 2020, in response to a SOBRAC request, post-mortem removal of CIEDs should be carried out "preferably by a physician and duly noted in the patient's medical record, as a safeguard during the time of the COVID-19 pandemic; hence, the importance of involving upper technical management so as to create the optimal protocol for each institution" (letter #2,628/2020 – DEPCO). SOBRAC warns that non-medical personnel (whether funeral directors or hospital staff) who may be assigned to this task must be properly trained to perform it, even though such a procedure is technically simple and does not endanger the life of the professional who performs it.

Understanding the aspects related to handling of CIEDs after death during the COVID-19 pandemic is essential to reducing the risk of disease spread.

The recommended CIED removal technique is as follows:

- don appropriate personal protective equipment in order to avoid contamination by bodily fluids;
- using a scalpel blade, deeply incise the skin overlying the pulse generator;
- divide the deep tissues bluntly (with fingers) or sharply (with scissors);
- pull out the generator and divide the electrodes with scissors;
- close the incision with gauze and tape—there is no need for sutures;
- dispose of the device safely, following the relevant technical recommendations and institutional protocols.

Author contributions

Conception and design of the research and Acquisition of data: Oliveira JC, Fagundes AA, Teixeira RA; Analysis and interpretation of the data: Oliveira JC, Fagundes AA, Teixeira RA, Baggio Junior JM, Armaganijan L, d'Avila A, Saad EB, Andrade VS, Moraes LGB, Kuniyoshi R, Rezende AGS, Pimentel M, Rodrigues TR, Brito Junior HL, Pisani CF, Arfelli E, Cintra FD, Kalil CAA, Melo SL, Cannavan PMS; Statistical analysis: Nadalin E; Writing of the manuscript: Oliveira JC, Fagundes AA, Teixeira RA, Baggio Junior JM, Armaganijan L, d'Avila A, Saad EB, Andrade VS, Moraes LGB, Kuniyoshi R,; Critical revision of the manuscript for intellectual content: Oliveira JC, Fagundes AA, Teixeira RA, Baggio Junior JM, Armaganijan L, d'Avila A, Saad EB, Andrade VS, Moraes LGB, Kuniyoshi R, Rezende AGS, Pimentel M, Rodrigues TR, Brito Junior HL, Nadalin E, Pisani CF, Arfelli E, Cintra FD, Kalil CAA, Melo SL, Cannavan PMS.

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Mechanical Aortic Prosthetic Thrombosis in a 65-Year-Old Woman with SARS-CoV-2 Infection

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Clinical data

A 65-year-old female patient was hospitalized, initially due to an episode of melena. Anticoagulation was suspended, and upper gastrointestinal endoscopy was performed, without detecting bleeding. In 2005, she had late post-operative history of mechanical aortic prosthesis and Bentall and de Bono surgery due to Stanford A aortic dissection; she was a former tobacco user, with obesity and chronic atrial fibrillation under regular use of warfarin. The following day, she had an acute myocardial infarction with ST-segment elevation in the anterior wall; she was submitted to angioplasty with an anterior descending drug-eluting stent, and she received aspirin, clopidogrel 75 mg daily, and anticoagulation with enoxaparin 100 mg every 12 hours. On that occasion, she underwent transthoracic echocardiogram that demonstrated mild ventricular dysfunction (LVEF: 50%) and aortic prosthesis leaflets with preserved mobility; the peak systolic pressure gradient between the left ventricle and the aorta was 58 mmHg, with a mean of 33 mmHg. Two days later, she began to present anosmia, headache, subfebrile temperature, and hypoxemia, and diagnosis of SARS-CoV-2 was confirmed by oropharyngeal swab PCR. Seven days later, while still on full enoxaparin, the patient started presenting atypical chest pain associated with dyspnea. During physical examination, the patient's overall condition was regular; she had dyspnea, without cyanosis. Pulse was present and full in all 4 limbs, and she had Glasgow score of 15, blood pressure 120/86 mmHg, heart rate 130 bpm, peripheral oximetry 97% while using a nasal oxygen catheter at 3 L/min, and capillary filling time of less than 3 seconds. Ictus cordis was in the left hemiclavicular line, at the level of the fifth intercostal space. She had normophonetic heart sounds, with moderate intensity ejective systolic murmur with metallic click in aortic focus. The patient's liver was not palpable, and there were mild and sparking crackles in the pulmonary fields bilaterally.

Keywords

Heart Valve Prosthesis; Thrombosis; COVID-19; SARS-CoV-2; Atrial Fibrillation; Atrial Fibrillation; Diagnosis, Imaging; Myocardial Infarction.

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Complementary exams

Electrocardiogram: Sinus tachycardia with ST elevation in the anterior wall.

Chest tomography: Multiple ground-glass pulmonary opacities, some associated with intervening septal thickening and others converging in small foci of consolidation, with bilateral, multifocal, and predominantly peripheral distribution, in the middle and lower fields (Figure 1).

Echocardiogram: The left ventricle showed decreased systolic function due to akinesia of the septum and the apical segment of the lower wall with an estimated ejection fraction of 40%. It was difficult to characterize of the mobility of the elements of the mechanical prosthesis; one of which apparently had reduced mobility. Discreet regurgitation was observed on Doppler and color flow mapping. The peak systolic pressure gradient between the left ventricle and the aorta was estimated at 79 mmHg, with a mean of 48 mmHg (increase of 15 mmHg compared to the exam 10 days prior). The maximum velocity of the aortic prosthesis was estimated at 4.47 m/s. The ratio of velocities of the left ventricular outflow tract and the aortic prosthesis was estimated at 0.21. The acceleration time in the aortic valve prosthesis was estimated at 105 ms. The left ventricular outflow tract was estimated at 2.2 cm (Figure 2).

Coronary cineangiography: It showed no evidence of new coronary lesion, but it did demonstrate an important decrease in the mobility of one of the aortic prosthesis leaflets (Figure 3).

Clinical diagnosis: Acute thrombosis of mechanical aortic prosthesis in a patient with Sars-CoV-2 infection and recent acute myocardial infarction.

Clinical reasoning: The patient in question had recently undergone anterior descending coronary intervention due to acute myocardial infarction with ST-segment elevation, and the initial hypothesis of acute stent thrombosis was raised; the patient was, therefore, promptly submitted to a new catheterization. Due to the reduced mobility of the prosthesis identified in the exam and to the absence of new coronary lesions, associated with the clinical findings of aortic stenosis murmur and echocardiographic findings of increased mean systolic gradient in the aortic valve, acute valve prosthetic thrombosis was suspected. Due to a recent bleeding episode, chemical thrombolysis was contraindicated, and surgery was performed. During the intraoperative period, the mechanical prosthesis had a normal anatomical aspect, but one of the leaflets was fixed by a surrounding thrombus, thus confirming the diagnosis. Mechanical thrombectomy was performed with cleaning of both leaflets, and mobility returned to normal.

Clinical evolution

The patient remained stable immediately after surgery, but she evolved with respiratory failure due to SARS-CoV-2,

Figure 1 - *Coronal plane tomography image showing multiple ground-glass pulmonary opacities characteristic of COVID-19 infection.*

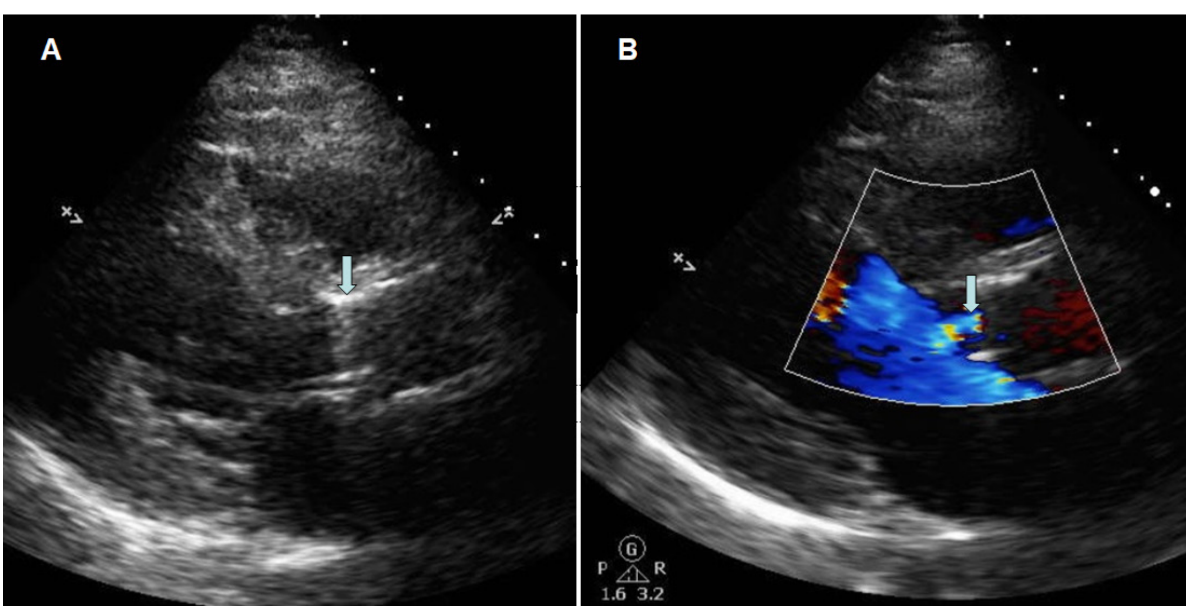

Figure 2 - *Longitudinal parasternal window of transthoracic echocardiogram showing minimal opening of the aortic valve prosthesis (left arrow) during systole (A) and in color Doppler mode (B), as well as the presence of laminar flow through the prosthesis (right arrow). These findings suggest an increase in the transvalvular gradient and acute prosthesis thrombosis.*

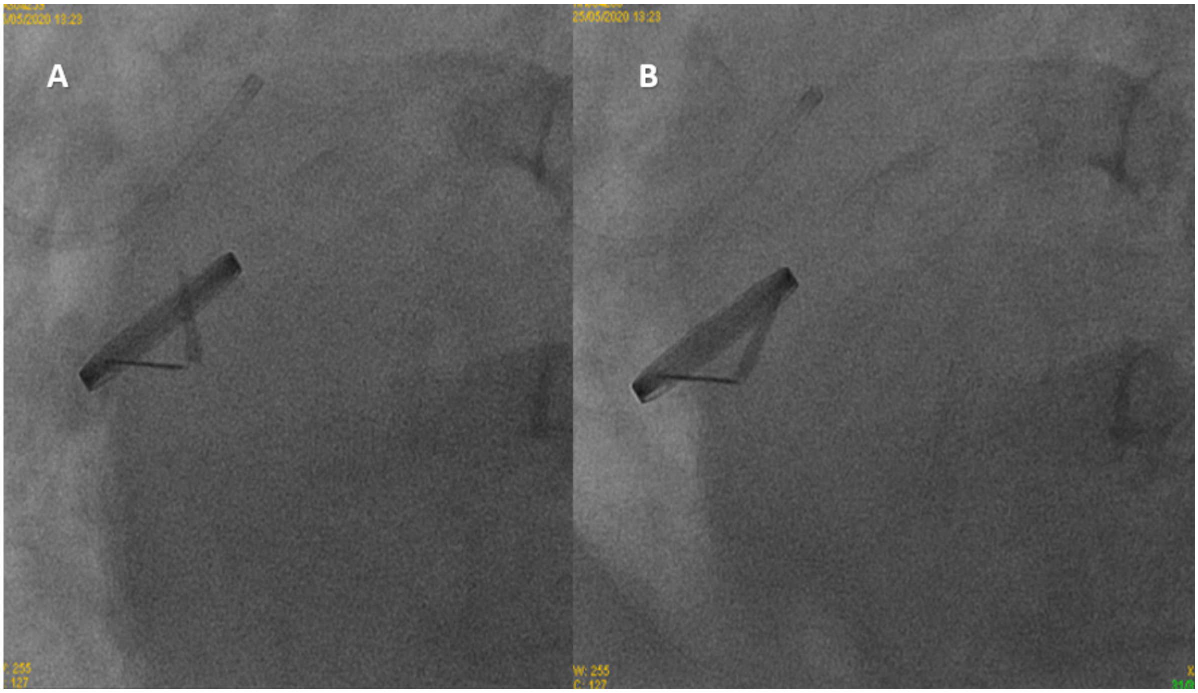

Figure 3 - *Coronary cineangiography demonstrating important decrease in the mobility of the aortic prosthesis leaflet during systole (A) and diastole (B).*

progressing with severe hypoxemia and refractory septic shock, progressing to death.

