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The legacy of Prof. Eduardo Sosa

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On June 20, 2020, we received some sad news: the death of Professor Dr. Eduardo Argentino Sosa, Associate Professor of Cardiology at Instituto do Coração da Universidade de São Paulo. This information filled everyone who knew him with deep sadness.

A Short Background

Eduardo Argentino Sosa was born in Corrientes, Argentina, on January 25, 1942. He started a medical course at the School of Medical Sciences of Universidad Nacional del Nordeste, in his hometown, but due to the political situation that affected the university in Argentina at that time, he transferred to the School of Medical Sciences of Córdoba and later to the School of Medical Sciences of Universidad Nacional del Litoral, in the city of Rosário, where he completed studies in April 1965.[1]

His interest in cardiology arose during his internship, when he was fascinated by the existing diagnostic methods, such as electrocardiography, vetocardiography, phono-cardiography and cardiac catheterization, which began at the time. Hence his first scientific study, presented at the 1st National Cardiology Day at the Argentine Federation of Cardiology, in the city of Carlos Paz, in Córdoba, entitled "Intermittent Left Branch Block. Phonographic and Polygraphic Study." He was soon hired as an assistant physician in the cardiology service, where he met Miguel Barbero Marcial, who later became his personal friend and changed the course of his life.[1]

From 1966 to 1967, still in Rosario, he traveled weekly to Buenos Aires to learn the techniques of catheterization at Hospital Ramos Mejia, at the service of Professor Blas Moia and Electrocardiography at Hospital de Salaberry, at the service of Professor Marcelo Rosembaum.[1]

On one of those visits, he met Professor Demétrio Sodi Pallares, from the National Institute of Cardiology in Mexico, at the time a world reference center in cardiology research.

Sosa planned to further develop his education in Mexico. However, his friend Miguel had moved to São Paulo and convinced him to come to Hospital das Clínicas, School of Medicine of Universidade de São Paulo (HC-FMUSP). The reason? He realized that there was an actual revolution underway in the treatment of cardiovascular diseases, with the advances of cardiovascular surgery and found in HC-FMUSP an exceptional academic group that worked with enthusiasm and inspiration, coordinated by Professors Euryclides de Jesus Zerbini and Luis Venere Décourt.

Sosa arrived in São Paulo on February 13, 1968, and was immediately admitted to the course of Prof. Décourt, an icon of Brazilian cardiology. Noticing his academic potential, Professor Giovanni Bellotti, assistant to Décourt, "adopted" him and made him one of the members of the team that did the first heart transplants in South America. (Figure 1) For his dedication, he was invited to stay permanently in Brazil.

In 1972, he had his medical diploma revalidated and, in 1974, he was hired through a public examination as an assistant physician at Segunda Clínica Médica do Hospital das Clínicas and started to work with Giovanni Bellotti in the Valves Group. He was then practicing Cardiology and was responsible for the patients seen in that group.

Sosa has always had a strong commitment to the patients' well-being and also enjoyed teaching and motivating residents and interns with brilliant interventions. However, he did not feel completely fulfilled, as he wanted great challenges. Whoever is having the first contact with Sosa in this tribute will realize that we are talking about Brazilian cardiology of almost 50 years ago. A time of few procedures, few medications and many diseases, with much more limited knowledge than today.

His interest in electrophysiology emerged after he had access to the study published by Scherlag et al. in 1969, demonstrating the feasibility of recording His bundle-electrogram in humans through vascular access.[2] In the following year, with professors Giovanni Bellotti, João Tranchesi, Radi Macruz and Donaldo Pereira Garcia, he managed to get the first His bundle-electrogram recording at HC-FMUSP and, in 1972, they made the first attempt at the surgical treatment of Wolff-Parkinson-White (WPW).[3]

One day, in 1974, Bellotti contacted Sosa and invited him to study electrophysiology in the WPW Syndrome for his doctoral thesis. They then had to learn to analyze electrophysiological tracings. Sosa was then introduced to this new world with countless challenges.

The first was to talk to Prof. Antonio Paes de Carvalho, Full Professor at Instituto de Biofísica e Fisiologia Carlos Chagas at UFRJ, great scientist and researcher of the electrophysiological mechanisms of cardiac arrhythmias at an experimental level, and internationally recognized.[4] With him, Sosa went to learn how to obtain and analyze intracardiac electrograms.

After a few days, he did the first electrophysiological study at HC, with Bellotti. Interestingly, the first tracings were rudimentary, with interferences and deflections everywhere. Bellotti would ask: "Sosa, what's the H?" — as there were three deflections, the question remained unanswered. But they learned that records should have less interference to be reliable. Sosa, in his pursuit of perfection, devised ways to achieve high-quality records for the time. (Figure 2)

Palavras-chave

Eduardo Sosa; Cardiology; Cardiovascular Diseases; Electrocardiography; Electrophysiology; Electrophysiologic Techniques Cardiac/trends; Research Personnel; Faculty/history.

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Figure 1 – *Photo from 1968 documenting Prof. Christiaan Barnard visiting Hospital das Clínicas of FMUSP. From right to left, Professor Christiaan Barnard, Professor Euriclides de Jesus Zerbini, Eduardo Sosa, Noedir Stolf and contributors of the time.*

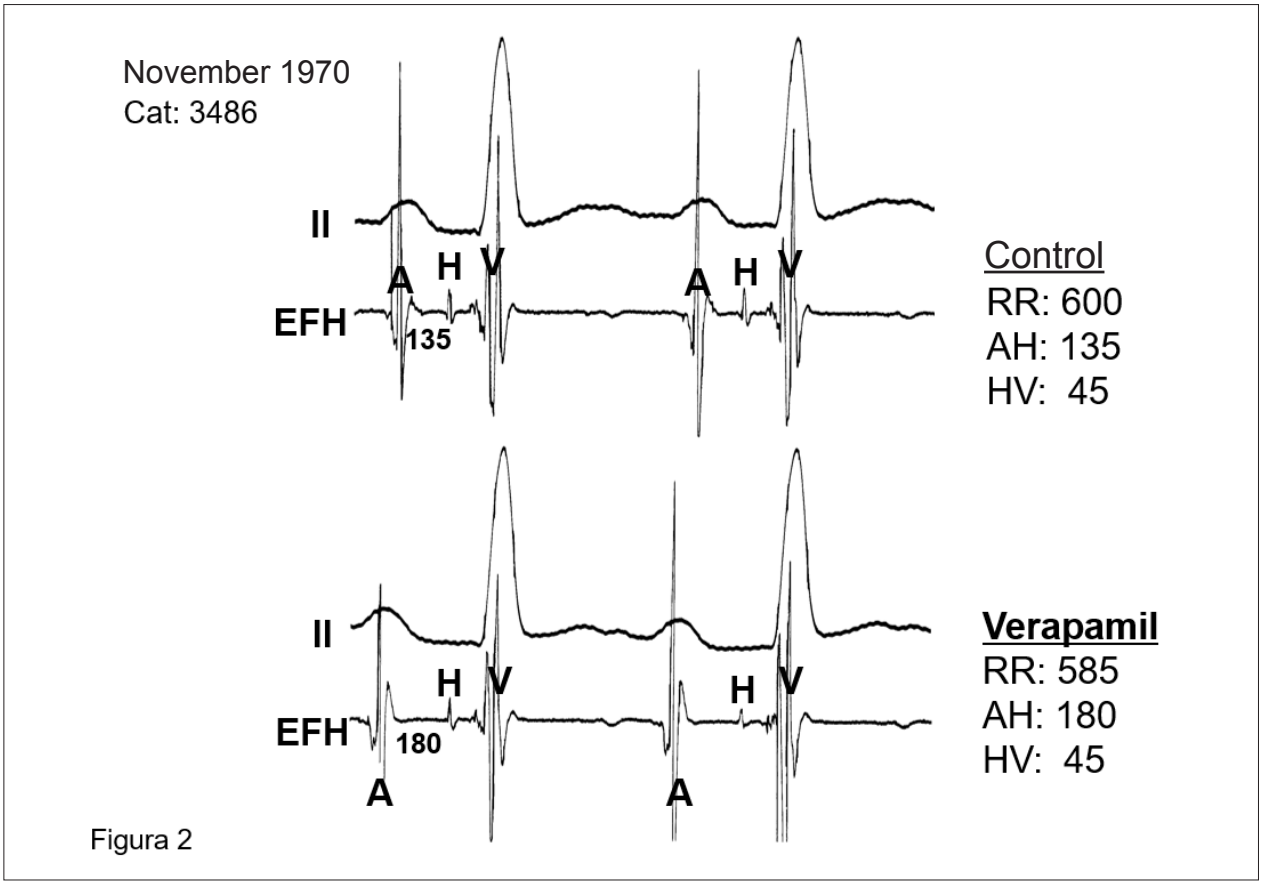

Figure 2 – *Electrophysiological record taken at HC-FMUSP in 1970, documenting the effect of venous infusion of verapamil on the basic intervals of the conduction system.*

Then, patient studies for Bellotti's thesis begin. They would spend the day inducing tachycardias with electrode-induced stimuli, analyzing tracings and interpreting the findings. At the end of each study, they felt deep satisfaction with the findings.

But the biggest surprise occurred on the day of Bellotti's thesis presentation. At the end of the presentation, the examiners praised the innovative study and wrapped up the questions & answers session in about 20 minutes. To date, this has been one of the University's shortest thesis presentations, possibly because the examiners knew little or nothing about the subject.[5]

In 1975, Bellotti was appointed head of the Cardiology ICU, on the 6th floor of HC. At that time, José Antonio Frachini Ramires started to work with him as an assistant of Internal Medicine and Cardiology ICU. "When we met Sosa in the corridors of the Hospital, with electrophysiological sheets in his hands, if he wanted to show us any details, we should be prepared to spend a long time helping him to unfold them, see the records and then fold them back again. Some assistants from the clinic escaped these meetings," Ramires says.

On that occasion, Cesar Grupi joined the group, helping him to carry out the first electrophysiological studies.[6,7] At that time, the studies were carried out under different conditions, such as in patients with acute myocardial infarction, as suggested by Prof. Radi Macruz and evaluation of the electrophysiological effect of antiarrhythmic drugs as some great news...[8,9]

With the transfer of Cardiology to Instituto do Coração, which had just been opened, Sosa served as head of the valve group and the incipient arrhythmia group. At his request, Bellotti and Prof. Fúlvio Pilleggi created two independent groups: the Arrhythmia Group and the Valvular Heart Disease Group, which remain so until today.

The cardiac electrophysiology laboratory was structured in 1980, becoming a key piece in the development of interventional treatment of various arrhythmias at Incor. Seeking improvement in their procedures, both visited services in the United States, particularly Kenneth Rosen's in Chicago and Mark Josephson's in Philadelphia.

It is worth noting that when they visited these services, they had done 10 WPW surgeries and 10 ventricular tachycardia surgeries, which impressed the local professors, as very few American services performed these procedures at the time.

Notably, Sosa and Miguel changed the paradigm of arrhythmia treatment in Chagas' disease, demonstrating that the recurrent sustained ventricular tachycardias were reentrant circuits related to scarring, and could be reproduced with programmed ventricular stimulation. More importantly, they observed that such circuits originated more frequently in a scar located in the lower, lateral and basal left ventricular wall, as, until then, it was believed that the apical aneurysm, so frequent in patients with Chagas disease, were the focus of such arrhythmias.[10] (Figure 3)

Throughout the 1980s and 1990s, the surgical treatment program for atrial, supraventricular and ventricular tachyarrhythmias progressed intensely, making Incor a reference center for the surgical treatment of refractory tachyarrhythmia and for the education of electrophysiologists and surgeons, not only from Brazil, but also from Latin America.[10-15]

In 1982, Gallagher et al.[16] published the first experience with catheter ablation to induce total atrioventricular block in patients with intractable supraventricular tachyarrhythmias. Once aware of this innovation, Sosa was able to develop connections between defibrillators and conventional catheters, with the help of Adib Jatene.

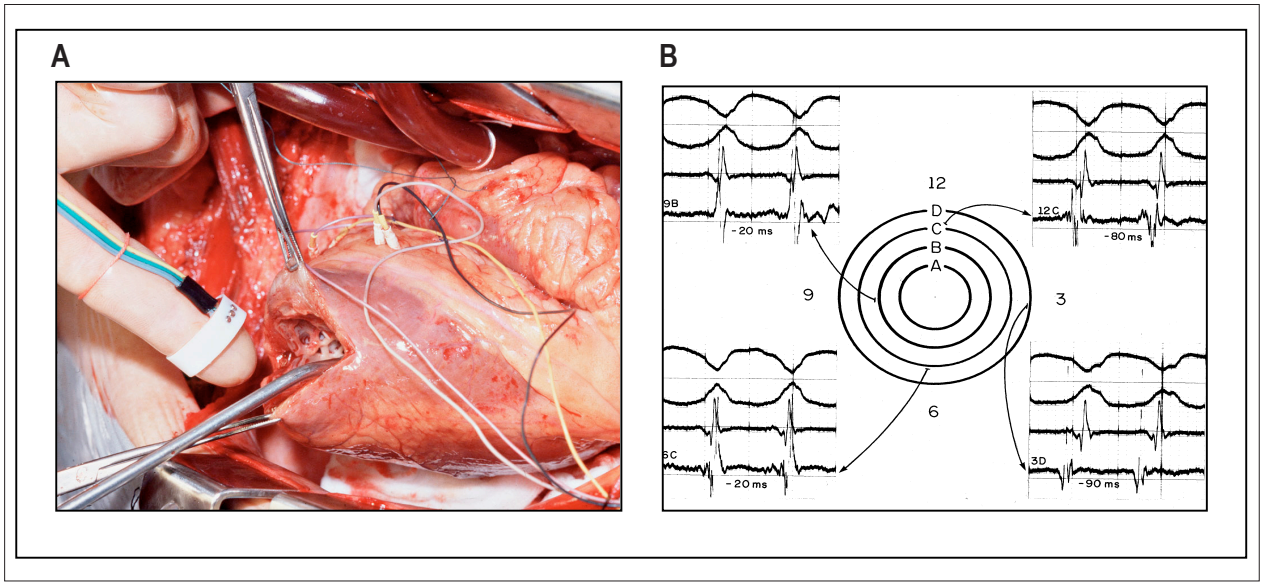

Figure 3 – *A and B) Intraoperative mapping of a patient with recurrent ventricular tachycardia secondary to Chagas' heart disease in the 1980s. A) Access for endocardial mapping was through the apical aneurysm. Note that point-to-point mapping was performed by bipolar electrodes attached to a device that allowed its direct positioning by the surgeon's finger. B) Electrophysiological records document the endocardial activation sequence of ventricular tachycardia induced in surgery by programmed stimulation.*

With Augusto Scalabrini and Silvio Barbosa, they performed the first catheter ablation successfully, using direct electrical discharge (Fulguration) to induce complete atrioventricular block (CHB).[17] These procedures were performed with conventional electrode catheters, as in the few international services that also began to perform it. It was then that the first structured laboratory of Interventional Electrophysiology was developed in Brazil, as a result of his innovative spirit.