Comments

SARS-CoV-2 infection causes hemostatic changes such as enlargement of the INR, thrombocytopenia, and increased products of fibrin degradation that are related to thrombogenesis.[1] These changes may be due to a specific effect of the virus or a consequence of the inflammatory cytokine cascade that precipitates the onset of systemic inflammatory response syndrome,[2] as observed in other viral diseases. Necropsy studies have demonstrated the presence of microthrombi in pulmonary alveoli, differentiating SARS-CoV-2 infection from other viral infections.[3] Among the clinical manifestations of thrombogenesis related to SARS-CoV-2 infection, we may highlight acute coronary syndrome, disseminated intravascular coagulation, stroke, and venous or arterial thromboembolism; acute thrombosis of a prosthetic valve has not yet been described.[4]

The annual incidence rate of valve prosthetic thrombosis varies from 0.1% to 5.7%, and it is more common in mechanical prostheses, during the early postoperative period, in mitral and tricuspid positions, and in cases of subtherapeutic anticoagulation.[5] In this case, the hypercoagulability represented by SARS-CoV-2 infection, in conjunction with the hemodynamic changes caused by the recent acute myocardial infarction, which generates a stunned myocardium with consequent reduction in dilution and washout of the periprosthetic coagulation activating factors, contributed to the thrombosis of the mechanism. Even under full subcutaneous anticoagulation, the patient presented thrombosis of the valve prosthesis, which was probably related to viral infection, demonstrating yet another of the various forms of pro-coagulant manifestations of forms of SARS-CoV-2.[5]

Author contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Jacob MHF, Leal TCAT, Soares PR, Soeiro AM; Analysis and interpretation of the data: Jacob MHF.

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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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Research Letter

The Role of the Endothelium in Severe COVID-19

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Introduction

Studies have unveiled a significant link between the severity of COVID-19 (***CO****rona****VI****rus* ***D****isease* 2019) and immune markers. It is well-known that the endothelium participates actively in the immune response and interacts closely with the coagulation system.[1] Chronic inflammatory processes of the endothelium are involved in the physiopathology of cardiovascular diseases (CVDs) and metabolic diseases.[2] These diseases can negatively impact the evolution of COVID-19 and an exacerbated immune response of the endothelium seems to be a determining factor of this effect.[3]

Coronavirus 2 of the Severe Acute Respiratory Syndrome (SARS-CoV-2) causes infection by means of the link of the S protein to the Angiotensin-Converting Enzyme 2 (ACE 2) on the surface of human cells.[3–5] In this sense, a reduction in the availability of this enzyme can be observed, which is widely expressed in a number of bodily tissues, most notably, the lungs, heart, and endothelium, with a disorder in the modulation of the renin-angiotensin-aldosterone system (RAAS).[6] Consequently, what can be seen is a favoring of the greater concentration of angiotensin 2 with a series of deleterious actions against our organism. Conditions associated with the chronic dysfunction of the endothelium, such as age, systemic arterial hypertension (SAH), CVD, diabetes, and obesity are the most common in patients with severe COVID-19 (Figure 1).[2,7]

This imbalance in the RAAS contributes to a pro-inflammatory, pro-oxidative state, with macrophage recruitment, an excess of circulating cytokines and increase in the release of aldosterone, tissue damage, and the dysfunction of multiple organs, all characteristic of the severe form of COVID-19.[6,8,9] All of these alterations triggered by SARS-CoV-2 can harm the endothelial function. Therefore, comorbidities linked to the endothelium confer a greater severity to the disease. In the physiopathogenesis of COVID-19 one can thus observe an interaction between the pro-inflammatory and the pro-thrombotic factors, making them important therapeutic targets.[1,3,8-10]

Keywords

Cardiovascular Diseases/physiopathology; COVID-19; Betacoronavirus; Endothelium; Immunity; Atherosclerosis; Thrombosis.

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Endothelial Response to COVID-19

The endothelium plays an important role in the response to infection. Endothelial cells release soluble substances, chemokines, which attract leucocytes to the infected location and produce cytokines, in turn activating the inflammatory response. Patients with chronic endothelial dysfunction present important alterations in the glycocalyx, intercellular junctions, and endothelial cells, which results in greater leukocyte adhesion and extravasation, as well as leads to a state of hypercoagulability and reduction in the fibrinolytic action. Chronic endothelial dysfunction thus contributes to the development of severe COVID-19.[8,9]

The endothelium is an active organ, which is essential for the regulation of the tonus and the maintenance of vascular homeostasis.[1] In COVID-19, the recruitment of immune cells, be it through direct or immune-mediated viral aggression, can result in a widespread endothelial dysfunction, associated with apoptosis.[3,11-13] Post-mortem histological studies have demonstrated a medical picture of lymphocytic endothelialitis in the lungs, heart, kidneys, and liver, as well as cell necrosis and the presence of microthrombi, which aggravate respiratory insufficiency in the lungs.[1,6,8,9,14,15]

The endothelium has already been studied in other viral diseases, such as in the human immunodeficiency virus (HIV) and influenza. Much like HIV, SARS-CoV-2 also appears to be directly impacted by endothelial agression.[13,16] Autopsy studies have found evidence of direct viral aggression from SARS-CoV-2 against the endothelial cell, coupled with widespread inflammation.[1,12] Ackermann et al.[1] demonstrated a quantity of microthrombi that is nine times greater in the lungs of COVID-19 patients than in those patients with influenza. In these same lungs, the neo-angiogenesis was also 2.7 times more prevalent in COVID-19 than in influenza.

The idea that subclinical chronic inflammatory states are responsible for the installation of diseases or for their worsening is well-defined in the literature. The association of inflammatory cells and their respective products is well-known in the physiopathology of atherosclerosis, a condition which has a great repercussion upon the endothelium and in the components of the metabolic syndrome (obesity, diabetes mellitus, and hypertension).[11,17]

Although the cardiometabolic disease can begin during childhood, it is in the adult and senile stage that it is more expressively prevalent. In atherosclerosis, as well as in COVID-19, there is a predominance of the T_H1 response, involving the interferon-gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and tumor necrosis factor beta (TNF-β), which amplifies the inflammatory response. The IFN-γ is considered to be one of the main pro-atherogenic cytokines, as it activates

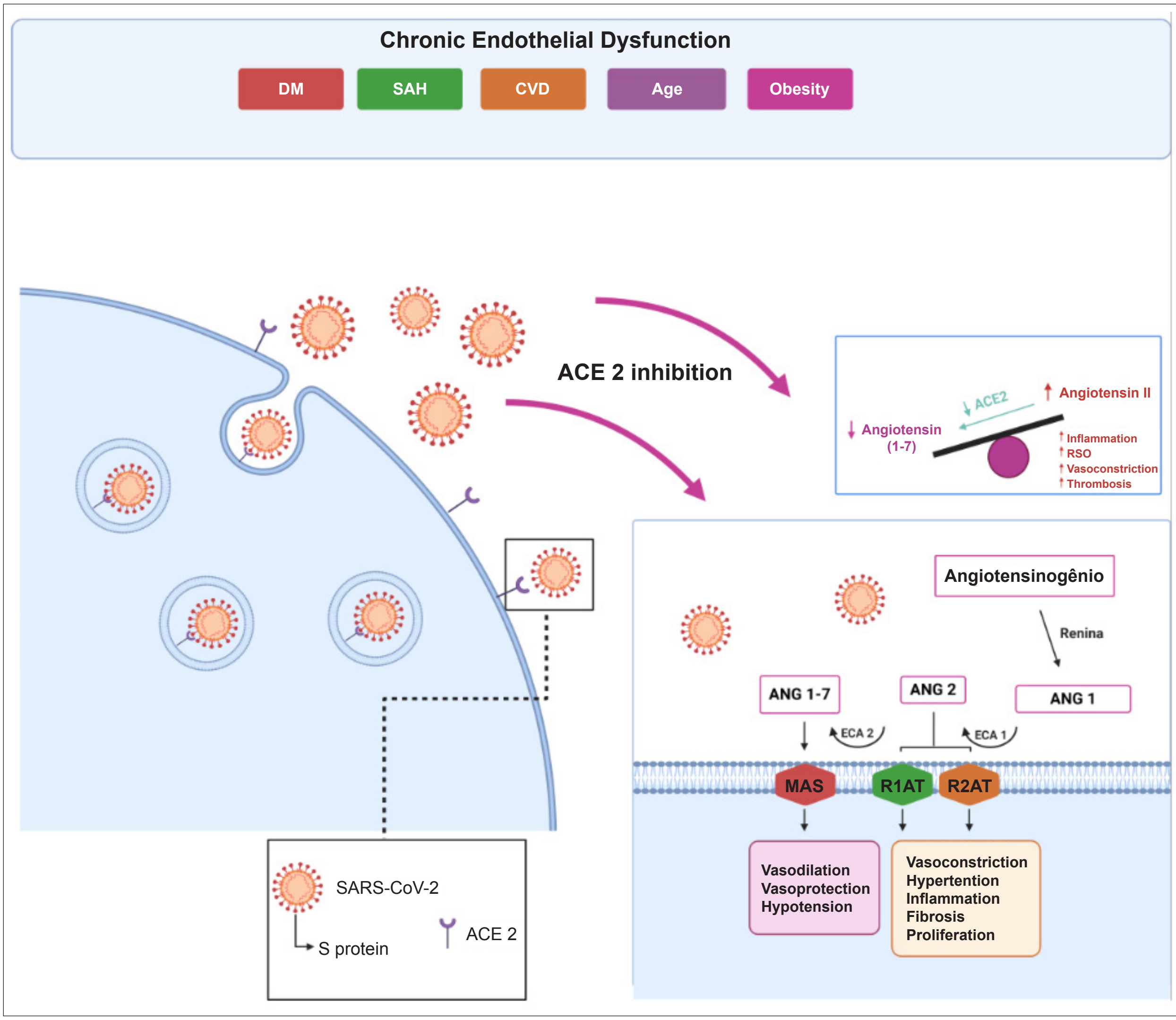

Figure 1 – *Consequences of the connection of coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2) to the ACE 2 receptor (angiotensin-converting enzyme 2). The S protein of SARS-CoV-2 connects to the ACE 2 receptor of the human cell, reducing its enzymatic activity. The ACE 1 (angiotensin-converting enzyme 1) and ACE 2 act in the angiotensin I (ANG I) and II (ANG II). The hypofunction of the ACE 2 leads to a reduction in the concentration of angiotensin 1-7 (ANG 1-7) and, consequently, to an increase in the quantity of ANG II, with deleterious effects to the organs and tissues. Comorbidities, such as DM, SAH, CVD, advanced age, and obesity, cause chronic endothelial dysfunction, which can be aggravated by the renin-angiotensin-aldosterone system, caused by SARS-CoV-2. DM: diabetes mellitus; CVD: cardiovascular diseases; RSO: reactive species of oxygen; SAH: systemic arterial hypertension; R1AT: receptor 1 of ANG II; R2AT: receptor 2 of ANG II; R-MAS: receptor of angiotensin 1-7. Source: Figure drafted by the authors. Created with biorender.com*

the macrophages and favors the participation of these in the inflammatory response.[11,12] It thus becomes evident that an amplification in the atherosclerotic process occurs as of a specific immune response, with the production of T_H1 cytokines, such as interleukin-12 (IL-12) and IFN-γ.[11,12]