During his administration as director of the Arrhythmia Unit, still in the 1980s, Sosa encouraged the development of the clinical practice of artificial cardiac stimulation with Martino Martinelli as an assistant and Silvana d'Ório and Anísio Pedrosa as contributors, which resulted in the Arrhythmia and Pacemaker Unit.[18,19]

With the expansion of InCor and an increased number of outpatient care rooms, in the early 90s, Sosa encouraged the creation of a syncope clinic attached to an autonomic evaluation laboratory; a teaching clinic; atrial fibrillation; ventricular tachycardia and genetics, and was helped by new assistants, Denise Hachul and Francisco Darrieux, who jointly developed a university extension program in clinical arrhythmia.[20,21]

Returning to the 70s, Ramires says that in his master's thesis on the topic of autonomic block in Chagas' disease patients, Sosa inspired the use of beta-blockers in patients with acute myocardial infarction and heart failure. Its benefit was proven through myocardial metabolic assessment and hemodynamic monitoring at the bedside. Since then, the use of beta-blockers was introduced in the therapeutic routine of both pathologies at our institution.[22,23]

But his great academic interest has always been interventional electrophysiology, on which he worked intensively with his assistant Mauricio Scanavacca. They trained countless electrophysiologists over the years, now responsible for arrhythmia and electrophysiology services not only in Brazil, but also abroad.[24-31]

In 1984, with fellow cardiologists involved in the treatment of patients with cardiac arrhythmias, particularly Ivan Maia in Rio de Janeiro, Adaberto Lorga in São José do Rio Preto, João Pimenta at Hospital do Servidor Público Estadual and Julio Gizzi at Instituto Dante Pazzanese de Cardiologia, both in São Paulo, founded the Arrhythmia, Electrophysiology and Artificial Cardiac Stimulation Study Group, embryo of what later became the electrophysiology department of SBC and later the Brazilian Society of Cardiac Arrhythmias. (Figure 4 A and B)

In the mid-90s, a significant challenge faced by electrophysiology was achieving better results in the ablation of ventricular tachycardia (VT). In our community, this challenge seemed to be greater in patients with Chagas' heart disease.

Noting the low rate of ablation success in these patients, Sosa, Mauricio and the anesthesiologist from João Piccioni's team developed the technique for mapping and epicardial ablation of ventricular tachycardia and demonstrated that the circuits were predominantly epicardial in patients with Chagas' heart disease.[32-36] (Figure 5) The group's findings, at that time with the participation of André D'Avila, reached

Figure 4 – *Two moments of Dr. Sosa participating in the scientific meetings of the specialty. A: Still young, at the first SBC Day of Cardiac Arrhythmias in Rio de Janeiro in 1984 and B: older in the mid-2000s, in one of the congresses of the Department of Cardiac Arrhythmias of SBC.*

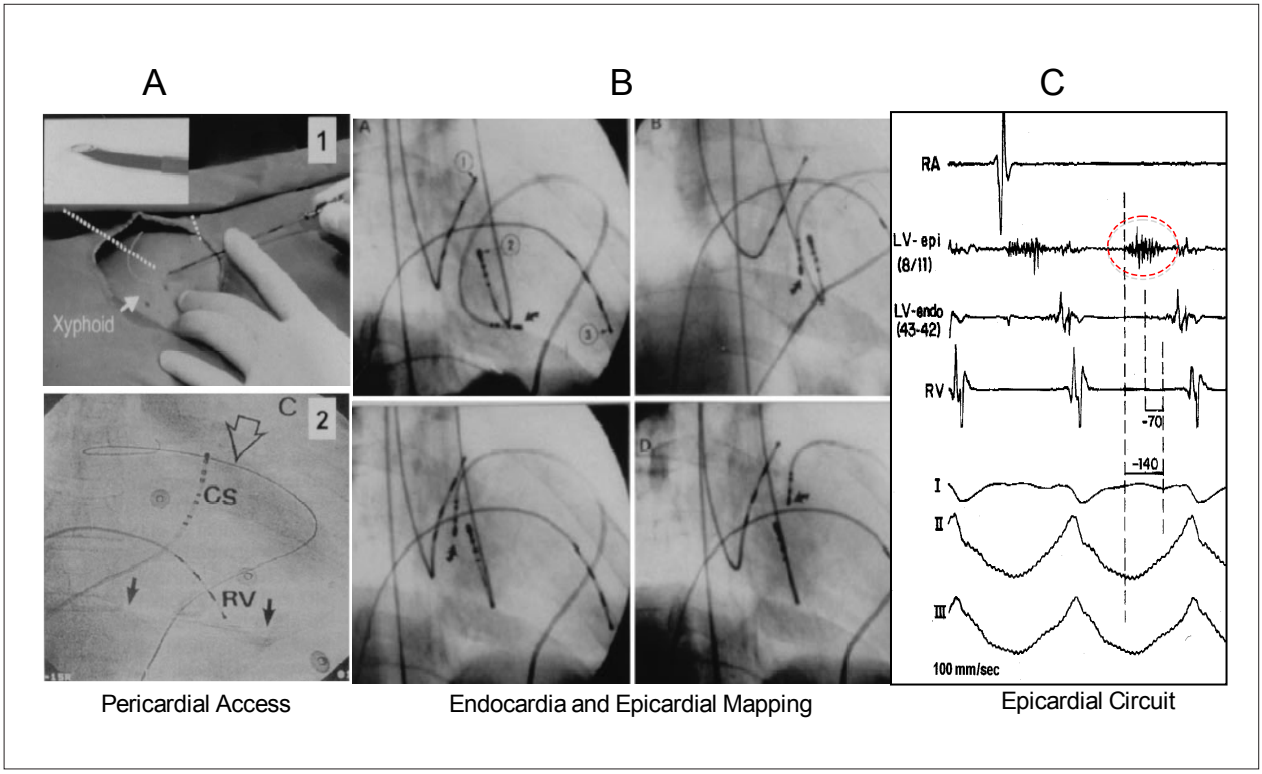

Figure 5 – *Figures from the cover of the Journal of Cardiovascular Electrophysiology of June 1996, promoting the article that described the technique of percutaneous access to the pericardial space. A: Pericardial access by subxiphoid puncture; B: epicardial mapping with catheter; C: records of bipolar electrograms during ventricular tachycardia in a patient with Chagas' disease demonstrating the presence of an epicardial circuit.*

the international scene and the technique started to be used in other types of arrhythmias, in addition to Chagas' disease VT.[31,37]

Since then, congresses of the American and European arrhythmia and cardiology societies have been a constant stage for presentations of epicardial mapping and ablation, including dedicated sessions, many of which are chaired and moderated by their creators.

After the publication of a study with findings from the new technique, a number of European, Latin American and North American electrophysiologists contacted InCor to learn the technique at the Arrhythmia and Electrophysiology Unit, in order to implement it in their services, such as Cleveland Clinic, Mayo Clinic, University of California, Stanford, Massachusetts General Hospital and several European Reference Centers. This was one of the peaks in the study by "discontented" Sosa, who was always looking for more.

There is no doubt that Sosa created a school with many disciples throughout Brazil, Latin America and other continents. Eduardo Argentino Sosa, Argentine by birth and Brazilian by heart, had a vision focused on the infinite.

Eduardo Sosa will remain forever in the memory of his friends, in the history of Incor and Brazilian Cardiology and his legacy will be immortalized by his disciples.

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A Reflection on Conflicts of Interest in Medical Guidelines

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Prescribing a drug directly to the patient, recruiting a volunteer for a clinical research, lecturing at a specialty congress, participating in a committee that elaborates clinical guidelines, supervising a clinical visit with residents, giving your opinion for colleagues over coffee.

All of these situations are characterized by human interaction, greater or lesser asymmetry of knowledge, and multiple interests, where the possible privilege of one may cause damage to another.

Thereby, the potential for confrontation between interests is established,[1,2] and this is called a potential conflict of interest. The use of the term "potential" brings about a possibility of the human condition that did not occur, and may never happen or materialize as an imperceptible reception or unconscious emission.

Quicksand is in the very essence of medicine: the need of professionalism under an ethical, moral and legal framework that demands clinical, technical, scientific and attitudinal actions under a strong irresolution about beneficence (conceptual) and benefit (individual), of (conceptual) (non-) maleficence and (individual) (non-) harm.

Clinical guidelines illustrate well the dilemma. They have gained first-rate recommendation status; their reliability is guaranteed by trustworthy specialist societies and serve as a reference for ethical criticism.

If, on the one hand, clinical guidelines aim at the esthetic excellence of the letter T—symbolyzing the comprehensiveness of knowledge in the horizontal bar and its depth in the vertical bar—in a proportion that follows evidence from clinical research, professional experiences and strong opinions, on the other hand, the bedside routine highlights the wisdom of individualized adjustments. The raw material for a potential conflict of interest is scientific evidence, but it is individualization that usually lights the match.

The collegiate selection of the effect dimension and the probability of carrying out methods in diseases and circumstances stand out in the creation of clinical guidelines. The steering committee members need to analyze evidence of reciprocal determinations between method and clinical settings.

Keywords

Medicine; Professionalism; Guidelines, Clinics; Conflict of Interest; Guideline Adherence; Bioethics.

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Inclusions, exclusions and prescriptive classifications must be guided by the idea of reciprocity of salt and water, that is: no matter the conditions, water dissolves salt and salt dissolves in water—as long as in liquid state, not fitting for ice or water vapor. At the same time, it must be borne in mind that each diagnostic, therapeutic or preventive method invariably represents a stick that carries benefit in one end and harm on the other; there is no zero iatrogenesis for the patient, as the medicines' leaflets teach us.

Does the manifestation of a conflict of interest on the part of a member of a guideline committee constitute a desirable moral vaccine? I do not think so. The audience calibrating the pores of its critical filter on what the speaker says is one thing; the foundation for the reader of clinical guidelines to assume bias is another.

From a pragmatic point of view, one cannot ignore that the qualification criteria for the choice of specialists to develop a guideline overlap with those used by the industry to associate itself with it in some way. Academic liaison, continued scientific production, credit among colleagues are common factors. As a result, the chances of thinking about a name and stumbling with any potential conflict of interest are high. Radical positions can impair selection, narrowing it towards the less experienced.

Bedside bioethics understands that the manifestation of a conflict of interest in a guideline has the sole purpose of stating: "I give my word of honor that I have such theoretical potentials, but I did not put them to practice".

One can assume that people help accountable at the Brazilian Society of Cardiology preceded the reading of a new clinical guideline in the Brazilian Archives of Cardiology, including the decision on the need for updating/first time, selection of names, criticism and final approval. So, the focus of trust and responsibility is on corporate management.

Management concerns can be simplified in the triad: absent information, biased information, qualified information. Any of these can be object of conflict of interest, hence the complexity. Hiding a novelty, forcing a recommendation or emphasizing endorsable evidence can embody personal interests or those of connected individuals.

Bedside bioethics prefers to focus on fidelity to one's conscience when performing functions subject to the imperfections of human condition.[3] Of course, strong associations with the industry should be avoided, as only being honest is not enough; one must avoid doubts.

'Nevertheless, it is essential to consider that the behavior of members of a guideline committee will invariably be responsibility of the group, with priority interest aimed for the collectivity, rejecting any automaton expression within the group, respecting the criticism by the lead coordinator, walking side to side with research findings and bedside reality; to sum up: freedom and independence well supported by the updated and validated scientific platforms.

One can guess that it would be naïve to trust the imperative of conscience[4] that even an expert, a professor PhD, any juror of Hippocrates, committed to society by the possession of a medical register, cannot help but be dragged by the superficiality of a spurious interest when deep knowledge and wisdom is required of them. It is a valid counterpoint, but—and there is always a but—who would deny that the manifestation of conflict of interests not only does not allow the necessary discounts to be defined at the reception, but also does not function as a moral agent 007, bearing a license to conflict. There are suppositions of strategic exaggeration, a tendency for the issuer to provide more biases to offset the reception discounts caused by conflicts of interest. On the other hand, it can inhibit opposition by the fear that it might lead to a conflict of interest.

Eubulides de Miletus asked this question 26 centuries ago: At what point does a pile of sand cease to exist? When grains are removed? Or do grains become a pile by successive addition? The answer is only possible if we look from an authoritarian point of view, if someone establishes a criterion with some type of imposing force. How much flexibility can be tolerated in a guideline committee member's opinion?