Since the imbalance in the immune system is present in the physiopathology of CVDs and the metabolic syndrome, people with these diseases, even younger people with incipient atherosclerosis, would be more susceptible to the most severe form of COVID-19, as they already have a hyperactive and uncontrolled immune "terrain".[5,11,18]

Another explanation for cardiometabolic diseases being risk factors for the severe form of COVID-19 involves the recognition receptors of the *Toll-Like-4* (TLR4) pathogens, which are molecular members of innate immunity.[5,18] It is well-known that the TLR4 participate in the pathogenesis of the CVDs and metabolic diseases, such as atherosclerosis, diabetes, and obesity. The TLR4 are expressed in different types of cells of the atherosclerotic plaque, and various pro-atherogenic ligands can activate them. The TLR4 are also involved in lipotoxicity and in pancreatic beta cell dysfunction. The hyperextension of the TLR4 can even be genetically codified.[5,18]

Interleukin-6 (IL-6) and TNF-α tend to be higher in the immunopathology of COVID-19. These cytokines are products of the activation of TLR4. In a study conducted using computer simulations illustrated that the S protein of SARS-CoV-2 is recognized by the TLR4.[5] Consequently, individuals with a greater expression of these receptors, once infected by SARS-CoV-2, would suffer greater activation and release of IL-6 and TNF-α, a condition observed in the severe form of COVID-19.

As mentioned above, another probable mechanism responsible for the poor evolution of COVID-19 involves the ACE 2 receptor.[19] The reduction in the ACE 2 activity caused by SARS-CoV-2 direct influences CVDs, as they increase the potential for the deregulation of RAAS and the immune system.[6,20] There is already evidence that the use of medications that block the RAAS, such as ACE 1 inhibitors (ACEI) and angiotensin receptor blockers (ARBs), are not related to the increase in mortality caused by COVID-19, and can even serve as protection factors.[19,21]

Alterations in COVID-19 Coagulation

Exacerbated inflammatory states culminate in blood stasis, platelet activation, and endothelial dysfunction, raising the probability of episodes of venous and arterial thrombosis. The coagulopathy in severe COVID-19 infection is similar to coagulopathy induced by sepsis, characterized by widespread intravascular coagulation and thrombotic microangiopathy. In addition, one can highlight hypoxemia, secondary to the pulmonary lesion caused by COVID-19, which is a risk factor for thrombosis.[8,9,17]

SARS-CoV-2 provokes SARS. In this syndrome, insoluble fibrin accumulates in the alveolar space. It can be said that the fibrinogen flows out of the plasma due to an increase in the vascular permeability and the widespread alveolar damage, with its incomplete elimination due to a state of hypofibrinolysis. Chronically, this insoluble fibrin contributes to pulmonary fibrosis and its negative repercussions.[8,9,15,17]

The main alterations in the coagulation present in COVID-19 are: rise in the D-dimer, fibrogen, and time of prothrombin, as well as a reduction in fibrinolysis. The platelet count can be reduced in the more advanced stages of the disease, and is a predictive factor of mortality.[8,9,15,17] The increase in the risk of thrombosis also occurs in the arteries and different clinical manifestations can appear, including: cerebrovascular accident, mesenteric ischemia, acute infarction of the myocardium, and arterial occlusion of the lower limbs, depending on the affected arterial bed.[22] Corroborating with the hypothesis of vascular aggression, some cases with features of toxic shock or pediatric multisystemic inflammatory syndrome similar to the Kawasaki disease have been described and related to COVID-19.[20]

Therapeutic Strategies

Considering that put forth above, it is possible to highlight the importance of the strict control of cardiometabolic risk factors.[5] The aim is to render the endothelium less reactive and less vulnerable to COVID-19. The optimization of the medicinal treatment with the use of anti-diabetic, anti-hypertensive, hypolipidemic (mainly statins), and anti-platelet (such as acetyl salicylic acid) medications can stabilize the endothelium.[5,20,23] Drugs, such as ACEI and ARB, seem to be essential in the reduction of the risk of severe outcomes caused by COVID-19, since it helps to balance the RAAS.[19] Regarding to the SARS-CoV-2, to date, no specific treatment has been proven to be effective in the fight against the virus. The therapeutic strategy has been based on the early recognition of the complications in the optimized support to alleviate the symptoms (Figure 2).

In the hyperinflammatory stage of COVID-19, the medications that inhibit or reduce the effects of the pro-inflammatory cytokines are quite pertinent and should be taken into consideration. The IL-6 inhibitors, as well as the glucocorticoids, can avoid or lessen the storm of cytokines.[23] New modulator medications of the inflammatory response are key in this stage to avoid excessive inflammation, which intensely attacks the endothelium and the diverse organs and can result in multiple organ failure and even death.

Regarding to venous thromboembolism, hospitalized patients should receive pharmacological thromboprophylaxis with heparin in a low molecular weight or fondaparinux (preferably unfractionated heparin), unless the risk of bleeding exceeds the risk of thrombosis, in which case, mechanical prophylaxis should be applied.[8,9,15,17] The adjustment in the heparin dose according to the body mass index (BMI), together with the clearance of creatinine, is recommended.[8,15] Full heparinization is recommended in cases in which there is a strong clinic suspicion or confirmation of venous thromboembolism.[8,15]

Heparin is a medication that is widely used in medicine because of its anti-coagulant action and its anti-inflammatory effect. However, in COVID-19, in addition to these effects, studies have suggested the use of heparin as a way to hinder viral replication. SARS-CoV-2 connects to the ECA2 receptor in order to penetrate the human cell and multiply. It is believed that, to achieve this link, the virus also needs to connect to the heparan sulfate, among other sites, present in the endothelial membrane. The use of heparin has been suggested as a strategy of connection to heparan sulfate, hindering the connection of SARS-CoV-2 to the ECA2 receptor, thus diminishing viral replication.[24]

Conclusion

In sum, it is important to highlight that the endothelial function is an essential factor in the progression of the clinical stages of COVID-19. The chronic dysfunction of the endothelium, which occurs in the pre-existing diseases, directly favors the evolution toward the severe form of the disease. Therefore, while we await a vaccine, the therapeutic targets (Table 1) must include the control of the cardiovascular, metabolic, and endothelial conditions of the at-risk population and the infected individuals, as well as a reduction in viral replication, hyperinflammation, and hypercoagulability.

Author Contributions

Conception and design of the research: Brandão SCS, Godoi ET, Sarinho ESC; Acquisition of data: Brandão SCS, Godoi ET, Ramos JOX, Melo LMMP, Dompieri LT; Analysis and interpretation of the data: Brandão SCS, Ramos JOX, Melo LMMP, Dompieri LT, Sarinho ESC; Writing of the manuscript:

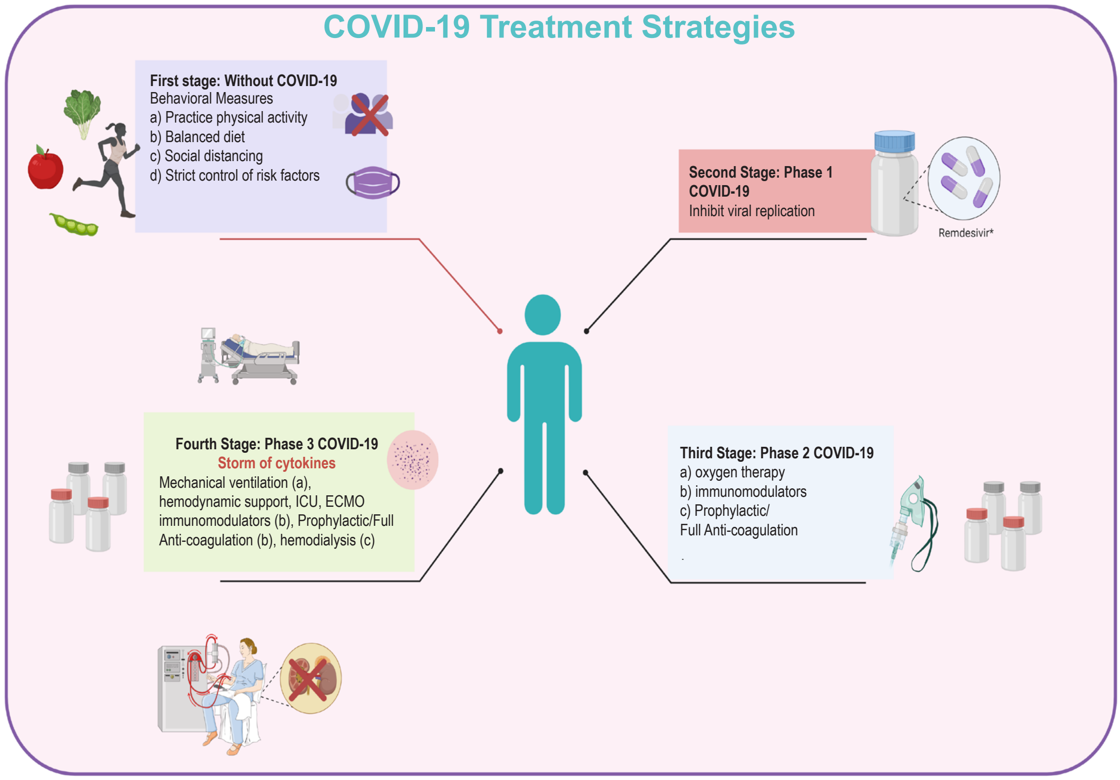

Figure 2 – *Treatment strategies for prevention and according to the stages of the disease caused by coronavírus-2 (COVID-19). Source: Figure drafted by the authors. Created with biorender.com*

Brandão SCS, Godoi ET, Ramos JOX, Melo LMMP, Sarinho ESC; Critical revision of the manuscript for intellectual content: Brandão SCS, Godoi ET, Brindeiro Filho DF, Sarinho ESC.