Given the presumption of professional honesty by the partners, which should prevail in a specialty society, and given the difficulty in perceiving conflicts of interest in the contemporary setting of medicine, full of undetermined and accelerated metamorphoses, I believe that a potential conflict of interests is an inseparable part of the elaboration of any clinical guideline, and that any kind of certainty of its absence is impossible. Therefore, a guideline is not a handcuff, but rather a compass. Individual adjustments are welcome.

Therefore, regardless of the expression of interests of each member of the guideline committee pertinent to the document, I propose a manifestation at the beginning of each guideline: since the decision of creation until the authorization of this publication, The Brazilian Society of Cardiology kept the confidence in the good faith of participants, a virtue that makes scientific truth a value underlying the relationships with oneself and with colleagues and patients.

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Pulmonary Vascular Volume Estimated by Automated Software is a Mortality Predictor after Acute Pulmonary Embolism

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Abstract

Background: Acute pulmonary embolism (APE) has a variable clinical outcome. Computed tomography pulmonary angiography (CTPA) is the gold standard for this diagnosis.

Objective: To evaluate if the pulmonary vascular volume (PVV) quantified by automated software is a mortality predictor after APE.

Methods: Retrospective cohort study where the CTPA imaging of 61 patients with APE was reanalyzed. Pulmonary vascular volume (PVV) and pulmonary volume (PV) were automatically estimated using the Yacta software. We calculated the adjusted PVV by the ratio: PVV(cm^3)/PV(liters). Classical prognostic CTPA parameters (clot load index, right ventricle/left ventricle diameter ratio, pulmonary artery/aorta diameter ratio, ventricular septal bowing, pulmonary infarction and reflux of contrast into the hepatic vein) were assessed. The outcome assessed was one-month mortality. We considered a p-value <0.05 as statistically significant.

Results: Seven deaths (11%) occurred at one month among these 61 patients. PVV<23cm^3/L was an independent predictor of one-month mortality in the univariate [odds ratio (OR): 26; 95% confidence interval (CI): 3-244; p=0.004] and multivariate analyses [adjusted OR: 19; 95%CI: 1.3-270; p=0.03]. The classical CTPA parameters were not associated with one-month mortality in this sample. The PVV<23cm^3/L showed a sensitivity of 86%, a specificity of 82%, a negative predictive value of 94% and a positive predictive value of 64% to identify the patients who died.

Conclusion: PVV<23cm^3/L was an independent predictor of one-month mortality after APE. This parameter showed better prognostic performance than other classical CTPA findings. (Arq Bras Cardiol. 2020; 115(5):809-818)

Keywords: Pulmonary Embolism; Tomography Computed; Prognosis; Diagnostic Imaging; Pulmonary Circulation; Emergency Medical Services; Mortality.

Introduction

Acute pulmonary embolism (APE) is a significant cause of dyspnea and chest pain in the emergency department.[1] The prognosis after an event is extremely variable. The majority of patients have an excellent clinical course. However, some patients may have a catastrophic clinical course developing into circulatory shock, cardiac arrest, and death.[2] Due to this heterogeneous clinical presentation, some parameters are used for prognostic stratification to allow more intensive surveillance among patients with a higher probability of complications. Currently, computed tomographic pulmonary angiography (CTPA) is the gold standard among diagnostic methods. Because of this, CTPA parameters are assessed to help in the prognostic stratification and the decision-making regarding the treatment.[3-5]

The most frequent CTPA parameter used for prognostic stratification is the right ventricle enlargement, which is mainly identified through the right ventricle/left ventricle (LV) diameter ratio≥1.[6] The clot load index, manually quantified as described by Qanadli, when higher than 40% aids to identify patients with right ventricular dilation.[7] However, in clinical practice, these isolated parameters have a weak association with mortality and shock development. Because of this, the guidelines recommend that these parameters should not be used alone and only combined with other prognostic markers, such as troponin and N-terminal pro–B type natriuretic peptide (NT-proBNP).[8]

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The objective of this investigation was to assess if fully automatic pulmonary vascular volume quantification using CTPA is a mortality predictor after APE and to compare its prognostic performance with other classical CTPA parameters in predicting the one-month mortality.

Methods

Single-center, retrospective cohort study that included patients with a primary diagnosis of APE admitted to our emergency department. Our hospital is exclusively dedicated to high-complexity emergency, and it has around 3000 medical appointments per month. This study was approved by the Research Ethics Committee of our institution and followed the Declaration of Helsinki.

Patients

Medical records of adult patients (>18 years old) admitted from January 2009 to December 2015 were reviewed. These patients had a primary diagnosis of APE, registered at hospital discharge through the codes I26.0 (pulmonary embolism with acute cor pulmonale) and I26.9 (pulmonary embolism without acute cor pulmonale), according to the International Statistical Classification of Diseases (ICD-10). The definitive diagnosis of APE was defined as the presence of compatible clinical condition associated with at least one criteria, which could be: CTPA with filling defects; or pulmonary ventilation and perfusion scintigraphy with perfusion defects in ventilated areas (high probability); or conventional pulmonary angiography with intraluminal filling defect; or lower-limb ultrasonography compatible with deep vein thrombosis; or necropsy with high thrombotic load in the pulmonary artery without evidence for other alternative diagnoses.

Demographic and clinical data were obtained by reviewing medical records. We used the diagnosis reported by the patient and included in the medical record. The outcome evaluated in this investigation was one-month all-cause mortality. For those patients who were discharged before completing 30 days, a nurse from the clinical research unit of our institution, who was trained to evaluate survival, made a telephone call, and when the occurrence of death was verified, the date of the event was requested.

CTPA technique and interpretation

CTPA was performed using multidetector CT (MDCT) scanners, and volumetric images were obtained after intravenous administration of iodinated contrast using a single bolus injection followed by a flush of saline solution and a bolus detection technique to identify pulmonary artery enhancement. Other typical parameters used were: slice thickness ≤ 2.5 mm, reconstruction interval of 1 mm, kVp of 120, mAs reference of 150-220, gantry rotation of 0.3 to 0.7s. Volumetric acquisitions were reconstructed with soft and hard filters. Two chest radiologists reanalyzed the images after retrieving them using the DICOM (Digital Imaging and Communication in Medicine) format, in calibrated and dedicated workstations. Both radiologists were blind to the clinical evolution of these patients.

We analyzed the classical prognostic parameters of CTPA described in the medical literature. RV/LV axial diameter ratio was obtained by measuring the short axes of the ventricles in the axial plane at their posterior third. An RV/LV diameter cutoff ratio of 1 was used as recommended in the literature. The transverse diameter of the main pulmonary artery (PA) and the transverse diameter of the ascending aorta at the same level were measured. Ventricular septal bowing was considered if there was both septal flattening and septum deviation convex toward the left ventricle. The presence of contrast reflux into the hepatic veins was also assessed. The presence of pulmonary infarction was defined if a pleural-based parenchymal opacity with convex, bulging borders and linear strands directed from the apex towards the hilum was identified. The clot load index was calculated using the method described by Qanadli et al.[7] An index higher than 60% was considered to indicate a high embolic burden.

The quantitative vascular analysis of CTPA imaging was carried out with the academic program Yacta (Heidelberg University, Heidelberg, Germany), version 2.7. The Yacta software works entirely automatically, requiring no user intervention at any stage of the process. Imaging analysis lasts about 10 minutes. Initially, Yacta segments (anatomically separate) the airways, blood vessels, lungs and, their lobes, then supply lung volumes and densities, together with the volume of blood vessels. This software uses an attenuation coefficient of −500 HU as the standard threshold for detection of vessels. In lungs with modified attenuation coefficients, Yacta calculates a new threshold based on the histogram. Intrapulmonary voxels with coefficients above the calculated threshold are then marked as vessels, and vessels with three-dimensional communication larger than 100 mm^3 are considered in the analysis.[9,10] Yacta software estimated the pulmonary volume (PV) in liters (L) and the pulmonary vascular volume (PVV) in cm^3. Since the PVV has a variation according to lung size, we performed an adjustment through the ratio: PVV (cm^3) /PV (L).

Statistical analysis

We used the Shapiro-Wilk test to evaluate the type of variable distribution. Categorical variables were expressed as percentages. Continuous variables with normal distribution were expressed as mean and standard deviation, and the other variables were expressed as median and interquartile range (25^{th} percentile, 75^{th} percentile). The chi-square test was used to compare two categorical variables. The unpaired Student's T-test was used to compare two continuous variables with normal distribution and the Mann-Whitney test to compare two continuous variables with non-normal distribution. In the univariate analysis, the odds ratio (OR) and its respective 95% confidence interval (95%CI) were calculated for each parameter, followed by the chi-square test. For the multivariate analysis, a logistic regression model was used, with adjustment for the variables: age, pulmonary embolism severity index (PESI), respiratory rate, cardiac arrest, and circulatory shock. Spearman's rank test was used to evaluate the correlation between two continuous variables. The area under the receiver operating characteristic (ROC) curve was used to compare the prognostic accuracy of each CTPA parameter. We used

the Youden index to determine the best cutoff point of the adjusted PVV to identify the patients who died. The cutoff point standardized in the medical literature was used for other CTPA parameters. In the survival analysis, the Kaplan-Meier curves were compared through the log-rank test. A p-value <0.05 was considered as statistically significant. The software STATA 13.1 (College Station, TX, USA) was used for the statistical analysis.

Results

Of the 231 individuals with suspected APE assessed in the emergency department, the diagnosis was confirmed in 123 patients (53%). The diagnosis was attained through the CTPA in 99 patients (80%). Considering the patients who underwent CTPA, the imaging was retrieved for reanalysis in 84 of them. Automated pulmonary vascular volume determination using the Yacta software was possible in 61 of these recovered image files. Flow charts of the patients included in this investigation and the reasons that made the Yacta analysis impossible are shown in Figure 1.

The baseline characteristics of these 61 patients are shown in table 1. Of these patients, 07 (11%) died in one month. When comparing non-survivors (n=7) with survivors (n=54), there were no significant differences between these two groups, except a higher respiratory rate in the non-survivors' group (31±7 cycles/min vs. 33±7 cycles/min, p=0.01).

Regarding the CTPA parameters analysis, the pulmonary vascular volume (PVV) and the adjusted PVV were significantly decreased in the non-survivors group in comparison to the survivor's group (56±24 cm^3 vs. 88±32 cm^3, p=0.015 and 21±6 cm^3/L vs. 30±7 cm^3/L, p=0.001, respectively). The other parameters evaluated by the CTPA (clot load index, RV/LV axial diameter ratio, PA/Aorta diameter ratio, ventricular septal bowing, pulmonary infarction, and contrast reflux into the hepatic vein) did not differ significantly between these two groups (Table 2).

The analysis using the area under the ROC curve (AUC), the 1/adjusted PVV showed the best prognostic accuracy performance with an AUC of 0.86 (95%CI: 0.68-1.00) compared to the other continuous variables [RV/LV diameter ratio with AUC of 0.56 (95%CI: 0.37-0.75), the PA/Aorta diameter with AUC of 0.55 (95%CI: 0.35-0.75) and the clot load index with AUC of 0.44 (95%CI: 0.16-0.74)], p<0.01(Figure 2).

The best cutoff point of the adjusted PVV to determine the one-month mortality was 23 cm^3/L [sensitivity: 86%(95%CI: 42-99), specificity: 82%(95%CI: 69-91), positive predictive value: 64%(95%CI: 49-77) and negative predictive value: 94%(95%CI: 70-99)].

In the univariate analysis, the adjusted PVV<23 cm^3/L [odds ratio (OR): 26 (95%CI: 3-244), p=0.004] and the respiratory rate [OR: 1.1(95%CI: 1.01-1.26), p=0.03] were the one-month mortality predictors. In the multivariate analysis, only the PVV<23 cm^3/L remained as an independent predictor of one-month mortality [adjusted OR: 19 (95%CI: 1.3-270), p=0.03]. The classical prognostic CTPA parameters were not associated with one-month mortality (Table 3).

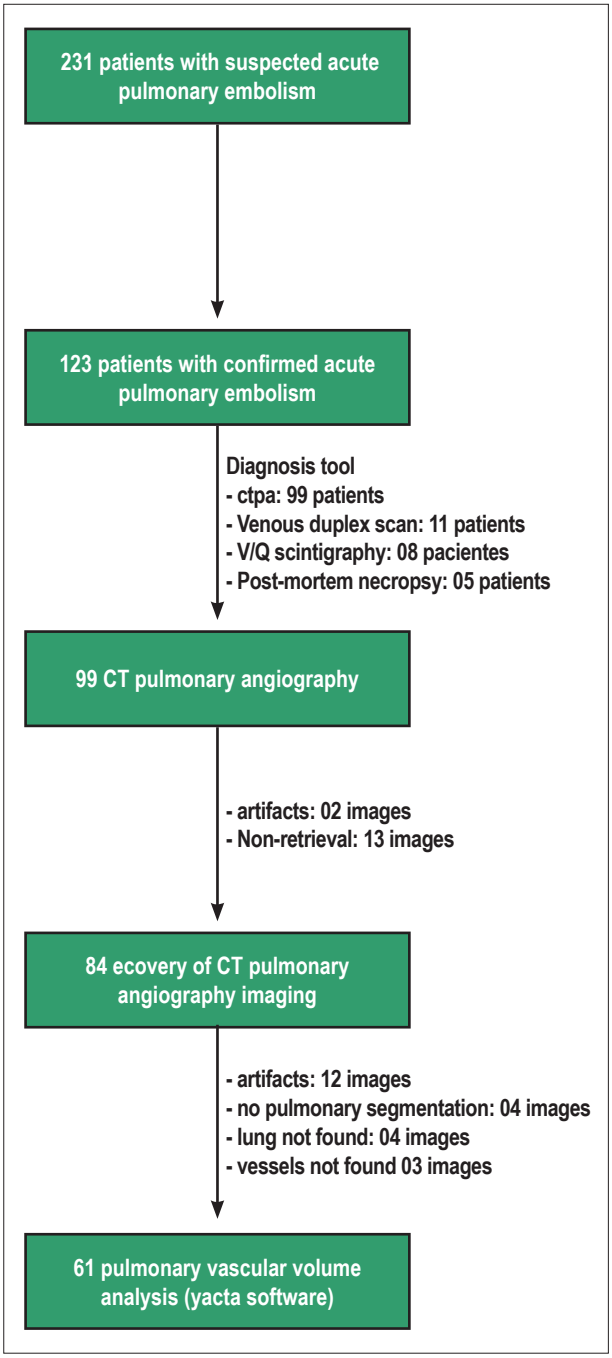

Figure 1 - *Flow chart showing the criteria selection for the patients included in this investigation.*

In the survival analysis, the PVV<23 cm^3/L was significantly associated with a higher mortality ratio [hazard ratio (HR): 21 (95%CI:2-193), p=0.0001] during the one-month follow-up(Figure 3).