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.

Table 1 – Potential therapeutic targets of potential drugs to fight COVID-19. As this is about a pandemic disease, the treatment stages should occur even before people are infected by the virus. Previously published clinical trials have shown no benefits.

Stages	Potential therapeutic targets	Medications
Without COVID-19	Anti-hipertension drugs	Mainly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.
	Statins	Simvastatin, Rosuvastatin, Atorvastatin, etc.
	Anti-platelet drugs	Acetyl-salicytic acid
	Vaccines	Multiple candidates. Research in progress.
Stage 2: Phase 1 of COVID-19	Entrance for ACE2 receptor	ACE2 soluble recombinant
	TMPRSS2 protease S priming	Protease inhibitor (camostat mesilate)
	Endocytosis of the receptor	Chloroquine or Hydroxychloroquine*
	RNA polymerase for replication	Remdesivir, Favipiravir
	Viral Proteases	Lopinavir/Ritonavir*
	Importin nuclear transportation	Ivermectin
Stages 3 and 4: Phase 2 of COVID-19 Hyperinflammation Phase 3 of COVID-19 “Storm” of cytokines	Anti-viral/anti-inflammatory	Convalescent plasma of patients with COVID-19, Interferon type I, immunoglobins, mesenchymal stem cells
	Activation through the excess of Interleukin 1	Anakinra, Canakinumab, Colchicine
	Storm of cytokines	Tocilizumab, Sarilumab, Siltuximab (IL-6 inhibitors), or baricitinib (JAK inhibitor), Lenzilumab (granulocyte- macrophage colony-stimulating fator inhibitor)
	Bacterial/inflammation infection	Azithromycon and other antibiotics
	Coagulopathy	Full and prophylactic anti-coagulation regime.
	Anti-viral/anti-inflammatory drugs	Convalescent Plasma
	Oxidative stress	Vitamin C, Deferoxamine

**ACE 2: angiotensin-converting enzyme 2. TMPRSS2: transmembrane protease, serine 2. Source: modified from reference 10*

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Research Letter

Emerging Topics in Heart Failure: The Future of Heart Failure: Telemonitoring, Wearables, Artificial Intelligence and Learning in the Post-Pandemic Era

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Telemonitoring in Heart Failure and Remote Management

Telemonitoring consists of monitoring and remote support for chronic heart failure (HF) patients. Telemonitoring can be non-invasive or invasive. Non-invasive telemonitoring includes telephone calls, periodic guidance through instructional material, control and monitoring of body weight, video calls and teleconsultations.[1,2] Invasive telemonitoring involves implantable devices that transmit hemodynamic and intrathoracic impedance data to a remote server.[3,4]

Clinical trials of non-invasive telemonitoring often show conflicting results. However, meta-analyses of observational and randomized studies on invasive and non-invasive telemonitoring have shown that they have a positive impact on HF prognosis. The reduction in overall mortality in HF patients can vary from 19 to 31% with invasive or non-invasive telemonitoring,[5,6] while reduction in the frequency of hospitalization for HF varies from 27 to 39%, mainly in functional class III/IV patients.[7-9]

Among invasive telemonitoring systems, CardioMEMS[7] has the most convincing evidence in HF. This device is implanted percutaneously in the pulmonary artery and transmits central blood pressure values to a secure server, guiding adjustments in diuretic and vasodilator dosage.

Keywords

Telemonitoring; Artificial Intelligence; Heart Failure; Learning.

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Wearables in HF: Monitoring Tools or More Electronic Gadgets?

Wearables are computational tools that can be worn on the body. They could be a watch, a shirt, a contact lens, or a shoe, for example. These devices contain sensors that obtain real-time data and transmit it to a cloud or another device, allowing analysis of an enormous amount of data, as well as facilitating diagnostic and therapeutic decision making. All of this has been made possible by the evolution of data transmission technology, particularly the advent of 5G networks.

Thus, the Internet of things will eventually become a reality in a number of countries. The Internet of medical things will be no different. The progressive cheapening of these technologies will overcome the cost-effectiveness barrier, and we will have the opportunity to test a multitude of wearables that can provide the health team with early access to telemonitoring data for variables such as blood pressure, pulse, blood oxygen, postural analysis, fall, respiratory rate, temperature, capillary blood glucose, etc.

This could have an impact on clinically relevant outcomes, such as hospitalizations, direct and indirect costs and even mortality. At the same time, the management of HF patients can be directed towards more personalized precision medicine - a new paradigm. Despite the fact that each gadget promising such benefits must undoubtedly be validated (considering the main barriers to its implementation), it seems clear that wearables are here to stay.[8,9]

Artificial Intelligence and Big Data in HF

Computer systems capable of carrying out tasks that originally required human performance are the basis of artificial intelligence. These systems were developed out of the need to interpret 'big data'. Systems must be able to quickly and accurately analyze simple or complex data, as well as adapt to the data without static programming.[10] Machine learning and deep learning are extensions of artificial intelligence. Machine learning uses algorithms to collect data, learn from them and then make predictions about things or even patients. To be useful and reliable, machine learning systems must be constantly fed real data. In addition, deep learning, which is the vanguard of interaction and adaptive learning, can involve neural connections and diversity to integrate different databases.[11]

Artificial intelligence, machine learning and deep learning applications are already being studied for HF with respect to diagnosis, prognosis assessment, telemonitoring or even the selection of patients with the greatest projected benefit from various therapies. This can occur, for example, by distinguishing phenotypes, allocating patients with different disease profiles;[12] by determining the best acute HF diagnostic accuracy in relation to the doctor;[13] and by targeting new or already established therapies, such as additional analysis of baseline electrocardiograms to identify the best patients for cardiac-resynchronization therapy.[14]

Medical Education About HF in These New Times

One of the greatest challenges for studies and clinical research is translating scientific results into clinical practice. Although there are several factors involved in this process, one particularly important factor is the ability to effectively transmit and apply knowledge to the greatest number of professionals in the least possible time.

Medical education and, consequently, the subject of HF, are undergoing a revolution.[15] For a long time, HF had been reduced almost exclusively to expository classes. However, in recent years, active teaching methodologies and synchronous hybrid models or digital asynchronous models have improved the teaching and learning process and, consequently, patient care.[16]

The current teaching model must offer the concept of andragogy,[17] which is associated with the AGES teaching model. This model involves short expository learning processes, which maintain viewer/student attention, and produces intrinsic motives that bring meaning to learning. That is, it involves emotions that can strengthen learning, so that learning is spaced over several stages. When incorporated, these approaches lead to more profound and effective learning, enabling doctors and health professionals to absorb and apply the best HF care practices.

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Emerging Topics in Heart Failure: Contemporaneous Management of Advanced Heart Failure

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Definition

Advanced heart failure (HF) is a condition characterized by persistent severe HF symptoms, frequent episodes of decompensation, and progressive cardiac dysfunction despite optimal evidence-based treatment.[1] These patients may be candidates for advanced therapies, such as heart transplantation (HT), mechanical circulatory support (MCS), and/or palliative care. It should be pointed out that some comorbidities, including pulmonary disease and liver and kidney dysfunction, are now included as possible major determinants of poor prognosis and should be considered during patient evaluation for advanced HF therapies.

Prognosis and risk scores

There are several risk scores for predicting outcomes in HF populations (Figure 1); each model has been developed for use in specific cohorts, including those with acute HF, HF with reduced ejection fraction, and/or HF with preserved ejection fraction. The MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score seems to have better accuracy than the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity), GISSI-HF (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure), and SHFM (Seattle Heart Failure Model) scores for predicting 1-year mortality.[2] Other risk stratification tools for short- and long-term MCS, such as the SAVE (Survival After Veno-Arterial Extracorporeal Membrane Oxygenation) and HeartMate II risk scores, respectively, may be helpful in patient selection, but are restricted to specific devices. Recently, the PREDICT-HF (Prognostic Models Derived in PARADIGM-HF and Validated in ATMOSPHERE and the Swedish Heart Failure Registry to Predict Mortality and Morbidity in Chronic Heart Failure) score used data from the PARADIGM-HF (Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure) trial to develop a prognostic model for patients receiving contemporary evidence-based therapies for HF. It has yet to be validated.[3]

Keywords

Advanced Heart Failure; Advanced Therapies; Heart Transplant; Mechanical Circulatory Support; Paliative Care.

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Treatment of advanced HF in the acute setting

Congestion management

Volume overload management remains clinically challenging and may require a combination of several strategies, including higher doses of intravenous loop diuretics, combined diuretic therapy, hypertonic saline, ultrafiltration and peritoneal dialysis.[4]

Although there has been relatively little innovation in this field, recent evidence suggests that remote patient HF monitoring may have potential benefits. Studies of non-invasive home telemonitoring have shown improvements in hospital length of stay and all-cause mortality.[5] Similar results were observed with the implantable CardioMEMS™ HF System, which provides direct pulmonary artery pressure monitoring. CardioMEMS™ proved safe and effective in real-life and post-marketing studies and was also found cost-effective,[6] with reproducible findings across European centers.[7] This promising strategy has translation potential for clinical practice.

Cardiogenic shock

Recently, the Society for Cardiovascular Angiography and Intervention (SCAI) has proposed a new consensus statement on the classification of cardiogenic shock (CS) to provide collective language for the different stages and appropriate management of CS. The 5-stage classification allows for a simple hemodynamic definition, providing granularity for the INTERMACS classification.[8] (Figure 2)

In recent years, strategies associated with early intervention in CS, including multidisciplinary team-based management (Shock Team), have highlighted the role of advanced HF specialists in coordinating timely therapeutic decisions.[9] Vasoactive agents are often used to provide hemodynamic and metabolic support, but low-dose combination therapies should be prioritized to avoid further tissue damage. A recent systematic review found no significant difference between vasoactive agents but stressed the importance of early goal-directed therapy, including early hemodynamic stabilization within predefined timelines.[10] Escalating doses of vasoactive