The clot load index manually quantified according to the Qanadli description and the adjusted PVV quantified automatically through the Yacta software did not show a significant correlation [Rho=-0.22, p=0.09] (Figure 4).

Table 1 – Baseline characteristics of the patients divided according to the one-month mortality

Parameter	Survivors n=54	Non-Survivors n=7	p
Demographic data			
Age, years (mean±sd)	54±16	61±17	0.34
Age>65years-old, n.(%)	19(35)	3(43)	0.69
Gender male, n.(%)	24(44)	2(29)	0.42
Clinical presentation			
Cardiac arrest, n.(%)	2(04)	1(14)	0.22
Circulatory shock, n.(%)	5(09)	2(28)	0.13
Dyspnea, n.(%)	46(85)	7(100)	0.27
Hemoptysis, n.(%)	7(13)	0(00)	0.31
Syncope, n.(%)	13(24)	0(00)	0.14
Cough, n.(%)	20(37)	3(43)	0.76
Pleuritic chest pain, n.(%)	17(31)	4(57)	0.18
Fever, n.(%)	7(13)	2(28)	0.27
Wells score, (median, 25^{th}-75^{th})	4.5 (3.0-7.0)	4.0 (1.5-4.5)	0.17
PESI score, (median, 25^{th}-75^{th})	78 (65-108)	97 (95-108)	0.13
Symptom duration, days (median, 25^{th}-75^{th})	3(1-6)	2(1-6)	0.29
Predisposing factors			
Previous PE/DVT, n.(%)	11(20)	0(00)	0.19
Active cancer, n.(%)	4(07)	2(28)	0.07
Recent surgery, n.(%)	7(13)	0(00)	0.31
Immobilization, n.(%)	13(24)	1(14)	0.56
Fracture, n.(%)	7(13)	0(00)	0.31
Previous stroke, n.(%)	7(13)	1(14)	0.92
Contraceptive use, n.(%)	7(13)	0(00)	0.31
Obesity, n.(%)	23(43)	3(43)	0.91
Heart failure, n.(%)	7(13)	0(00)	0.31
COPD, n.(%)	4(07)	1(14)	0.53
Thrombophilia, n.(%)	5(09)	1(14)	0.67
Physical examination			
Heart rate; bpm, (mean±sd)	94±16	106±23	0.07
Respiratory rate, cycles/min (mean±sd)	23±7	31±7	0.01
Respiratory rate > 20 cycles/min, n.(%)	36(67)	6(86)	0.12
SBP, mmHg (mean±sd)	123±28	113±14	0.37
DBP, mmHg (mean±sd)	75±14	69±19	0.32
Laboratory tests			
Creatinine, mg/dL (mean±sd)	1.08±0.27	1.16±0.83	0.59
Hemoglobin, g/dL (mean±sd)	13±2	12±3	0.05
Oxygen Saturation, % (mean±sd)	92±7	87±8	0.09
Troponin I, µg/L (mean±sd)	0.16±0.29	0.13±0.12	0.79
NT-proBNP, µg/L(mean±sd)	2604±3040	3433±2343	0.60
Treatment			
Thrombolytic, n.(%)	14(26)	2(29)	0.88
Unfractionated heparin, n.(%)	7(13)	1(14)	0.81
Low molecular weight heparin, n.(%)	38(70)	6(86)	0.12

PESI: pulmonary embolism severity index; PE: pulmonary embolism; DVT: deep vein thrombosis, COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure, NT-proBNP: N-terminal type B natriuretic peptide.

Table 2 – Computed tomography pulmonary angiography (CTPA) findings divided according to the one-month survival rate

Parameter	Survivors n=54	Non-survivors n=7	p
Yacta parameters			
Pulmonary volume (L), mean±sd	2.91±0.90	2.73±1.31	0.64
Pulmonary vascular volume (cm^3), mean±sd	88±32	56±24	0.01
Adjusted pulmonary vascular volume (cm^3/L), mean±sd	30±7	21±6	0.001
Classical CTPA parameters			
Clot load index (%), mean±sd	47±21	40±26	0.40
Central clot, n. (%)	5 (09)	2(28)	0.13
Bilateral clot, n. (%)	45(83)	5(72)	0.59
Unilateral clot, n. (%)	4(08)	0(00)	1.00
RV/LV axial diameter ratio, mean±sd	1.20±0.36	1.25±0.28	0.74
RV/LV axial diameter ratio>1, n.(%)	36(67)	6(86)	0.30
PA/Aorta diameter ratio, mean±sd	0.91±0.17	0.91±0.90	0.92
Ventricular septal bowing (VSB), n. (%)	32(59)	5(71)	0.53
Pulmonary infarction, n. (%)	25(46)	2(29)	0.37
Reflux of contrast into the hepatic vein, n. (%)	20(37)	3(43)	0.76

RV: right ventricle; LV: left ventricle; PA: pulmonary artery

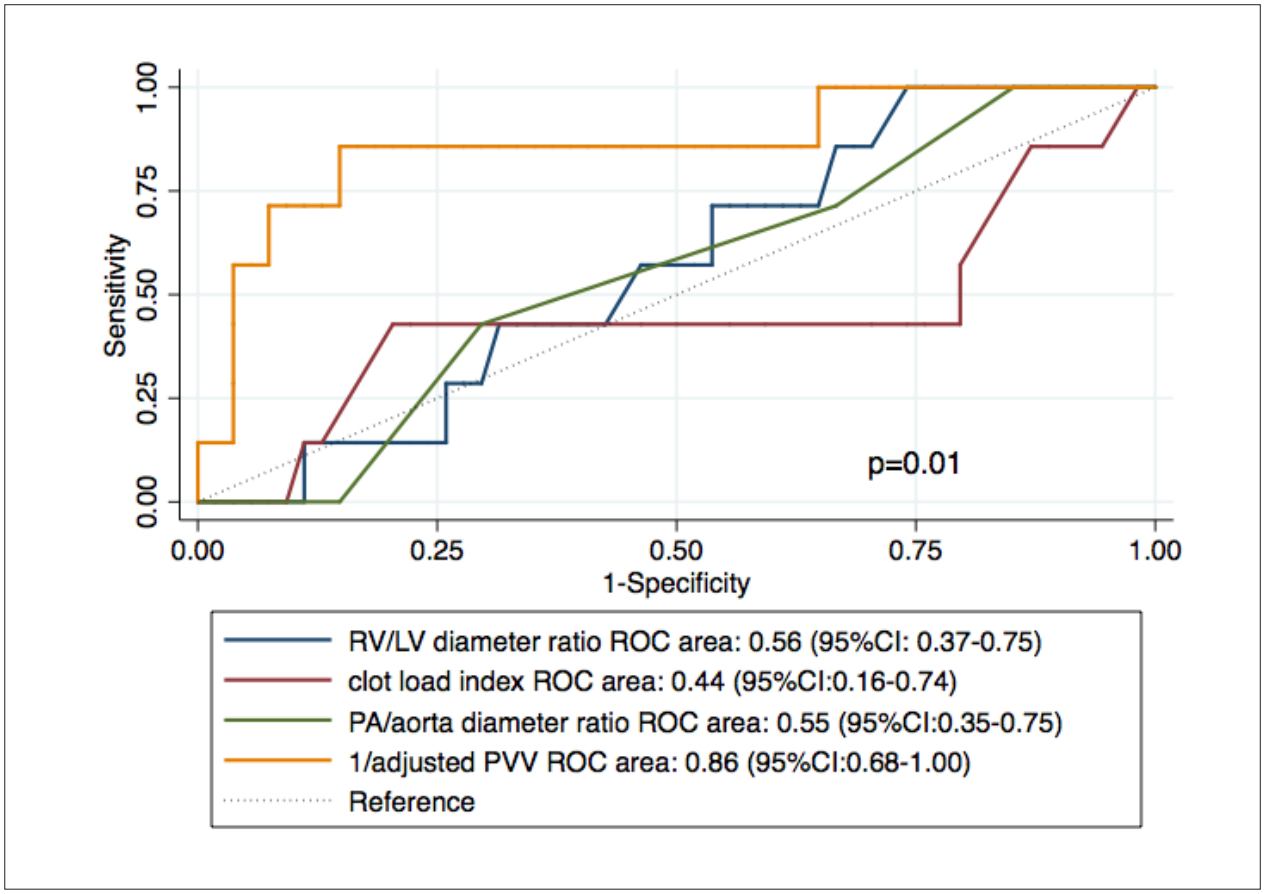

Figure 2 – *ROC-curves showing the prognostic performance of the continuous CTPA parameters (clot load index, RV/LV diameter ratio, PA/Aorta diameter ratio) compared to the adjusted PVV in predicting one-month mortality after APE. CTPA: computed tomographic pulmonary angiography; RV: right ventricle; LV: left ventricle; PA: pulmonary artery; PVV: pulmonary vascular volume; APE: acute pulmonary embolism.*

Table 3 – Predictors of one-month mortality after APE in the univariate and multivariate analysis

Parameters	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Demographic/ clinical data						
Age	1.0	0.97- 1.0	0.34			
Gender	0.5	0.09-2.8	0.43			
Active cancer	5.0	0.73-34.5	0.10			
Circulatory shock	3.9	0.60-25.7	0.15			
Cardiac arrest	4.3	0.34-55.2	0.26			
Heart rate	1.0	0.99-1.1	0.09			
Respiratory rate	1.1	1.01-1.26	0.03	1.56	0.95-2.57	0.08
PESI score	1.0	0.99-1.00	0.12			
Imaging						
Adjusted pulmonary vascular volume ≤ 23 cm^3/L	26.0	3.0-244	0.004	19.0	1.3-279.0	0.03
Clot load index	0.9	0.95-1.0	0.44			
Clot load index ≥ 40%	0.5	0.0-2.3	0.36			
Clot load index ≥ 60%	2.6	0.5-13.4	0.24			
RV/LV diameter ratio	1.5	0.2-12.6	0.73			
RV/LV diameter ratio ≥1	3.0	0.3-26.8	0.32			
Ventricular septal bowing	1.7	0.3-9.6	0.53			
Pulmonary infarction	0.5	0.8-2.6	0.38			
Reflux of contrast into the hepatic vein	1.3	0.2-6.3	0.76			

OR: odds ratio; CI: confidence interval; PESI: pulmonary embolism severity index; RV: right ventricle; LV: left ventricle.

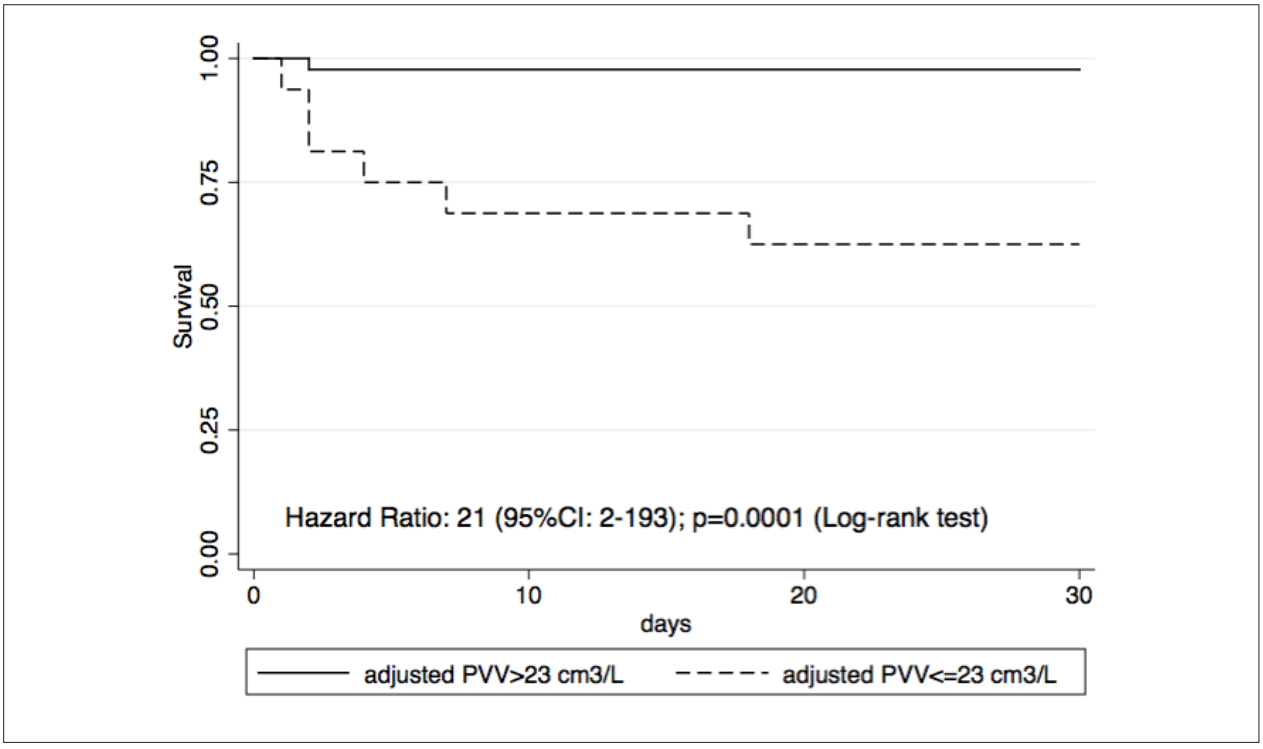

Figure 3 – *Kaplan-Meier curves comparing the one-month survival between the patients with adjusted pulmonary vascular volume (PVV) lower and higher than 23 cm^3/L.*