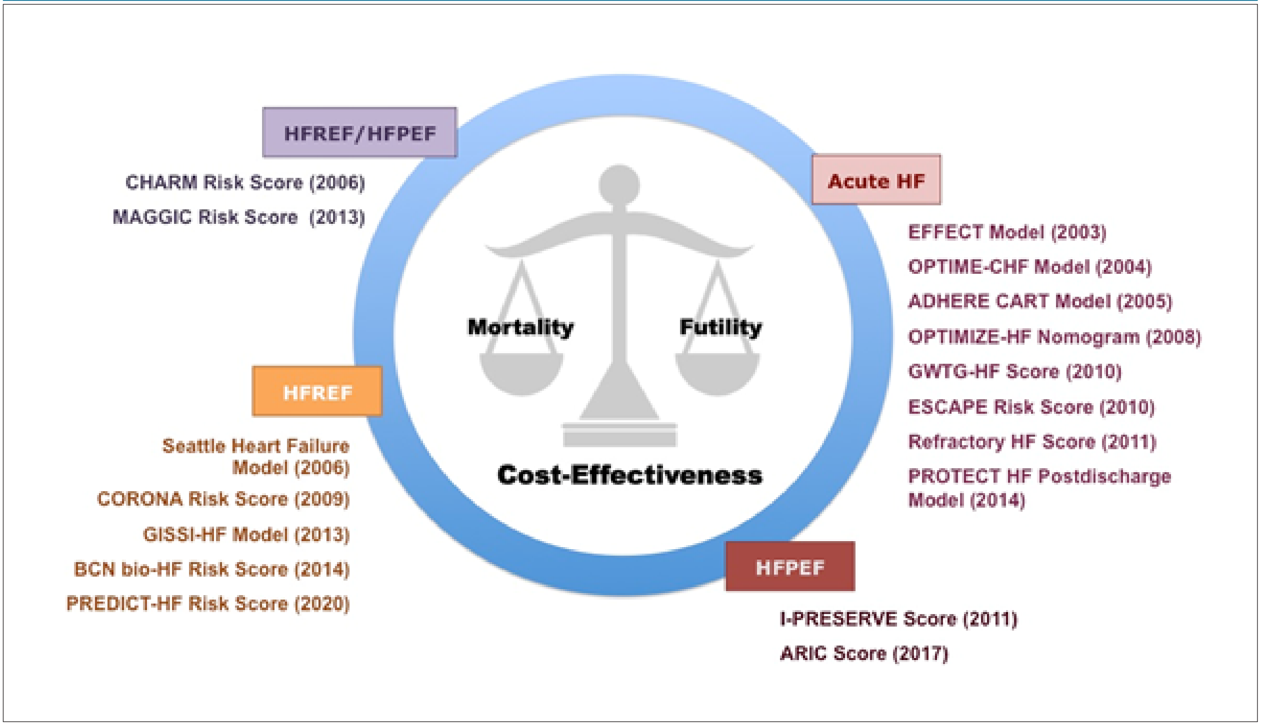

Figure 1 – *Risk scores for heart failure. ADHERE CART: Acute Decompensated Heart Failure National Registry Classification and Regression Tree Analysis; ARIC: Atherosclerosis Risk in Communities; BCN bio-HF: Barcelona Bio-Heart Failure; CHARM: Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CORONA: Controlled Rosuvastatin Multinational; EFFECT: Enhanced Feedback for Effective Cardiac Treatment; ESCAPE: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; GISSI-HF: Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure; GWTG-HF: Get With the Guidelines–Heart Failure; HF: heart failure; HFPEF: heart failure with preserved ejection fraction; HFREF: heart failure with reduced ejection fraction; I-PRESERVE: Predicting death for severe acute respiratory distress syndrome on venovenous extracorporeal membrane oxygenation; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure; OPTIME-CHF: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; PREDICT-HF: Prognostic Models Derived in PARADIGM-HF and Validated in ATMOSPHERE and the Swedish Heart Failure Registry to Predict Mortality and Morbidity in Chronic Heart Failure; PROTECT HF: Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function.*

agents should prompt consideration of MCS candidacy to prevent irreversible hemodynamic/metabolic derangements of the CS spiral.

Short-term MCS devices are designed to provide uni- or biventricular support for a wide range of conditions, including CS, acute HF, high-risk percutaneous coronary intervention, and cardiac arrest.[11] The most commonly used percutaneous assist systems include intra-aortic balloon pumps (IABP), Impella®, TandemHeart® and veno-arterial extracorporeal membrane oxygenation (VA-ECMO).[4] Despite the preemptive improvement in hemodynamics with these devices, randomized trials have not demonstrated significant reduction in CS mortality.[12] Moreover, recent observational studies hinted at higher rates of adverse events and costs with Impella than IABP.[13] Despite certain limitations, the IABP remains the most widely used MCS device in CS.

In clinical research, the NuPulseCV intravascular ventricular assist system (iVAS) is a novel minimally invasive device that provides long-term ambulatory counterpulsation via a durable pump placed through the subclavian artery and controlled by an external drive unit.[14] The iVAS overcomes many limitations of the IABP and may be a promising option for patients with advanced HF.

Advanced therapies for HF

The characteristics of candidates for advanced HF therapies, such as HT and left ventricular assist device (LVAD), have changed dramatically over the years, leading to a more complex selection process. Below, we highlight some advances and challenges in the field.

Regarding HT, the treatment of choice for patients with advanced HF,[15] strategies to increase the donor organ pool have been suggested; in fact, in the United States, the United Network for Organ Sharing (UNOS) recently changed its donor organ allocation policy.[16] Given that post-transplant survival is worse with pre-operative VA-ECMO than LVAD, the new system assigns high priority to patients supported with short-tem MCS devices, while stable patients supported with LVAD or inotropes alone are assigned a lower status. In Brazil, some states are making similar changes. Another recent suggestion is the use of predicted heart mass (PHM), rather than body weight as an ideal metric for donor-recipient size matching. Studies have shown that PHM mismatch is a better predictor of primary graft dysfunction and 1-year mortality after HT than weight, height, or body mass index mismatch,[17] and it also predicts right ventricular-pulmonary arterial coupling after

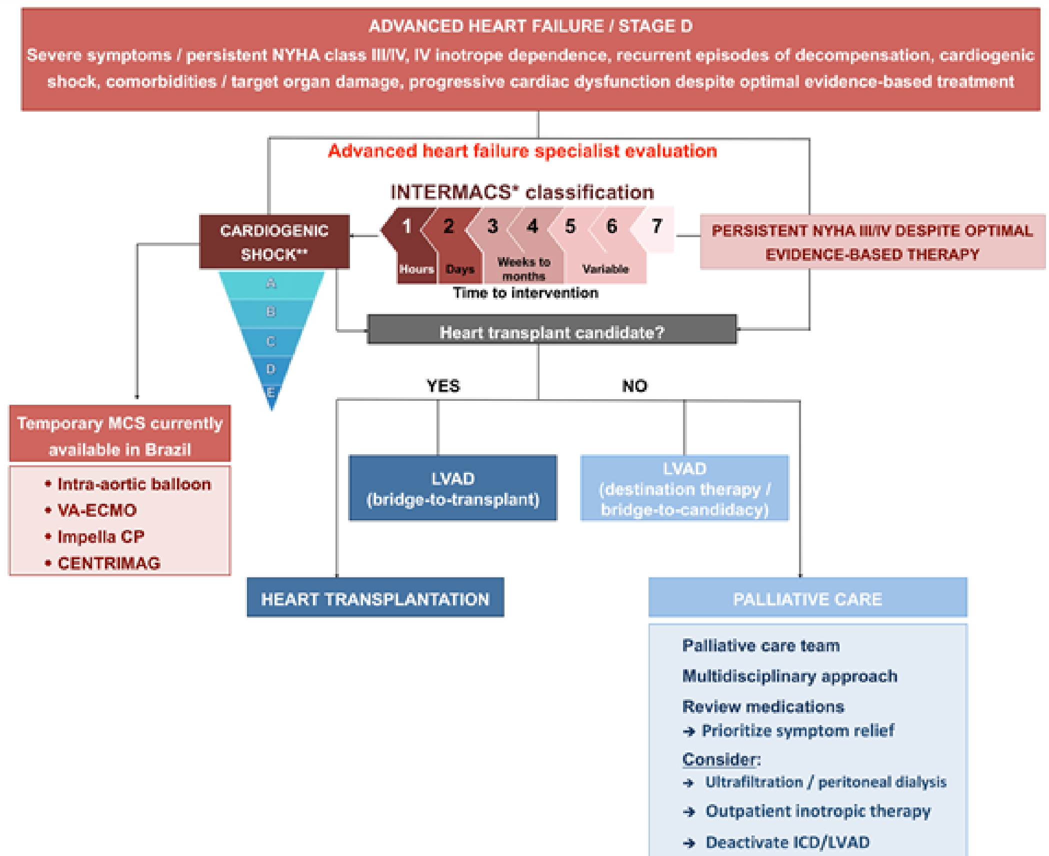

Figure 2 – *Decision-making algorithm for patients with advanced heart failure. * Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles of advanced heart failure. Profile 1: critical cardiogenic shock; Profile 2: progressive decline on inotropic support; Profile 3: stable but IV inotrope dependent; Profile 4: resting symptoms home on oral therapy; Profile 5: exertion intolerant; Profile 6: exertion limited Profile 7: advanced NYHA Class III symptoms. **Cardiogenic shock classification scheme proposed by the Society for Cardiovascular Angiography and Intervention (SCAI). Stage A is "at risk" for cardiogenic shock; stage B is "beginning" shock; stage C is "classic" cardiogenic shock; stage D is "deteriorating"; stage E is "extremis". Baran, DA, Grines, CL, Bailey, S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94: 29– 37. doi:10.1002/ccd.28329. IABP: intra-aortic balloon pump; ICD: implantable cardioverter-defibrillator; IV: intravenous; LVAD: left ventricular assist device; MCS: mechanical circulatory support; VA-ECMO: veno-arterial extracorporeal membrane oxygenation; NYHA: New York Heart Association.*

HT.[18] Finally, the advent of direct-acting antiviral agents (e.g. sofosbuvir) for treating hepatitis C virus infection has enabled allocation of organs from hepatitis C virus-infected donors to uninfected recipients.[19]

In the field of LVAD, the HeartMate 3™ has been associated with meaningful clinical benefit, with a significant reduction in the rates of ventricular arrhythmias, readmissions, and hemocompatibility-related adverse events (bleeding, thrombosis and stroke).[20] Further technological advances are needed, such as the miniaturization of devices and the development of a truly internalized power system.

Finally, palliative care has proven indispensable in advanced HF management, playing a central role in cases that are not considered eligible for HT or LVAD. Intermittent use of ultrafiltration, peritoneal dialysis, or inotropic infusions can be considered in the hospital, the hospice, or even at home to control symptoms.[1]

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Emerging Topics in Heart Failure: Future Perspectives

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Introduction

The *Heart Failure Summit Brazil 2020* addressed new perspectives for assessment, diagnosis, risk stratification, and management of heart failure (HF), which may soon be available for widespread use in the clinic. These strategies involve the use of novel biomarkers, genetic assessment, potential new therapeutic targets, and personalized medicine.

Novel Biomarkers

Among novel biomarkers, two—both related to the process of fibrosis—are worthy of note. Galectin-3 (Gal-3) is expressed in various tissues and cells, including the myocardium. In the heart, Gal-3 activates quiescent fibroblasts, transforming them into myofibroblasts that alter the extracellular matrix to produce fibrosis; research has shown it is a predictor of remodeling in HF. In addition to being a marker of risk, Gal-3 appears to play an active role in the fibrosis process, and may thus constitute a potential therapeutic target.[1] Soluble ST2 is another marker of fibrosis in HF, providing additional information as an adjunct to natriuretic peptides and troponins.[2] More recently, growth differentiation factor-15 (GDF-15) has been shown to be a predictor of events in HF.[3]

Although these biomarkers are promising, there is still no conclusive evidence from large studies that they add information to conventional.

Genetic Assessment

Advances in genetics are improving our understanding of the various hereditary heart diseases, especially cardiomyopathies, which are frequent causes of HF. Diseases such as dilated cardiomyopathy and hypertrophic cardiomyopathy have been impacted by such research;[4] new evidence has clarified certain etiopathogenetic aspects. One example is the finding that truncating variants of the titin gene account for up to a quarter of all dilated cardiomyopathies. Advances in genetics have also changed the approach to initial assessment of arrhythmogenic cardiomyopathy, the topic of a recently published consensus statement.[5] Once associated exclusively with right ventricular cardiomyopathy caused by mutations in desmosomal protein genes, we now know that this umbrella term covers a wide spectrum of genetic, systemic, and inflammatory conditions. The advent of next-generation sequencing has increased the sensitivity of genetic tests, which allows for early diagnosis with an interventional perspective. However, not all clinicians are aware of the applicability of this tool, nor of the pitfalls that arise with its incorporation into practice. There is a clear need for more efficient ways of using genetics, especially in family counseling, to achieve more safe and sustainable outcomes in the management of these patients and their families.

Keywords

Biomarkers; Genetic Assessment; Omecamtiv Mecarbil; Mavacamten; Telemedicine; Imunization; Vaccins; Danon; Fabry; Amiloidosis.

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New Therapeutic Targets

Two new drugs targeting myosin have yielded promising results in phase 1 and 2 trials for the treatment of HF and hypertrophic cardiomyopathy.

Omecamtiv Mecarbil

This is a selective myosin activator and is thus believed to address the core abnormality of ventricular dysfunction, improving compromised ventricular contraction in cases of HF with reduced ejection fraction. Its mechanism of action is distinct from that of current treatments, which counteract elevated neurohormonal stimulation. Mechanistic trials, such as ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) and COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure), have shown that this drug improves contractility, improving ejection fraction, stroke volume, and cardiac output, in addition to other parameters suggestive of improved cardiac function. Studies have shown that omecamtiv mecarbil promotes a reduction in NT-proBNP levels. Elevation of troponin levels, with no clinical repercussions, has also been reported. Nevertheless, the ATOMIC-AHF study of patients with acute HF did not observe a reduction in dyspnea in patients treated with the drug. A study, GALACTIC-HF (Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure

With Reduced Ejection Fraction) fail to demonstrate long-term survival benefit, and showed only a 5% reduction for first HF hospitalization.[6] Further studies in acute HF patients and patients with terminal HF are necessary to stablish the usefulness of this drug.

Mavacamten

Mavacamten is a cardiac myosin-specific inhibitor. Studies have shown that it enhances physical performance in patients with obstructive hypertrophic cardiomyopathy, with improved oxygen consumption.[7] Its administration was associated with a reduction in NT-proBNP and troponin levels, suggesting reductions in stress in the myocardial wall, ventricular obstruction, and ejection fraction. In the MAVERICK study, adverse events were frequent and a not-insignificant percentage of patients experienced excessive decline in ejection fraction, which was however reversible upon discontinuation. Proper dose adjustment appears to be essential, and the ejection fraction response has been proposed as a guide. Again, survival studies are needed to ensure that mavacamten is safe and to better understand the reductions in contractility and ejection fraction that appear to follow its use.

Telemedicine

Telemedicine is a broad platform of unique strategies with varied complexities that have emerged in the medical field as a promising tool to improve the treatment adherence of patients with chronic diseases and reduce health inequalities. Unfortunately, implementation of telemedicine has been erratic in Latin America and in many parts of the world, due to logistical difficulties in establishing the necessary technological support structures in a manner that is efficient and feasible for most patients. In addition, several telemonitoring strategies have been tested in HF, with inconsistent results. The lack of conclusive effectiveness may be explained by differences in the content and intensity of each intervention and by the heterogeneous nature of the patient populations included in different studies. Most studies that demonstrated beneficial effects of telemedicine strategies in HF have involved unstable and vulnerable patients with a history of recent hospitalization. It also seems essential that specific strategies be adapted to each health setting, considering social, economic, cognitive, and cultural aspects. An analysis of 15 systematic reviews on the effectiveness of these strategies for patients with HF suggests that home telemonitoring interventions reduce the relative risk of all-cause mortality and HF-related hospitalization compared to usual care. Risk reductions in all-cause mortality and hospitalization appeared to be greater in patients who were recently discharged (≤ 28 days) in the setting of acute decompensation after a recent exacerbation of HF.[8]

New Therapies in Heart Failure with Preserved Ejection Fraction (HFPEF)

Among promising therapies for HFpEF, those that have drawn the most attention and interest are the sodium-glucose cotransporter inhibitors (SGLT2i), such as empagliflozin (evaluated in the EMPEROR-Preserved [Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction] and EMBRACE-HF [Empagliflozin impact on hemodynamics in patients with heart failure] trials), dapagliflozin (evaluated in PRESERVED-HF [Dapagliflozin in preserved ejection fraction heart failure]), and ertugliflozin (ERADICATE-HF [Ertugliflozin trial in diabetes with preserved or reduced and reduced fraction mechanistic evaluation in heart failure]). Other drugs are also at the investigational stage, such as TRC4186 (an inhibitor of advanced glycation end products), trimetazidine, praliciguat and vericiguat (soluble guanylate cyclase stimulants), neladenoson (a partial adenosine A1 receptor agonist), and pirfenidone (an antifibrotic agent), as is an invasive procedure (creation of an atrial septal defect to relieve high pressure in the left atrium).

Immunizations in HF

Until recently, there was no data on the impact of influenza on outcomes in patients with HF,[9] but a population-based study has since demonstrated a relationship between influenza season and higher incidence of hospitalization for HF, which coincided in four consecutive periods. In a subanalysis of the PARADIGM (Prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity) trial, the 21% of participants who had received the influenza vaccine were found to have a 19% lower overall mortality after propensity matching. In a Danish cohort study of 134,048 patients with HF, one or more vaccinations between 2003 and 2015 were also associated with an 18% reduction in overall mortality and all-cause mortality; more than three vaccinations resulted in a 28% reduction in overall mortality and a 29% reduction in cardiovascular mortality.[10] A database study of 6,435 patients with HF, 695 of whom were vaccinated before or during the winter of 2017–2018, showed a 22% reduction in overall mortality and a 17% reduction in cardiovascular death or hospitalization due to HF. The benefit of vaccination on overall mortality was greatest in patients over age 70 years, with a >25% reduction.[11] There are no studies on the impact of pneumococcal vaccination. Several prospective studies are at the enrollment stage.

Personalized HF Management

The promise of personalized medicine in HF management is progressively becoming reality and a new field in its own right, supported by cardiac imaging, genomics, and data sciences. In 2015, the U.S. government launched the Precision Medicine Initiative, a major challenge and research effort designed to support research initiatives for chronic diseases aimed at incorporating the precision medicine paradigm. This effort has led to significant advances at several academic centers. HFpEF is currently one of the greatest challenges in clinical practice due to the absence of drugs capable of reducing morbidity and mortality. Accordingly, a new outlook for HFpEF research has arisen which relies on bioinformatics techniques and identification of phenotypic networks, seeking to identify patterns that may be associated with different prognoses and, possibly, present differential responses to pharmacotherapy.[12]

Leveraging bioinformatics and data science techniques has enabled successful prediction of the clinical course of hereditary cardiomyopathies such as Danon disease and Fabry disease.[13] Great strides have been made in hypertrophic cardiomyopathy with the possibility of characterizing phenocopies—conditions that mimic the morphological presentation of hypertrophic cardiomyopathy, such as Fabry disease, cardiac amyloidosis, Pompe disease, Danon disease, etc. Genetic manipulation techniques, such as clustered regularly interspersed short palindromic repeats (CRISPR)-based gene editing, have potential for future utility in the treatment of monogenic diseases, and are already being tested in animal models.

For diagnosis of cardiac amyloidosis and characterization of its main subtypes through a combination of molecular imaging, biomarkers, and genetic testing have been used.[14] Serum measurement of immunoglobulin light chain and immunofixation in blood and urine, technetium pyrophosphate myocardial perfusion scanning, a multimodal approach of advanced Doppler echocardiography techniques such as speckle tracking, and cardiac magnetic resonance, all in combination with genetic tests. This approach has successfully replaced adipose tissue and/or endomyocardial biopsy for the accurate diagnosis of transthyretin-mediated cardiac amyloidosis (ATTR-CM). New drugs with disease-modifying capacity, such as the transthyretin stabilizer tafamidis and the small interfering RNA molecule patisiran, are examples of the increasingly personalized approach to management of cardiac amyloidosis. A recent case report of regression and normalization of technetium pyrophosphate myocardial perfusion scan findings in a patient with ATTR-CM treated with these new drugs is representative of this new and future paradigm.[15]

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Mitral Valve Mass in a Patient Suspected of Systemic Lupus: Tumor, Endocarditis or Both?

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Abstract

We present a case report of a patient with an infected mitral valve myxoma and a literature review on the subject. A 33-year-old female presented with a history of fever and dyspnea evolving over a few days. On admission, she had a lupus-like syndrome with positive blood cultures for *Haemophilus species*. Echocardiogram revealed a giant mass involving both mitral leaflets causing severe regurgitation, requiring biological mitral valve replacement. Microscopy showed an infected myxoma and the patient was discharged asymptomatic upon completion of antibiotics. She did well on follow-up. This is the sixth case of an infected mitral valve myxoma reported in the literature and the third case of a cardiac myxoma infected by the HACEK group. Exceedingly high incidence of embolic events makes prompt imaging, antibiotic therapy and surgery crucial for better outcomes. Time to diagnosis was much briefer than usually reported in other cases of HACEK endocarditis. Valve replacement was the most common surgical procedure and all patients from previous reports did well on follow-up.

Introduction

Heart valve myxomas are exceedingly rare.[1] The triad of constitutional, obstructive and embolic symptoms make its differential diagnosis with endocarditis challenging. In the most exceptional scenario, myxomas themselves may be infected.

Methods

The case of a female patient with an infected mitral valve myxoma by *Haemophilus species* is reported. A search on Medline and Lilacs was conducted from inception to 2019 for epidemiological purposes.

Keywords

Mitral Valve/surgery; Mitral Valve/pathology; Diagnostic, Imaging; Echocardiography; Magnetic Resonance; Endocarditis; Lupus Erythematosus; Cardiac, Neoplasms.

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Results

A previously healthy 33-year-old female presented in December , 2017, with progressive shortness of breath, high-grade fever, night sweats and weight loss. Within a month she was admitted to a general hospital in overt respiratory distress and septic shock with diffuse alveolar infiltrates. Jaundice, bloody sputum and petechiae in the lower limbs ensued. She was intubated and needed hemodynamic support. A soft systolic mitral murmur was heard. There was marked leukocytosis with a left shift, low platelet count, abnormal liver and kidney function tests with near nephrotic proteinuria and complement depletion. Antinuclear antibodies were 1/80 despite normal anti-double stranded-DNA, anti-SM and anti-PR3 levels. After ceftriaxone she improved clinically. Yellow fever, dengue, Chikungunya, leptospirosis, HIV and viral hepatitis were ruled out. Blood cultures were positive for *Haemophilus species* in all six samples collected. Transthoracic echocardiogram demonstrated an amorphous echogenic mass with an irregular surface and a few mobile elements that involved both leaflets of the mitral valve measuring 20x17mm on the anterior leaflet and 19 mm in its greatest diameter on the posterior leaflets, resulting in severe regurgitation by flail and perforation (Figure 1). MRI showed small splenic abscesses, treated conservatively. An uncomplicated mycotic aneurysm of the left middle cerebral artery was managed by percutaneous embolization. Thirty days from admission she underwent successful mitral valve replacement with a biological prosthetic valve Sorin® size 29mm and extensive tumor resection. Moderate aortic regurgitation due to a lesion to the mitroaortic intervalvular fibrosa and retraction of the non-coronary cusp was treated conservatively. Pathology confirmed an infected mitral valve myxoma (Figure 1). The patient completed 28 days of ceftriaxone and gentamicin, being discharged asymptomatic. At one-year follow-up she had no evidence of recurrence and only mild aortic regurgitation. Infected myxomas present a greater risk of embolic events, though clinical features may be indistinguishable from uninfected tumors.[2] The present case appears to be the sixth reported infected mitral valve myxoma by fulfilling previously published definitive criteria and the third caused by a microorganism from the HACEK group (table 1).[3-8] Of 64 mitral valve myxomas published from 2006 to 2012, symptoms were cardiovascular in 36,7%; 9.5 to 21.6% of mitral valve myxomas underwent valve replacement and the timing until surgery varied from a few hours to 42 days.[2,9] Operative and overall mortality was reported to be respectively 2.6 to 3% and 5.1 to 21%.[2,10] In the present series most patients had overt heart failure, underwent mitral valve replacement and all of them did well on follow-up.