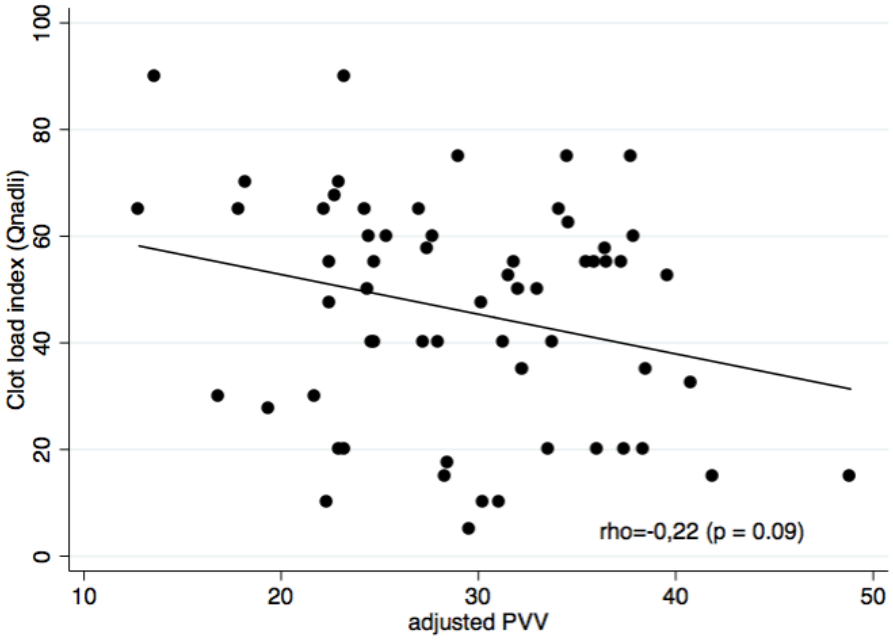

Figure 4 – *Scatter plot showing the association between the adjusted pulmonary vascular volume (PVV) quantified through the Yacta software and the clot load index manually quantified according to Qanadli.*

Figure 5 depicts the CTPA and the pulmonary vessel quantification imaging (Yacta software) examples in two patients with different clinical outcomes included in this investigation.

Discussion

Currently, CTPA is the most often used tool for APE diagnosis in the emergency department.[5,11] The development of parameters using CTPA to stratify the risk of complications in these patients is desirable and could help to individualize the treatment according to the severity of each presentation. [4,12] Our investigation showed that a fully automatic quantification of adjusted PVV in patients with APE was an independent predictor of one-month mortality. The prognostic performance of this new tool was superior to the classical prognostic CTPA parameters evaluated in this setting, such as the RV/LV diameter ratio and clot load index.

The high rate of positive CTPA for APE (53%) in this investigation can be explained because the selection of patients was performed through the ICD code during the hospital discharge and, probably, in the majority of patients in whom the PE diagnosis was excluded through negative CTPA; the ICD of acute pulmonary embolism was not included during the discharge, and these patients were not identified.

The RV/LV diameter ratio is a parameter that indirectly evaluates right ventricular dilation and RV dysfunction observed during the APE.[13] Among the parameters obtained by the CTPA, the RV/LV diameter ratio is the most frequently evaluated in the scientific literature; despite this fact, there is lack of standardization regarding the technical aspects of its measurement and disagreements about the most appropriate cutoff point. Most of the studies used an RV/LV diameter ratio ≥ 1 as abnormal.

Isolated studies have not demonstrated the usefulness of RV/LV diameter ratio ≥1 in the prognostic stratification after APE. Coutance et al.[6] analyzing the CTPA of 383 patients with this diagnosis, showed that the RV/LV diameter ratio ≥1 was not associated with mortality [OR: 1.54; 95%CI: 0.70-3.40], had a low sensitivity [46%; 95%CI: 27-66], a low specificity [59%; 95%CI: 54-64%] and low positive predictive value [08%; 95%CI: 5.0-14.0] in predicting the one-month mortality.[6]

Moroni et al.[14] when analyzing 225 CTPA of patients with non-severe APE, observed that the RV/ LV diameter ratio > 1 was only a predictor of mortality when associated with low embolic burden (<40%), but in the multivariate analysis, the RV/LV diameter ratio > 1 and the shape of interventricular septum were not associated with death.[14]

Kumamaru et al.[15] retrospectively analyzed 1698 CTPAs in patients with APE. The traditionally evaluated parameters were also not associated with all-cause mortality at one month. The parameters assessed were: the location of the most proximal embolus (p=0.14), parenchymal infarction (p=0.90), RV> LV diameter (p= 0.69), contrast reflux to the hepatic vein (p=0.40), bowing of the septum (p=0.40), and PA/Aorta diameter (p=0.93). On the other hand, nontraditional findings were predictors of mortality, such as pleural and pericardial effusion; lung, liver and bone lesion suggesting malignancy, ascites, etc. [15] These findings are probably much more related

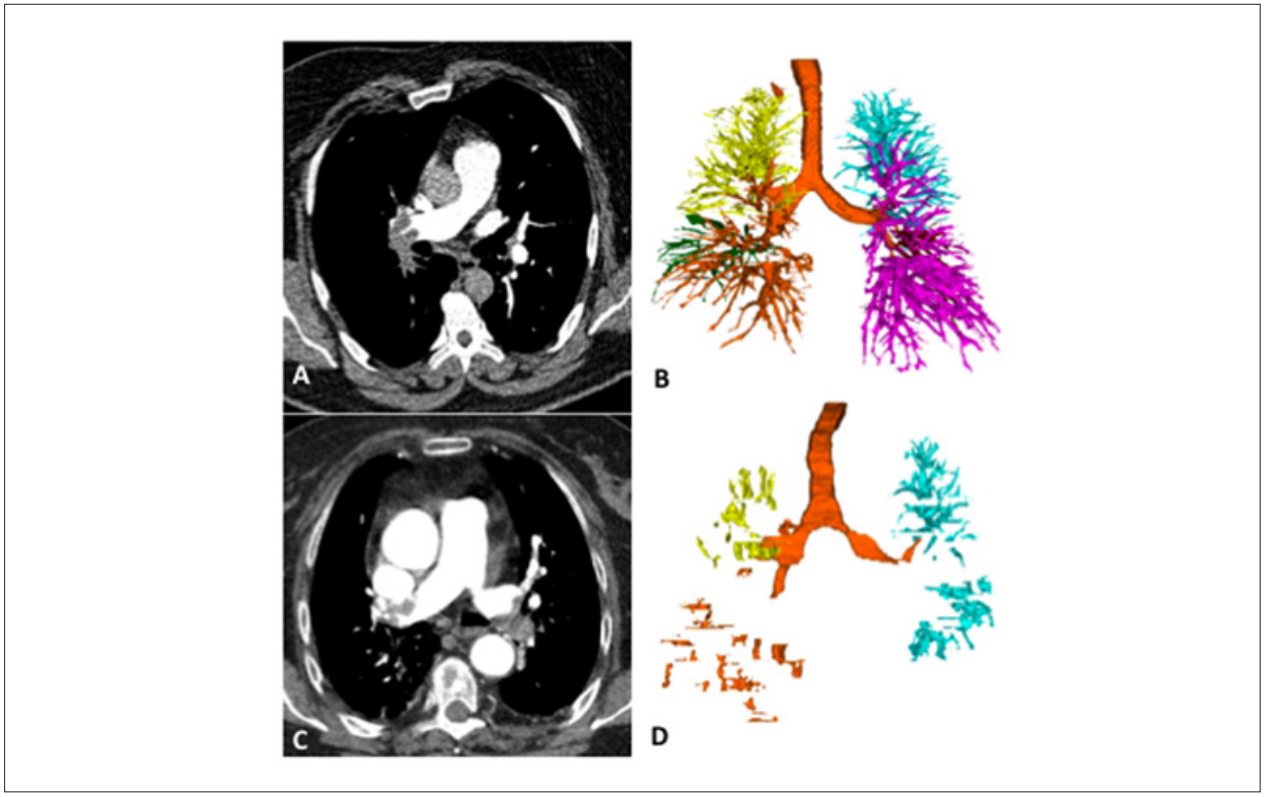

Figure 5 – *Examples of fully automated pulmonary vascular quantification using the Yacta software in two different patients with acute pulmonary embolism (APE). The first patient (survivor), man, 47 years old, was diagnosed with APE in the right lung (CTPA image in A) and after vascular segmentation and analysis (B) showed a pulmonary vascular volume (PVV) of 157 cm³ and an adjusted PVV of 33.7 cm³/L. The second patient (non-survivor), woman, 75 years old, had a bilateral APE (CTPA image in D) and after lung (E) and vascular segmentation (F) showed a pulmonary vascular volume (PVV) of 19 cm³ and an adjusted PVV of 12.8 cm³/L.*

to the prognosis of associated diseases such as cancer than the APE itself. An investigation by van der Meer *et al*. also showed no association between the PA/Aorta diameter ratio (p=0.66) and the presence of ventricular septal bowing (p=0.20) with mortality.[16]

A recent meta-analysis involving a large number of patients was able to demonstrate the prognostic association of the RV/LV ratio after APE. When comparing 2612 patients with abnormal RV/LV diameter ratio with 2049 patients who had this parameter within the regular range, the increased RV/LV ratio showed to be associated with the one-month mortality in the analysis that included all patients [OR: 2.08; 95%CI: 1.63-2.66; p <0.00001], and which included only patients with hemodynamic stability [OR: 1.64; 95%CI: 1.06-2.52; p=0.03].[17] In our investigation, the adjusted PVV<23 cm³/L showed a better prognostic performance than the RV/LV diameter ratio.

The pulmonary artery obstruction scores or clot load index obtained through CTPA were initially described by Qanadli et al.[7] in 2001. In this initial study, they compared CTPA findings with invasive pulmonary angiography and showed good agreement between the methods (r = 0.867, p <0.0001) for the quantification of the obstruction degree. A clot load index ≥ 40% identified more than 90% of patients with RV dilation.[7]

In early studies, such as the ones by Wu et al.[18] and van der Meer et al.[16] the quantification of the pulmonary artery embolic obstruction was associated with mortality.[18,16] However, subsequent studies failed to demonstrate an association of these pulmonary artery obstruction scores with important clinical outcomes, such as mortality. Kong et al.[19] analyzed these obstruction scores together with the presence of pulmonary perfusion defects in the CTPA of 55 patients stratified through clinical and laboratory tests as high, intermediate, and low-risk. The obstruction scores failed to differentiate these three groups adequately, and the quantification of perfusion defects showed a better performance to make this discrimination.[19] Atasoy et al.[20] when analyzing the CTPA of 67 patients, observed that a clot load index ≥ 40% was not associated with mortality [OR: 0.989; 95%CI: 0.95-1.03; p = 0.486].[20] Araoz et al.[21] evaluated 1193 CTPAs positive for APE, and observed that neither the thrombotic burden nor the RV/LV diameter ratio was associated with mortality, and only ventricular septal bowing was associated with mortality [OR: 1.97, p=0.05], albeit with very low sensitivity (18-21%).[21]

Even in patients with severe APE admitted to the intensive care unit, the clot load in the pulmonary artery using four different scoring systems was not associated with the mortality rate during the hospital stay.[22]

In our investigation, the clot load index was also not a predictor of one-month mortality, although they are interrelated variables; the adjusted PVV was an independent

predictor of one-month mortality in these patients with APE. This fact could be explained by the technical troubles in the manual quantification of the clot load, which is mainly restricted to the evaluation of the larger-caliber vessels. The Yacta software allowed a better evaluation of the small-caliber vessel obstruction, and it could more adequately reflect the prognosis after APE.

Some limitations of our study deserve to be considered. First, the Yacta software was not able to adequately measure pulmonary vascular volumes in 27% of patients, mainly due to the presence of artifacts. However, software improvements and enhancements in imaging acquisition may reduce this failure. The use of ECG-gated CTPA can improve the imaging quality and allow better performance of this software. Second, this investigation had a small sample size, and maybe it was underpowered to evaluate the predictive effect of the classical CTPA parameters, such as the RV/LV diameter ratio. However, even in this small sample size, the adjusted PVV was a strong predictor of mortality, leading to a possible understanding that this parameter had a better prognostic performance. Third, there was a statistical tendency in the correlation between the manually quantified clot load index and the adjusted PVV; the small sample size could explain this lack of significant correlation. Fourth, this new parameter needs to be evaluated in other multicenter and prospective studies. Fifth, in this investigation, only the CTPA parameters were analyzed, and the inclusion of these imaging findings in the APE management algorithm associated with other instruments, such as the pulmonary embolism severity index (PESI) and biomarkers such as troponin or NT-proBNP need to be further evaluated.[23,24] Sixth, vessel detection by the program is based not only on attenuation values but also on the three-dimensional analysis of vascular anatomy; the presence of pulmonary opacities does not preclude the correct analysis of the vascular volume. The Yacta segmentation algorithm is very robust and effective because it uses different tools to identify the lungs, airways, and vessels. What can alter the pulmonary vasculature is the presence of airway disease and emphysema, which can lead to hypoxic vasoconstriction or vascular destruction, and can be confounded with thrombosis/embolism. Despite this fact, our investigation had a low prevalence of patients with COPD. Finally, all-cause mortality was the evaluated outcome, although not necessarily secondary to APE; however, in the majority of the studies that evaluated these CTPA parameters, only all-cause mortality was assessed.