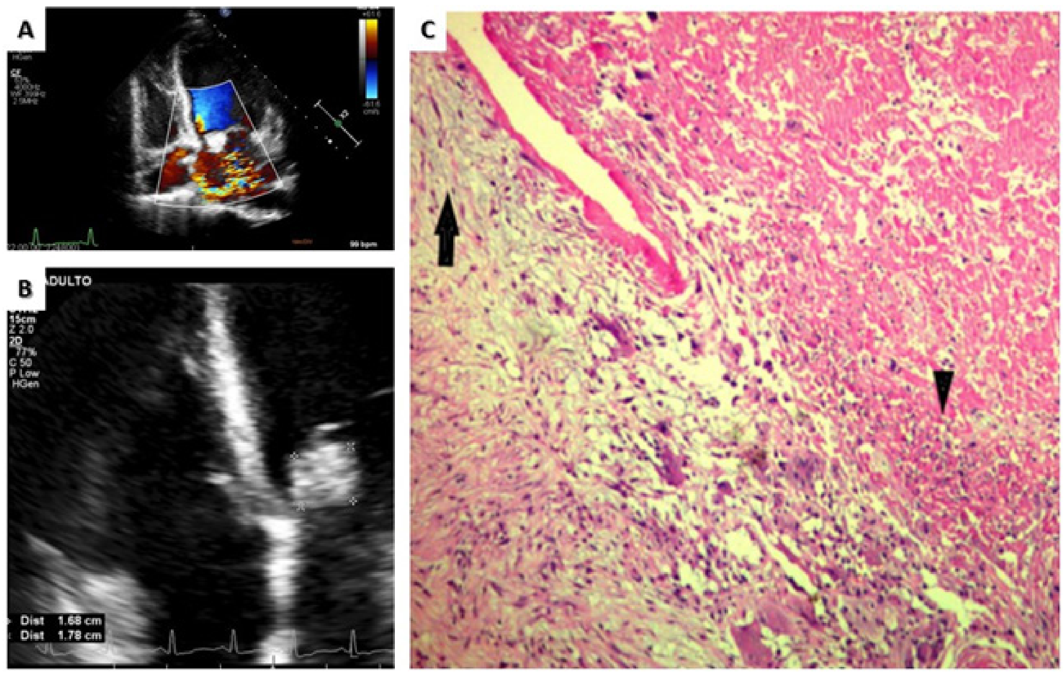

Figure 1 – *A) Apical four-chamber echocardiographic view demonstrating severe mitral regurgitation. B) Apical four-chamber echocardiographic view. C) Hematoxylin eosin staining 40x, myxoma is seen on the blue area formed by stellate cells in a myxoid stroma (arrow), with neutrophil infiltration and necrosis (arrowhead).*

Conclusion

This case of a mitral valve myxoma infected by the HACEK group and further complicated by septic emboli and immune-mediated manifestations is most interesting. On literature review, we found that the mitral valve was more severely damaged by the infected tumor compared to uninfected tumors and to other cases of HACEK endocarditis, leading to a higher rate of cardiovascular symptoms and shorter time to diagnosis. Despite extensive surgery with greater incidence of valve replacement in an urgent setting, patients did well on follow-up.

Author Contributions

Conception and design of the research: Coutinho TS, Amorim GDT, Lamas CC; Acquisition of data: Coutinho TS, Amorim GDT, Zappa M, Weksler C, Lamas CC; Analysis and interpretation of the data: Coutinho TS, Almeida BCR, Amorim GDT, Zappa M, Weksler C, Lamas CC; Obtaining financing: Lamas CC; Writing of the manuscript: Coutinho TS, Almeida BCR, Zappa M, Lamas CC; Critical revision of the manuscript for intellectual content: Amorim GDT, Weksler C, Lamas CC.

Potential Conflict of Interest

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia - INC under the protocol number 3.777.454. 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.

Table 1 – Infected mitral valve myxomas described in MEDLINE and LILACS

Ref.	Author	Year/ Country	Sex/ Age(y/o)	Organism	Diagnosis	Presentation	Location/Surgery	Postoperative complications	Outcome
PR	Coutinho	2020 Brazil	F/33	Haemophilus spp.	Echo Definitive criteria	Constitutional symptoms Septic shock and respiratory distress Severe mitral regurgitation Splenic abscess Mycotic aneurism	Anterior leaflet 20x17mm tumor Tumor resection and biological mitral valve replacement	Atrial flutter (immediate) Moderate to severe aortic regurgitation (late)	Survived NYHA I No recurrence 1-year follow-up
(8)	Ghazi	1988 UK	F/17	Haemophilus parainfluenzae	Echo Definitive criteria	Constitutional symptoms Vomiting, diarrhea and abdominal pain Sepsis Mitral regurgitation	Posterior leaflet 10mm tumor Tumor resection and annuloplasty	Uneventful	Survived NYHA I No recurrence 9-month follow-up
(7)	Mrozinski	1997 Poland	F/4	Staphylococcus aureus	Echo Definitive criteria	Constitutional symptoms Acute heart failure Severe mitral regurgitation	Both leaflets 30mm tumor Tumor resection and mechanical mitral valve replacement	Uneventful	Survived NYHA I No recurrence Unclear follow-up time
(6)	Toda	1999 Japan	M/20	Negative blood cultures Bacteria seen on pathology	Echo Definitive criteria	Constitutional symptoms Syncope Acute limb arterial occlusion Moderate mitral regurgitation	Posterior leaflet 20mm tumor Tumor and chordae resection, mechanical mitral valve replacement	Uneventful	Survived NYHA I No recurrence 2-year follow-up
(5)	Liu	2005 China	F/12	Neisseria lactamica	Echo Definitive criteria	Constitutional symptoms Acute heart failure Severe mitral regurgitation	Anterior leaflet 35x25mm tumor Tumor and papillary muscle resection, mechanical mitral valve replacement and urgent bypass graft surgery	Uneventful	Survived No data on functional status No recurrence 6-year follow-up
(4)	Guler	2007 Turkey	F/12	Staphylococcus aureus	Echo Definitive criteria	Acute onset of fever, sweating and fatigue Sepsis Mild mitral regurgitation	Anterior leaflet 29x18mm tumor Tumor resection	Ruptured saccular abdominal aortic aneurysm and bilateral renal infarction (late)	Survived No data on functional status No recurrence 6-moth follow-up

PR: present report; F: female; M: male; N/D: no data; Echo: echocardiogram; NYHA: New York Heart Association functional class.

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Case Report

Pulmonary Thromboembolism in a Young Patient with Asymptomatic COVID-19

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Case presentation

A male patient, 22 years old, with no previous comorbidities and medication use was referred to our hospital on 06/24/2020. Without symptoms, on 06/12/2020 he was diagnosed with COVID-19 after a PCR screening test required at his company and remained in bed rest during most of his isolation. He continued asymptomatic for 11 days; however, on 06/24/2020, he was admitted to the emergency department with ventilatory-dependent pain in the right hemithorax. Vital signs revealed hypertension (132/78 mmHg), tachycardia (127 bpm), hypoxia (SpO_2 of 90% at ambient air), and fever (38.7 °C). On physical examination, attention was drawn to the decrease in breath sounds in the right hemithorax during pulmonary auscultation. Padua and Wells risk stratification scores were applied, and the criteria indicated a low risk (3 points) and a moderated risk (6 points), respectively. D-dimer (6.652 μg/L), C-Reactive Protein (94 mg/L) and Troponin (119 pg/mL) were among the laboratory tests performed. A computed tomography (CT) scan of the chest was requested (Figure 1), which demonstrated the presence of Hampton's hump, a pleural-based opacification in the lung most commonly due to pulmonary embolism. Moreover, consolidative pulmonary opacities and peripheral ground-glass areas, both multifocal and bilateral, associated with septal thickening, with a small area of consolidation in between, more accentuated in the right lower lobe and with moderate pulmonary involvement (25-50%) were also found. On 06/25/2020, a computed tomography pulmonary angiogram (CTPA) was also requested (Figure 2), which demonstrated filling defects in the pulmonary arteries bilaterally, extending to its upper, middle and lingual branches, compatible with massive acute pulmonary thromboembolism. The patient was transferred on 06/25/2020 to the Intensive Care Unit (ICU), hemodynamically stable, and then nasal swab and oropharynx material collection for SARS-CoV-2 was requested, which came back with a positive diagnosis on 06/26/2020. Therapy was started with Ceftriaxone (2g daily), Azithromycin (500mg daily), Dexamethasone (6mg daily) and Oseltamivir (75mg daily), associated with Enoxaparin (80mg full dose) as prophylaxis for venous thrombosis. The patient showed progressive improvement. He was discharged from the ICU to the infirmary on 06/28/2020 and on 06/29/2020 he was discharged from the hospital, using Rivaroxaban (15mg BID), being referred for future outpatient reassessment. After the discharge, tests were requested to investigate thrombophilia, including: Functional Protein S, Functional Protein C, Homocysteine, Leiden Factor V, Prothrombin gene mutation, Antithrombin III, Lupus Anticoagulant and Anticardiolipin IgM. The increase in Antithrombin III (999%), the weak presence of Lupus Anticoagulant (1.43) and undetermined IgM Anticardiolipin levels stand out. In addition, echocardiography and Doppler ultrasonography of the lower limbs were requested, which were both within normal standards, ruling out possible signs of thrombosis, either recent or late.

Keywords

SARS-CoV-2; Young; Pulmonary Thromboembolism; Virchow's Triad; COVID-19; Coronavirus-19; Carrier State

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Discussion

Many patients with COVID-19 have coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation or thrombotic microangiopathy.[1] Coagulopathy resulting from COVID-19, can occur in both venous and arterial circulation, and is associated with the release of pro-inflammatory cytokines, such as (IL-2, IL6, IL-7, IL-10).[2] The findings of the most recent studies are consistent with the close association between thrombosis and inflammation, two processes that reinforce each other since, during SARS-CoV-2 infection, the endothelium is capable of switching to a responsive inflammatory phenotype after its activation, expressing cytokines and vascular adhesion molecules, which can further aggravate the cytokine storm.

These cytokines, in turn, can cause dysfunctions of the glycocalyx present in endothelial cells, which are responsible for creating a barrier against the aggregation of platelets and blood cells, thus contributing to the development of thrombotic and endothelial events. Additionally, the systemic inflammatory state also results in endothelial dysfunction, inducing the affected cells to a cell death process called pyroptosis.[3] All these changes in the pro-inflammatory response of the host, in addition to endothelial dysfunction, also imply a wide disarray in several hemostasis parameters, among which D-dimer,[4] which is a potential marker of prognosis and/or mortality of patients affected by the disease.[5]

Despite not having risk factors for complications, the patient in this report developed massive acute PTE. This could be explained from the Virchow's Triad theory, in which endothelial dysfunction, stasis and blood hypercoagulability converge for the development of thrombotic processes, and among them, pulmonary thromboembolism stands out. The state of hypercoagulability and endothelial dysfunction can be justified due to the viral infection that reflected in an important change in serum D-dimer level (6652 μg/L), which is associated with greater COVID-19 severity; moreover, the patient reported that after being diagnosed with COVID-19, he remained in bed rest in his residence, which corroborates the presence of pulmonary blood stasis. Post-diagnosis isolation recommendations should also aim to prevent situations that influence blood stasis.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Borges NH, Godoy TM, Curcio M, Stocco RB, Hessel V, Baena CP, Lenci G

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 Pontifícia Universidade Católica do Paraná under the protocol number 30188020.7.1001.0020. 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.

Figure 1 - *CT scan performed at admission, showing Hampton's hump, a well-defined pulmonary pleural-based opacity representing hemorrhage and necrotic lung tissue in a region of pulmonary infarction caused by acute pulmonary embolism.*

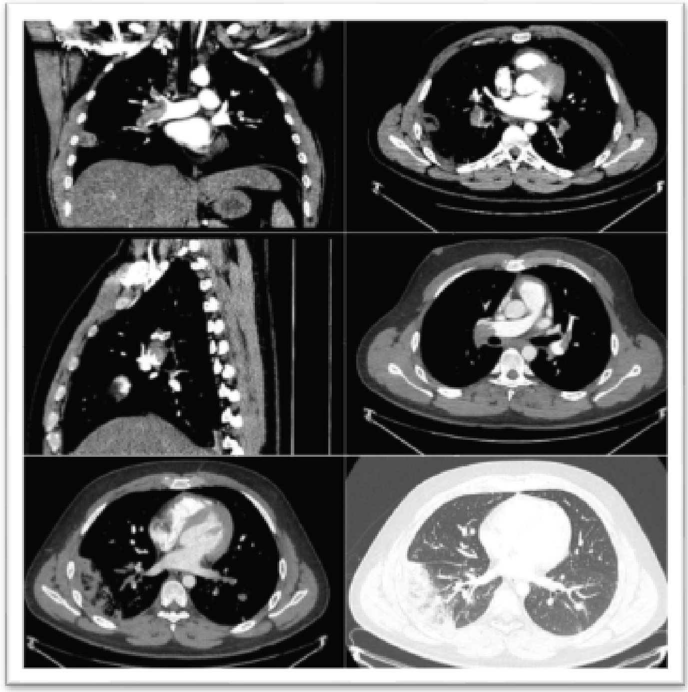

Figure 2 - *CTPA performed on day two, demonstrating filling defects in the pulmonary arteries bilaterally, reinforcing the diagnosis of massive acute pulmonary thromboembolism.*

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Letter to the Editor

Brazilian Cardiovascular Rehabilitation Guideline: Values and Limitations

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Dear Editor,

The Brazilian Cardiovascular Rehabilitation Guideline – 2020[1] is of great interest and relevance to the professionals involved in the care of cardiovascular disease (CVD) patients. With internationally agreed core components,[2] cardiovascular rehabilitation (CR) is a well-established model of secondary prevention that mitigates the CVD burden. Despite its benefits, the CR is available in only 40% of low-middle income countries, with insufficient capacity even where it does exist.[3] Therefore, guidelines for healthcare providers in countries where CR is not widely available are sorely needed.

Although these guidelines show conceptual improvements over previous versions, some points deserve greater attention. First, the title refers to CR in general and, since the document focuses on exercise training it fails to address other important CR core components in detail, as well as relevant features of exercise assessment and prescription. Although it is widely known that the cornerstone of CR is exercise, the management of CVD patients is multifactorial, including not only exercise but patient education, promoting behavior change, psychosocial support, nutrition counseling, optimizing medication, smoking cessation strategies, etc. Comprehensive CR programs (i.e., exercise combined with all of the aforementioned components) have provided additional benefits to patients, including reduction in all-cause mortality rates.[4] In Brazil, the first-ever randomized controlled trial in a low-and-middle income country confirmed that comprehensive CR can improve clinical outcomes, heart health behaviors, and disease-related knowledge, as well as decrease morbidity, with 1-year maintenance of gains.[5]

A multifactorial approach for the care of CVD patients is achieved with a multi-professional team (doctors, physiotherapists, nurses, dietitians, physical education professionals, psychologists, etc.). It is necessary to consider and value all of the healthcare providers involved in the care of CR patients, i.e., those who enable these programs to run and be effective. The complexity of CVD patients' problems is a good example of the real need to use a team approach that involves different disciplines, expertise, and skills. It is also important to consider the historical structure of CR in Brazil, where multidisciplinary teams and the autonomous role that each professional can play are undervalued. Centralization of the CR process may turn out to be one more barrier, along with the many others in our country, such as lack of funding.

Structuring CR programs according to risk stratification and professional certification can represent a new and promising stage that hastens a methodological transition.[6] Brazilian and international institutions are in constant development regarding multidisciplinary CR and may share efforts to improve the availability and effectiveness of programs, reducing the possible burden on cardiologists, who are usually engaged in other professional assignments.

It is worth noting that guidelines aim to influence healthcare professionals, providing evidence-based support so that decision makers can improve the quality of care. According to the AGREE Consortium,[7] the benefits of guidelines are related to the quality of the documents themselves, such as their scope and purpose, stakeholder involvement, and rigor of development, which is mainly related to a systematic approach, as well as their clarity of presentation. Some of these domains are not clear in the Brazilian Cardiovascular Rehabilitation Guideline – 2020. Stakeholder involvement and a systematic approach toward scientific evidence, for example, must be carefully reconsidered in the next version.

Keywords

Cardiovascular Diseases; Secondary prevention; Reabilitation; Exercise; Health Education; Health Care Providers.

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Reply

First of all, we would like to thank the authors of the letter "Brazilian Cardiovascular Rehabilitation Guidelines: values and limitations" for their interest in the Brazilian Cardiovascular Rehabilitation Guideline – 2020,[1] for recognizing that there has been a conceptual evolution in relation to the previous versions of our guidelines and positions and, particularly, for their criticisms, which provided us with a unique opportunity to resolve questions and address topics of great relevance, many of which were not included in the document due to authors' decisions, as will be justified below.

We agree "*ipsis literis*" with the statement that one of the biggest problems with cardiovascular rehabilitation (CR) worldwide is the scarcity of structured programs,[2] including in Brazil,[3] where, as we emphasize in our document, the chronic situation calls for urgent public health strategies to make CR viable in both public (SUS) and private (ANS) health systems, since it is clearly an important health policy issue that must be resolved.[1,3,4]

We also agree that guidelines are needed to influence health professionals. In this context, we should point out that the Brazilian Society of Cardiology (SBC) has been doing so for more than two decades,[4] i.e. the current guideline is the sixth such document to specifically address CR.[1,4-8] We should also add that the two SBC prevention guidelines,[9,10] in addition to physical exercise, addressed other topics such as global prevention strategies, which obviously must be considered in the context of CR.

Other health professionals have even participated in some of these SBC documents,[4,5,9,10] which shows our recognition of and strong commitment to an interdisciplinary, multi-professional approach to make CR more effective.[11] We are unaware of other guidelines or positions on CR in Brazil by other societies or associations of health professionals. Therefore, this is an important gap to be filled, including discussion about the performance of each professional in the interdisciplinary approach.

Although the title of the current guideline refers to CR in general, the introduction clearly states that "as in previous documents the Brazilian Society of Cardiology […] has published on the subject,[4-8] the guideline exclusively addresses interventions based on physical exercise aimed at treating patients with cardiovascular diseases, with the class (or degree) of recommendation always based on the highest available level of scientific evidence".[1]

Thus, the main objective of the current guideline was clearly defined, although this obviously does not mean disregarding a broader approach to a structured change of behavior. Promoting a healthy lifestyle includes patient education processes, psychosocial support, nutritional counseling, optimization of and adherence to pharmacological treatment, smoking cessation strategies, strategies for modulating stress, etc. This requires multiprofessional participation and an interdisciplinary approach, which, as explained above, has been duly considered in other SBC guidelines and positions on prevention, the latest update being 2019 document.[10]

In addition to the reduced availability, the inclusion and treatment adherence of those eligible for CR services are low.[11] We consider that, particularly in Brazil, one of the main barriers to CR is the lack referral by attending physicians,[12] including the "fear" of exercise for more severe patients. This denotes ignorance about CR, despite consistent and well-documented publications on its safety and efficacy, specifically its reduction of morbidity, mortality and hospitalization, combined with increased quality of life.[13,14]

Therefore, the main goal of the Brazilian Cardiovascular Rehabilitation Guideline – 2020[1] was to update information about the method, emphasizing exercise programs and the importance of more active participation by attending physicians and members of CR programs. Thus, we focused the search for scientific evidence on the indications and benefits of CR, especially regarding exercise as a treatment for cardiovascular diseases.

The current Guideline cites 382 references, practically half of which were published in the last five years, which shows our concern with using current scientific evidence to assess the impact of physical activity on numerous diseases and clinical situations, not merely coronary disease and heart failure. The effects of exercise were described in detail, enabling safe and effective prescription in individuals with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, myocarditis, valvulopathy, heart transplantation, implantable cardiac devices and peripheral obstructive arterial disease, for example.[1]

In view of the above, we would like to emphasize that:

1. The Brazilian Cardiovascular Rehabilitation Guideline – 2020 was developed by members of the SBC, i.e. a medical society. Twenty-two experienced authors from different public and private services in various regions of Brazil worked on the CR and, as previously mentioned, its main goal was to update and expand information about the impact of exercise on patients with cardiovascular disease, aiming to value physician intervention and increase patient referrals to formal CR services.

2. Although our focus on multiprofessional performance was purposely limited, it was not treated as irrelevant. We stated that "the multiprofessional team usually consists of doctors, physical educators, physical therapists and nursing professionals. Other professionals can also be included in the team, such as nutritionists, psychologists and social workers". We also explained that "like physicians, when the other members of the team perform their respective functions, they must follow the norms and rules that guide the program, respecting the recommendations of their respective professional councils".

3. In Brazil, we believe that more direct participation by medical professionals is still necessary, unlike in other countries, such as Canada, since the decision to include CR in the context of full clinical treatment is initially up to the attending physician.

4. The SBC guidelines have always considered stakeholders, historically enabling more effective and competent performance for the benefit of patients, as well as providing effective measures for the competent bodies (ANS and SUS) to define therapeutic strategies. We believe that the latter should be one consequences of this document.

Tales de Carvalho

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