Conclusion

Adjusted PVV, estimated using the Yacta software, seems to be a promising tool for the prognostic stratification after APE, mainly when compared to other classical prognostic CTPA parameters.

Author contributions

Conception and design of the research and Statistical analysis: Miranda CH; Acquisition of data: Soriano L, Vilalva K, Castro TT, Wada DT; Analysis and interpretation of the data and Writing of the manuscript: Santos MK, Miranda CH; Critical revision of the manuscript for intellectual content: Santos MK, Weinheimer O, Muglia V, Pazin Filho A, Miranda CH.

Potential Conflict of Interest

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

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Ventricular Repolarization as a Tool to Monitor Electrical Activity of the Heart

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Short Editorial related to the article: Pulmonary vascular volume estimated by automated software is a mortality predictor after acute pulmonary embolism

Acute pulmonary embolism has a heterogeneous clinical presentation and the development of clinical tools for better stratification of the patients prognosis is extremely desired. Being able to discern which patient is most likely to have complications or even death is critical in the age of precision medicine. This may assist in choosing a more intensive and individualized treatment.[1]

Computed tomography pulmonary angiography (CTPA) is already the most used method in emergencies for the diagnosis and stratification of patients with APE. The great variability of clinical presentations, whether in patients with cancer or different thrombogenic conditions, makes some quantitative data more attractive than just the qualitative analysis of the exam.[2-5]

Thus, the work of Soriano et al.[6] which develops a fully automated data analysis algorithm capable of extrapolating parameters that differentiate individuals most likely to die in a short period of time, is of great value.[6]

The main result is the adjusted pulmonary vascular volume (aPVV) was significantly decreased in the non-survivors group in comparison to the survivor's group (21 ± 6 cm^3/L vs. 30 ± 7 cm^3/L, $p=0.001$).[6] And the best cutoff point of the aPVV to determine the one-month mortality was 23 cm^3/L.[6]

At this stage, I would like to raise specific points that are fundamental for a good reading and understanding of the direction that this work provides us.

The sample size was probably not enough to have power to conclude that this method can be extrapolated to other populations, but it serves to advance a possible trend and encourage new studies. As discussed by the group, most of the studies already published recruited a much larger number of participants such as Coutance et al.[7] with 383 patients with APE, Moroni at al.[8] with 225 CTPA with non severe APE and Kamamaru et al.[9] with 1698 CTPA from APE patients.

There is a clear selection bias because the pulmonary embolism (I26) code was not used as selection criteria in the hospital database record using the International Statistical Classification of Diseases (ICD-10). In this study, we have only the codes referring to pulmonary embolism with acute cor pulmonale (I26.0) and pulmonary embolism without acute cor pulmonale (I26.9).

Also, from 84 retrieved CTPA studies, just 61 (73%) were possible to be automated analyzed by the Yacta software. Generally, patients with more severe cases, greater dyspnea and hemodynamic instability will be those who will have datasets with more artifacts, making it difficult for the Yacta's algorithm.

Another point that I still doubt is the use of this method for different types of computed tomography scanners. Therefore, I am pleased to see the development achieved, but I still see many questions to be answered in a prospective and multicentric trial, with multivendor CT scanners.

Finally, I hope that the use of artificial intelligence adjusting to a database should be able to improve the software efficiency reducing the cases that are currently excluded. I also believe that this database may be used to categorize the findings. Let more studies come!!!

Keywords

Acute, Pulmonary Embolism/complications; Prognosis; Precision Medicine; Compute Tomography/methods; Algorithms; Software; Artificial Intelligence/trends

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Original Article

Maximal Oxygen Uptake and Ventilation Improvement Following Sacubitril-Valsartan Therapy

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Abstract

Background: **Sacubitril/valsartan had its prognosis benefit confirmed in the PARADIGM-HF trial. However, data on cardiopulmonary exercise testing (CPET) changes with sacubitril-valsartan therapy are scarce.**

Objective: **This study aimed to compare CPET parameters before and after sacubitril-valsartan therapy.**

Methods: **Prospective evaluation of chronic heart failure (HF) patients with left ventricular ejection fraction ≤40% despite optimized standard of care therapy, who started sacubitril-valsartan therapy, expecting no additional HF treatment. CPET data were gathered in the week before and 6 months after sacubitril-valsartan therapy. Statistical differences with a p-value <0.05 were considered significant.**

Results: **Out of 42 patients, 35 (83.3%) completed the 6-month follow-up, since 2 (4.8%) patients died and 5 (11.9%) discontinued treatment for adverse events. Mean age was 58.6±11.1 years. New York Heart Association class improved in 26 (74.3%) patients. Maximal oxygen uptake (VO_2max) (14.4 vs. 18.3 ml/kg/min, p<0.001), VE/VCO_2 slope (36.7 vs. 31.1, p<0.001), and exercise duration (487.8 vs. 640.3 sec, p<0.001) also improved with sacubitril-valsartan. Benefit was maintained even with the 24/26 mg dose (13.5 vs. 19.2 ml/kg/min, p=0.018) of sacubitril-valsartan, as long as this was the highest tolerated dose.**

Conclusions: **Sacubitril-valsartan therapy is associated with marked CPET improvement in VO_2max, VE/VCO_2 slope, and exercise duration. (Arq Bras Cardiol. 2020; 115(5):821-827)**

Keywords: **Heart Failure; Oxygen Consumption; Stroke Volume; Pulmonary Ventilation; Sacubitril-Valsartan; Hypertension; Antihypertensive Agents**

Introduction

The prognosis of heart failure (HF) patients remarkably changed following the publication of cornerstone trials (1987 – CONSENSUS,[1] 1999 – CIBIS-II,[2] and RALES[3]), which demonstrated the benefit of using neurohormonal antagonists [angiotensin-converting enzyme inhibitors (ACEI), beta-blockers (BB), and mineralocorticoid receptor antagonist (MRA), respectively] to improve patient survival and reduce ejection fraction.

Twenty-seven years after the CONSENSUS trial, the PARADIGM-HF trial showed that sacubitril-valsartan, a combination of neprilysin inhibitor and angiotensin II receptor blocker (ARB), could reduce both HF hospitalization and cardiovascular mortality in 20% in comparison with Enalapril.[4]

As a result, sacubitril-valsartan has a Class I recommendation, level of evidence B, as a replacement for ACEI to ambulatory patients with HF with reduced ejection fraction (HFrEF) who remain symptomatic despite optimal treatment with ACEI (or ARB if ACEI is not tolerated), BB, and MRA.[5] However, the use of sacubitril-valsartan has not been as high as expected.[6]

The treatment goals for HF patients are not only to prevent hospital admission and reduce mortality but also to improve their clinical status and functional capacity. Cardiopulmonary exercise testing (CPET) is a powerful predictor of mortality in HF patients. It is considered the standard criterion for evaluating the need for elective heart transplantation,[7] with maximal O_2 uptake (VO_2max) and the relationship between ventilation and CO_2 production (VE/VCO_2 slope) as the most adopted risk assessment tools.[8]

Information has been increasing recently, as some trials demonstrated a significant symptomatic and functional improvement following the initiation of sacubitril-valsartan therapy.[9-12] Nonetheless, its impact on functional capacity needs additional research since most trials had retrospective designs, and, to the best of our knowledge, only one prospective study shows CPET parameter changes after sacubitril-valsartan therapy.[13]

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This study aimed to prospectively analyze the effectiveness of sacubitril-valsartan therapy in a cohort of chronic HF patients with optimized standard of care therapy by comparing CPET data before and after treatment.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee and the National Commission for Data Protection (*Comissão Nacional de Proteção de Dados* – CNPD, authorization number 5962) approved the study protocol.

All patients provided written informed consent.

Patient population

The study included a prospective single-center analysis from October 2017 to June 2018.

During this period, all ambulatory patients with optimized standard of care therapy for chronic HF, left ventricular ejection fraction ≤40%, and New York Heart Association (NYHA) class ≥ II were advised to start sacubitril-valsartan therapy according to the current guidelines.[5]

Definition of chronic HF with optimized standard of care therapy

Optimized standard of care therapy for chronic HF was defined as more than six months of treatment with the maximum tolerated dose of an ACEI or ARB, as appropriate, a BB, and an MRA. Implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) can be used if indicated by the current guidelines and if the subject has been adequately treated per applicable standards for coronary artery disease and mitral regurgitation (MR)[5] and no additional HF treatment was expected to change in the next 6 months. Patients who started an exercise program in the three months previous to or during sacubitril-valsartan therapy were excluded.

Study protocol

All patients provided written informed consent. Thereafter, clinical, laboratory, transthoracic echocardiography (TTE), and CPET data were obtained in the week before starting sacubitril-valsartan therapy.

A washout period of 36 hours allowed switching from an ACEI to sacubitril-valsartan. Sacubitril-valsartan therapy was preferentially started at 49/51 mg twice daily or 24/26 mg twice daily in patients with a dose <10 mg/day of Enalapril or equivalent. Attempts to double the dose were made every 2 to 4 weeks to reach the target maintenance dose of 97/103 mg twice daily, except in patients with systolic blood pressure <100 mmHg, symptomatic hypotension, hyperkalemia > 5.5 mEq/L, or a decrease in glomerular filtration rate (GFR) to less than 60 ml/min, as assessed by the Cockcroft-Gault equation.

All patients were followed for six months from the test completion date, and clinical, laboratory, TTE, and CPET data were collected again after six months of sacubitril-valsartan therapy.

The supplementary appendix provides information regarding all data collected.

Cardiopulmonary exercise testing

A maximal symptom-limited treadmill CPET was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). Gas analysis was preceded by calibration of the equipment. Minute ventilation, oxygen uptake, and carbon dioxide production were acquired breath-by-breath, using a SensorMedics Vmax 229 gas analyzer. The VO_2max was defined as the highest 30-second average achieved during exercise and was normalized for body mass index.[14] Anaerobic threshold (AT) was determined by combining the standard methods (V-slope preferentially and ventilatory equivalents). VE/VCO_2 slope was calculated by least-squares linear regression, based on data acquired throughout the whole exercise. Patients were encouraged to perform the exercise until the respiratory exchange ratio (RER) was ≥1.10.

Statistical analysis

Baseline characteristics are expressed as frequencies (percentages) for categorical variables and as means and standard deviations for continuous variables. All analyses compare patients' parameters at baseline and after six months of sacubitril-valsartan therapy.

Normal distribution of continuous variables was verified by the Kolmogorov-Smirnov test. Paired samples *t*-test compared the variables before and after sacubitril-valsartan therapy. Statistical differences with a p-value <0.05 were considered significant. Data were analyzed in the software Statistical Package for the Social Science for Windows, version 24.0 (SPSS Inc, Chicago, IL).

Results

Overview of the study population

A total of 42 patients were enrolled in the study. Out of them, 35 (83.3%) completed the six-month follow-up with sacubitril-valsartan, since 2 (4.8%) patients died (1 with intracranial hemorrhage after trauma and 1 with sudden cardiac death) and 5 (11.9%) patients discontinued treatment due to adverse events (2 with reversible acute kidney injury and 3 with symptomatic hypotension with the lowest sacubitril-valsartan dose). No patient was lost to follow-up during the six months.

Table 1 presents the baseline characteristics of the 35 patients who completed the six-month follow-up with sacubitril-valsartan. Mean age was 58.6±11.1 years, with 29 (82.9%) male patients and ischemic etiology in 15 (42.9%) participants.

These patients were highly symptomatic, as revealed by an NYHA class ≥ III in 51.4% of them and by 42.9% of hospitalizations for worsening HF in the year prior to sacubitril-valsartan therapy. All patients were on ACEI or ARB associated with a BB, and 94.3% were taking an MRA. ICD was already implanted in 30 (85.6%) patients, out of which 7 (20.0%) had a CRT-D system. Three (8.6%) patients had formerly undergone percutaneous mitral valve repair using a MitraClip® system.

Sacubitril-valsartan dose

Sacubitril-valsartan therapy was started at 24/26 mg twice daily in 18 (51.4%) patients and 49/51 mg twice daily in 17

Table 1 – Baseline characteristics of the study population (n=35)

Characteristics	n (%)
Mean age (years)	58.60 ± 11.14
Ischemic etiology	15 (42.9%)
Male gender	29 (82.9%)
NYHA ≥ III	18 (51.4%)
Mean body mass index (kg/m^2)	28.09 ± 3.77
Heart failure hospitalization in the previous year	15 (42.9%)
Mean BNP (pg/ml)	375.30 ± 342.19
Current smoker	7 (20.0%)
Previous hypertension	25 (71.4%)
Dyslipidemia	25 (71.4%)
Diabetes mellitus	11 (31.4%)
Peripheral arterial disease	4 (11.4%)
Family history of heart failure	1 (2.9%)
Atrial fibrillation	14 (40%)
Chronic kidney disease	2 (5.7%)
Chronic liver disease	0 (0.0%)
Angiotensin-converting enzyme inhibitors	29 (82.9%)
Angiotensin II receptor blocker	6 (17.1%)
Beta-blockers	35 (100.0%)
Mineralocorticoid receptor antagonist	33 (94.3%)
Ivabradine	13 (37.1%)
Digoxin	9 (25.7%)
Implantable cardioverter-defibrillator	30 (85.6%)
Cardiac resynchronization therapy (CRT-D)	7 (20%)
Percutaneous mitral valve repair using MitraClip®	3 (8.6%)

NYHA: New York Heart Association; BNP: B-type natriuretic peptide.

(48.6%) patients. At six months, a dose of 24/26 mg twice daily was administered to 10 (28.6%) patients, 49/51 mg twice daily to 11 (31.4%), and 97/103 mg twice daily to 14 (40.0%).

We found no significant changes regarding the dose expressed as a percentage of the target dose of BB (68.8 ± 28.6% vs. 70.6 ± 28.0%, p=0.278) and MRA (51.6 ± 19.0% vs. 53.2 ± 24.4%, p=0.352) or the loop diuretic dose expressed as furosemide equivalents (43.6 ± 27.6% vs. 39.1 ± 26.5%, p=0.191) at baseline and after six months of sacubitril-valsartan therapy.

Clinical assessment

The 35 patients who completed six months of sacubitril-valsartan treatment showed a relevant improvement in NYHA class, since only 9 (25.7%) patients remained in the same class, while 24 (68.6%) improved one NYHA class and 2 (5.7%) improved two classes. No patient had a worsening in their NYHA class during the six months of sacubitril-valsartan therapy, and only 3 (8.6%) remained in class III.

Transthoracic echocardiography assessment

Table 2 presents the results of the TTE analysis. Left ventricular (LV) dimensions and atrial volumes were significantly lower at six months of treatment. Tricuspid annular plane systolic excursion showed no significant differences, regardless of the presence of a decrease in pulmonary artery systolic pressure at 6 months of therapy. Left ventricular ejection fraction had a mean absolute raise of 5.9%.

CPET analysis

Sacubitril-valsartan therapy showed a remarkable impact on functional capacity (Table 3). The VO_2max, predicted VO_2max, VE/VCO_2 slope, and duration of exercise presented an important improvement after therapy, without a significant difference in exercise effort, as assessed by the exchange ratio. We found no significant differences regarding heart rate (HR) and blood pressure parameters.

Table 4 provides CPET parameters by sacubitril-valsartan dose. Patients on 24/26 mg and 49/51 mg doses at 6 months of sacubitril-valsartan therapy had the highest increase in VO_2max and VE/VCO_2 slope values.

Both ischemic (16.9 ± 7.1 ml/kg/min vs. 20.2 ± 4.2 ml/kg/min, p=0.014) and non-ischemic (12.6 ± 4.6 ml/kg/min vs. 17.0 ± 5.1 ml/kg/min, p=0.004) HF patients showed VO_2max improvement at 6 months of sacubitril-valsartan therapy.

Discussion

CPET is a powerful predictor of mortality in HF patients. It is considered the standard indication criterion for heart transplantation,[7] with VO_2max and VE/VCO_2 slope as the most adopted risk assessment tools.[8] Several HF treatments (ACEI, BB, MRA, ICD, CRT) have proven to improve patient survival and reduce ejection fraction. Whether to revise the existing listing criteria for heart transplantation was a matter of debate,[15] since the trial that defined the use of a cut-off point ≤14 ml/kg/min for the procedure was published before several advancements in HF treatment.[16]

Several trials with BB failed to demonstrate an increase in VO_2max.[17,18] However, BB therapy seemed to provide a better prognosis with the same VO_2max value,[19,20] which was used to reduce the cut-off point for heart transplantation selection from 14 ml/kg/min to 12 ml/kg/min.[21] On the other hand, CRT showed an increase in exercise capacity in one trial, with a mean growth of 1.1 ml/kg/min at 6 months,[22] but failed to do the same in other trials.[23,24]

Aiming at improving patients' functional capacity, some recent HF treatments, like cardiac contractility modulation, revealed an improvement in VO_2max from 0.65 ml/kg/min[25] to 0.84 ml/kg/min[26] at 6 months, while percutaneous repair for secondary mitral regurgitation had preserved functional capacity in one trial, as assessed by the 6-minute walk test,[27] but no differences in another.[28] Exercise training has also shown a VO_2max improvement in previous trials, from 0.6 ml/min/kg at 3 months[29] to 2.1 ml/min/kg at 2 months.[30]

After the PARADIGM-HF trial confirmed that sacubitril-valsartan therapy could reduce both HF hospitalization and

Table 2 – Echocardiographic data before and after six months of sacubitril-valsartan therapy

	Time 0	6 months	p
ECHOCARDIOGRAPHIC DATA			
Left ventricular end-diastolic diameter (mm)	71.3 ± 8.4	66.9 ± 7.6	0.001
Left ventricular end-systolic diameter (mm)	57.8 ± 9.4	53.1 ± 9.3	0.002
Interventricular septum (mm)	9.6 ± 1.7	9.9 ± 1.9	0.280
Left ventricular ejection fraction (%)	29.3 ± 6.4	35.17 ± 8.6	0.001
Left atrial volume (ml/m^2)	51.5 ± 22.6	43.7 ± 15.8	0.004
Right atrial volume (ml/m^2)	33.1 ± 4.4	28.5 ± 13.5	0.036
Pulmonary artery systolic pressure (mmHg)	38.3 ± 12.2	30.9 ± 10.6	<0.001
Tricuspid annular plane systolic excursion (mm)	19.2 ± 4.4	20.0 ± 4.8	0.404

Values are expressed as mean ± standard deviation.

Table 3 – Cardiopulmonary exercise testing data before and after six months of sacubitril-valsartan therapy

	Time 0	6 months	p
Cardiopulmonary exercise testing data			
Maximal heart rate (bpm)	114.1 ± 27.2	118.9 ± 24.7	0.110
Maximal predicted heart rate (%)	70.7 ± 16.0	73.9 ± 14.7	0.083
One-minute heart rate recovery (bpm)	17.0 ± 12.3	17.8 ± 12.9	0.720
Initial systolic blood pressure (mmHg)	115.8 ± 18.3	109.3 ± 16.5	0.094
Maximal systolic blood pressure (mmHg)	140.0 ± 29.8	139.7 ± 23.6	0.946
Maximal oxygen uptake (ml/kg/min)	14.4 ± 6.0	18.63 ± 4.9	<0.001
Predicted maximal oxygen uptake (%)	49.6 ± 18.7	65.7 ± 15.5	<0.001
VE/VCO_2 slope	36.7 ± 7.2	31.1 ± 5.8	<0.001
Peak respiratory exchange ratio	1.0 ± 0.1	1.0 ± 0.1	0.396
Duration of exercise (sec)	487.8 ± 289.3	640.3 ± 269.3	<0.001
Duration of exercise until AT (sec)	269.7 ± 277.1	292.5 ± 253.2	0.623
Oxygen uptake at AT (ml/kg/min)	12.0 ± 4.3	13.7 ± 3.6	0.087

Values are expressed as mean ± standard deviation; AT: anaerobic threshold.

cardiovascular mortality by 20% in comparison with Enalapril,[4] information has been increasing, as some trials revealed a significant symptomatic and functional improvement following the initiation of sacubitril-valsartan therapy.[9-12] Nevertheless, most trials had retrospective designs, and, to the best of our knowledge, only one prospective study shows CPET parameter changes after sacubitril-valsartan therapy.[13] In this trial, with a median follow-up of 6 months, VO_2max increased by 2.6 ml/min/kg on average, and VE/VCO_2 slope had a mean reduction of 2.4.

Our results show a group of highly symptomatic chronic HFrEF patients, as revealed by an NYHA class ≥ III in 51.4% of them (only 23.9% in the PARADIGM-HF trial), a baseline Heart Failure Survival Score (HFSS) of 7.2, and a hospitalizations rate for worsening HF in the year prior to the study of 42.9%. Patients were on optimized standard of care therapy, with a numerically higher percentage of individuals treated at baseline with BB (100% vs. 93.1%), MRA (94.3% vs. 52.2%), ICD (85.6% vs. 14.9%), and CRT (20% vs. 7%) when compared to the PARADIGM-HF trial.[4] Sacubitril-valsartan therapy was started at 24/26 mg twice daily in 18 (51.4%) patients and 49/51 mg twice daily in 17 (48.6%) patients. This procedure is in line with a recent real-world data study that started sacubitril-valsartan therapy at 24/26 mg twice daily in 51% of patients, 49/51 mg twice daily in 38%, and 97/103 mg twice daily in 11%.[31] In our trial, the mean daily dose at six months was slightly higher than the previous trial (251 mg/day vs. 207 mg/day) but lower than the PARADIGM-HF trial (375 mg/day).[4]

In this highly symptomatic population, sacubitril-valsartan therapy was able to improve the NYHA classification by at least one class in 74.3% of patients. In addition to the reduction in NYHA class, CPET data demonstrated a mean VO_2max increase of 3.9 ml/kg/min and a mean VE/VCO_2 slope decrease of 5.6, which is numerically higher than the benefit previously reported.[13] Higher values of left ventricular ejection fraction and VO_2max led to significant HFSS growth (7.2 ± 1.0 vs. 7.9 ± 0.9, p=0.001).

Table 4 – Cardiopulmonary exercise testing data by sacubitril-valsartan dose

	Time 0	6 months	p
Cardiopulmonary exercise testing data			
Maximal oxygen uptake (ml/kg/min)			
24/26 mg dose	13.5 ± 5.9	19.2 ± 6.6	0.018
49/51 mg dose	13.5 ± 6.6	17.6 ± 4.3	0.019
97/103 mg dose	15.5 ± 5.9	18.1 ± 4.4	0.085
Predicted maximal oxygen uptake (%)			
24/26 mg dose	44.9 ± 20.6	62.8 ± 18.3	0.004
49/51 mg dose	47.8 ± 18.6	69.1 ± 14.1	0.008
97/103 mg dose	53.7 ± 18.2	65.2 ± 15.6	0.048
VE/VCO_2 slope			
24/26 mg dose	38.0 ± 8.9	28.1 ± 3.1	0.033
49/51 mg dose	38.8 ± 5.5	31.9 ± 3.0	0.005
97/103 mg dose	34.6 ± 7.3	32.0 ± 7.7	0.148

Values are expressed as mean ± standard deviation.

These results could be important when considering patients not on sacubitril-valsartan therapy for heart transplantation based on CPET values, since at 6 months of treatment, the percentage of patients with VO_2max ≤12 mL/min/kg decreased from 37 to 11% and with VE/VCO_2 slope >35, from 52.4 to 17.1%. Further trials are necessary to verify whether the current cut-off points for heart transplantation should be maintained with sacubitril-valsartan therapy.

Surprisingly, patients receiving 24/26 mg and 49/51 mg doses at 6 months of sacubitril-valsartan therapy had the highest increase in VO_2max and VE/VCO_2 slope values, revealing the benefit of this treatment as long as the highest tolerated dose was administered. These results can complement the background of sacubitril-valsartan use in the HFrEF population, since the 24/26 mg dose was not used in PARADIGM-HF trial.[4]

The highest increase in VO_2max and VE/VCO_2 slope values with the lowest sacubitril-valsartan dose is not easy to explain. Nonetheless, this scenario could represent a bias since patients who tolerated the highest dose of sacubitril-valsartan had high VO_2max baseline values and small VE/VCO_2 slope values, possibly making this group less prone to a greater benefit with the therapy.

Study limitations

Our study has limitations that should be referenced when interpreting the results. This is a single-center prospective experience; therefore, the findings might reflect local practice. Although the sample was not large, the study showed promising results after only six months of therapy, which can be considered a motivation to increase the use of sacubitril-valsartan in patients with such indication, as recommended by the guidelines.[5]

Despite being a prospective study, the results were compared between baseline and after six months of sacubitril-valsartan therapy without a control group that would continue ACEI or ARB therapy. After the results of the PARADIGM-HF trial,[4] leaving some patients without a therapy that has proven to improve survival would not be ethical.

A strategy to try to reduce bias related to concomitant improvement caused by therapies other than sacubitril-valsartan was choosing study patients with previous optimized standard of care therapy (except for sacubitril-valsartan therapy) for more than six months and non-recent major cardiovascular procedure (ICD or CRT implantation, coronary revascularization procedure, valvular treatment, or catheter ablation of atrial fibrillation). This is demonstrated by the lack of differences in BB and MRA dosage after six months of therapy and because no new coronary revascularization procedure, valvular treatment, or catheter ablation of atrial fibrillation was performed.

Conclusions

Sacubitril-valsartan therapy seemed to increase the functional capacity of chronic HF patients, with a marked improvement in VO_2max, predicted VO_2max, VE/VCO_2 slope, and duration of exercise, as well as a reduction in NYHA class. These results can complement the background of sacubitril-valsartan use in the HFrEF population, showing benefit even with the lowest dose of therapy as long as this was the highest tolerated dose.

Author contributions

Conception and design of the research: Gonçalves AV, Pereira-da-Silva T, Galrinho AIVO, Soares R, Feliciano J, Ferreira RC; Acquisition of data: Gonçalves AV, Pereira-da-Silva T, Galrinho AIVO, Rio P, Moreira RI, Silva S, Alves S; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Gonçalves AV; Critical revision of

the manuscript for intellectual content: Pereira-da-Silva T, Galrinho AIVO, Rio P, Soares R, Feliciano J, Ferreira RC.

Potential Conflict of Interest

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

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*Supplemental Materials

For additional information, please click here.

Angiotensin Receptor-Neprilysin Inhibition Therapy and Improved Exercise Parameters in Heart Failure with Reduced Ejection Fraction

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Short Editorial related to the article: Maximal Oxygen Uptake and Ventilation Improvement Following Sacubitril-Valsartan Therapy

Heart failure (HF) with reduced ejection fraction (HFrEF) has increased significantly in the last three decades and is associated with high morbidity and mortality.[1] In patients with HF, exercise intolerance suggested by dyspnea or fatigue during exertion is the hallmark of the disease. Additionally, health-related quality of life is known to be markedly reduced in HFrEF patients. The severity of this exercise limitation and low quality of life has been shown to correlate to worse prognosis.[2] For this functional and objective assessment, cardiopulmonary exercise testing (CPET) has played an important role on identifying those worse-prognosis patients and has been able to evaluate the effectiveness of different therapies for this HF population,[3] such as the switch of angiotensin-converting enzyme inhibitors (ACEI) to angiotensin receptor neprilysin inhibition (ARNI).

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized HFrEF patients with New York Heart Association functional class (NYHA) II-IV to the angiotensin receptor neprilysin inhibitor (sacubitril-valsartan) 200 mg twice daily or enalapril 10 mg twice daily and showed a consistent reduction on cardiovascular death, all-cause death and HF-related hospitalizations in the sacubitril-valsartan group.[4] Moreover, the PARADIGM-HF showed improvement in overall quality of life as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[5] Specifically, the greatest baseline limitations and improvements after sacubitril-valsartan were related to activities such as jogging and sexual intercourse, which might be a surrogate marker of better exercise capacity after switching the therapy, although very subjective.

Even though that current guidelines have endorsed the CPET as a gold-standard tool for prognostic assessment and exercise capacity evaluation for HFrEF patients,[1,6] larger trials focusing on objective parameters on exercise capacity are lacking. Additional data has been reported in a small study with 35 patients. Malfatto et al.[7] reported considerable benefits on CPET parameters such as the increase in peak oxygen consumption (VO_2), oxygen pulse and the reduction in V_E/VCO_2 slope, along with the improvement on left ventricular ejection fraction (LVEF) and pulmonary hypertension after six months of treatment.[7] In this issue of *Arquivos Brasileiros de Cardiologia*, the study[8] presented important data that contributes to the advance of current knowledge of how ARNI therapy exerts favorable effects in patients with HFrEF.

Gonçalves et al.[8] conducted the study, an open-label, non-randomized, single-center investigation that included 42 HFrEF patients (but only 35 patients completed the six-month follow-up) who primarily had NYHA class III or more in 51,4% of the population and 42,9% had had a previous HF hospitalization and were taking beta-blockers (100%), ACEI/ARB (100%) and mineralocorticoid receptor antagonist (94,3%). In this prospective study, all patients have been switched to ARNI and followed by 6 months and there was no control group mainly related to ethical concerns of withholding ARNI therapy in HFrEF patients. The main objective was to compare CPET parameters (peak VO_2 and peak predicted VO_2, V_E/VCO_2 slope, anaerobic threshold, and duration of the exercise test) before and after 6 months of ARNI therapy and also evaluated markers of reverse remodeling through the echocardiogram (LVEF, left atrium volume, left ventricle end-diastolic and end-systolic diameters). Patients were treated with escalating doses of sacubitril-valsartan, targeting 97/103 mg twice daily.

In this study, peak VO_2 (14.4 ± 6.0 vs 18.63 ±4.9, $p<0.001$) and peak predicted VO_2 (49.6% ± 18.7 vs 65.7% ± 15.5) presented an important increase after the introduction of ARNI therapy and also a significant reduction in V_E/VCO_2 slope (36.7 ± 7.2 vs 31.1 ± 5.8, $p<0.001$). Those CPET variables have been strongly related to HF prognosis and their improvement is well correlated to better outcomes.[9] Additionally, the CPET parameters benefits were also observed in the non-maximal target ARNI dose subgroups.

Furthermore, there was an increase in the duration of exercise during the test and it is likely reflecting the reported benefit on the NYHA class after the treatment, which was reported as an impressive percentage (74,3%) of the patients that presented at least one NYHA class improvement.

Those favorable NYHA class changes were also reported in a real-world retrospective cohort although with a lower percentage of the patients that improved the NYHA class. Lau et al.[10] collected baseline and follow-up data in 201 patients that received sacubitril-valsartan and were followed by 221 ± 114 days.[10] In contrast, the real-world CPET data have not shown a significant difference in 45 patients under ARNI therapy but there was an improvement in the patient-level activity at home. Those divergent findings could be explained by the fact that the real-world population was

Keywords

Heart Failure; Stroke Volume, Fatigue; Mortality; Morbidity; Prognosis; Exercise, Intolerance.

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older and less symptomatic (more NYHA class II which might reduce the effect of the therapy), along with the limitations of a retrospective observational cohort and incomplete data collection.

Assessing the ability of the ARNI treatment to promote reverse remodeling through echocardiographic parameters, the study also showed a significant increase in the mean LVEF of 5.9% and there was evidence of reverse remodeling (lower left ventricular volumes as well as atrium volumes, reduction on pulmonary artery systolic pressure). These echocardiographic parameters improvements were very similar to the magnitude of the reverse remodeling observed in the PROVE-HF trial, which showed an increase in the mean LVEF at six months (5.2%) and twelve months (9.4%).[11]

There are clinical implications from these 2 studies (PROVE-HF and by Gonçalves et al.[8]). First of all, the observed reverse remodeling is likely to promote a significant improvement in LVEF and might avoid cardioverter-defibrillator therapy for primary prevention. Additionally, the impressive CPET and NYHA benefits of this current study are likely to be translated into a better quality of life and functional capacity and might also preclude the cardiac-resynchronization therapy indication for some HF patients. Last, Gonçalves et al.[8] study adds supportive evidence to the evidence-based recommendations of ARNI efficacy and provide further initiatives to the widespread dissemination of this treatment to HFrEF patients.[12]

Nevertheless, the Gonçalves et al.,[8] study, as well as the PROVE-HF trial, were not randomized trials and the absence of a control group represents a considerable limitation and the notable effects on the CPET parameters might be related to other HF therapies. Besides, the HF population of the by Gonçalves et al.,[8] study was sicker than PARADIGM-HF and PROVE-HF trials, with a higher percentage of patients with a previous HF-related hospitalization and more patients with NYHA III and IV, which is likely to have influenced the magnitude of the benefit of ARNI therapy and might in part explain the lack of CPET benefit in a real-world cohort of patients.[9] Regarding CPET variables, there were some important missing parameters such as exercise oscillatory breathing ventilation, oxygen pulse trajectory, oxygen uptake efficiency slope, and peak PETCO2 that could have added insights into the effect of ARNI in that population.

In conclusion, the Gonçalves et al.,[8] study reported in this issue of *Arquivos Brasileiros de Cardiologia* strongly suggests that ARNI therapy can promote significant changes in the functional capacity and measured CPET parameters of exercise tolerance as well as a considerable improvement on echocardiographic variables related to reverse remodeling of HFrEF patients. Although this was a not randomized trial, it certainly adds more beneficial data of the ARNI therapy in the HFrEF population. Specifically for the HF-related morbidity burden that characterizes this disease, more targeted approaches are warranted to provide a better quality of life and health-related outcomes.

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Frequency and Reasons for Non-Administration and Suspension of Drugs During an Acute Coronary Syndrome Event. The ERICO Study

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Abstract

Background: **Few studies have discussed the reasons for pharmacological undertreatment of Acute Coronary Syndrome (ACS).**

Objectives: **To determine the frequency and reasons for the non-administration and suspension of medications during in-hospital treatments of ACS in the Strategy of Registry of Acute Coronary Syndrome (ERICO) study.**

Methods: **The present study analyzed the medical charts of the 563 participants in the ERICO study to evaluate the frequency and reasons for the non-administration and/or suspension of medications. Logistic regression models were built to analyze if sex, age ≥65 years of age, educational level, or ACS subtype were associated with (a) the non-administration of ≥1 medications; and (b) the non-administration or suspension of ≥1 medications. The significance level was set at 5%.**

Results: **This study's sample included 58.1% males, with a median of 62 years of age. In 183 (32.5%) participants, ≥1 medications were not administered, while in 288 (51.2%), ≥1 medications were not administered or were suspended. The most common reasons were the risk of bleeding (aspirin, clopidogrel, and heparin), heart failure (beta blockers), and hypotension (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers). Individuals aged ≥65 (odds ratio [OR]:1.51; 95% confidence interval [95% CI]:1.05-2.19) and those with unstable angina (OR:1.72; 95% CI:1.07-2.75) showed a higher probability for the non-administration of ≥1 medication. Considering only patients with myocardial infarction, being ≥65 years of age was associated with both the non-administration and the non-administration or suspension of ≥1 medication.**

Conclusions: **Non-administration or suspension of ≥1 medication proved to be common in this ERICO study. Individuals of ≥65 years of age or with unstable angina showed a higher probability of the non-administration of ≥1 medication and may be undertreated in this scenario. (Arq Bras Cardiol. 2020; 115(5):830-839)**

Keywords: **Acute Coronary Syndrome/mortality; Withholding Treatment /drug therapy; Morbidity; Health Care (Public Health).**

Introduction

Coronary artery disease (CAD) continues to be the leading cause of mortality and disability-adjusted life years worldwide, including Brazil.[1-4] Appropriate and timely treatment may reduce morbidity and mortality.[5] There is evidence that the quality of pharmacological treatment in the hospital phase of an acute coronary syndrome (ACS) event, defined by the early administration of guideline-oriented medications, is associated with in-hospital survival[6] and six-month survival.[7]

In the largest Brazilian study reporting the frequency of guideline-oriented medication prescriptions in hospitalized ACS patients to date, Wang et al.[8] evaluated data from 2,453 individuals with ACS from 65 Brazilian hospitals (approximately 90% tertiary hospitals) in the study of the Acute Coronary Care Evaluation of Practice (ACCEPT) Registry from August 2010 to December 2011. Among the drugs analyzed in their study, aspirin was the most commonly prescribed drug in the first 24 hours (97.6%). Statins also presented a high frequency of prescription (90.6%).

Few studies have discussed the reasons for ACS undertreatment. This is especially important as the mean age of ACS patients is on the rise. Adverse effects and contraindications are more frequent[9] in older individuals, contributing to their associated higher morbidity and mortality.[10,11] Marino et al.[12] evaluated 583 individuals diagnosed with ACS in six emergency hospitals in Montes Claros. In the first 24 hours of treatment, the use of medications for ACS treatment varied from 63.8% (heparins) to 96.6% (aspirin). Of 181 patients (31.0% of their sample) who did not receive beta blockers within 24 hours, 39 (21.5%) presented identifiable contraindications. No other descriptions of the reasons for under treatment during the first 24 hours were reported.

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The present article seeks to analyze data from ACS events, which led to the enrollment of 563 participants in the Strategy of Registry of Acute Coronary Syndrome (ERICO) study, a prospective study that is still ongoing at the University Hospital of the University of São Paulo (HU-USP in Portuguese). Our team aimed to determine the frequency of use, along with the reasons for the non-administration and suspension of medications used during the in-hospital treatment of an ACS event and their associated factors.

Methods

ERICO Study design

The design of the ERICO study has been described in detail elsewhere.[13,14] Briefly, ERICO is a prospective observational study of 1,085 individuals admitted to the HU-USP due to an ACS event between February 2009 and December 2013. HU-USP is a community hospital in Butantã, a district in the city of Sao Paulo, Brazil, with an estimated population of 428,000 inhabitants in 2010 and marked socioeconomic inequalities.

For participation in the ERICO study, participants were required to meet the diagnostic criteria for ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA). For a diagnosis of myocardial infarction (MI), both of the following criteria must be present: (I) Symptoms consistent with cardiac ischemia within 24 hours of hospital admission and (II) Troponin I levels above the 99th percentile with a test-specific coefficient of variation <10%. The STEMI diagnosis requires both of the following criteria: (I) Criteria for MI diagnosis and (II) One of the following: (a) persistent ST segment elevation of ≥ 1 mm in two contiguous electrocardiographic leads or (b) the presence of a new or presumably new left bundle branch block. For the NSTEMI diagnosis, participants must present: (I) Criteria for MI diagnosis and (II) Absence of criteria for STEMI diagnosis. For UA diagnosis, all of the following three criteria must be fulfilled: (I) Symptoms consistent with cardiac ischemia 24 hours prior to hospital admission, (II) Absence of MI criteria, and (III) At least one of the following: (a) history of coronary artery disease; (b) positive coronary disease stratification test (invasive or noninvasive); (c) transient ST segment changes ≥ 0.5 mm in two contiguous leads, new T-wave inversion of ≥ 1 mm and/or pseudo-normalization of previously inverted T waves; (d) troponin I > 0.4 ng/ml; or (e) diagnostic agreement of two independent physicians. Non-ST elevation acute coronary syndrome (NSTEACS) is a common term that encompasses NSTEMI and UA.

At baseline, trained interviewers obtained data on sociodemographic and cardiovascular risk factors, as well as previous medications. During the in-hospital phase, all subjects were treated at the discretion of the hospital staff, with standard procedures and with no influence from the study protocol. Long-term follow-up is currently ongoing, with annual telephone contacts.

ERICO-APS study design

The present paper is an analysis of an ancillary ERICO study (Strategy of Registry of Acute Coronary Syndrome – Primary Health Care; ERICO-APS study). Further detail about the ERICO-APS study can be found in a previous publication.[15] ERICO-APS aims to study determinants of quality of care and mortality, with a special focus on the unit of first contact (primary care or hospital) during the index ACS event. ERICO-APS comprises 130 participants for whom a primary care facility was the unit of first contact during the index event, and 700 participants who came directly to the hospital, all enrolled in the main study from February 2009 to December 2012.

Study sample

In our analyses, 700 ERICO-APS participants who came directly to the hospital were eligible. This study excluded 44 (6.3%) participants whose medical charts could not be retrieved and 93 (13.3%) whose medical chart data were incomplete (for example, due to transfer to other hospitals). Our final sample consisted of 563 ERICO-APS participants.

Study variables

Hypertension, diabetes, dyslipidemia, and previous coronary artery disease (CAD) diagnoses were defined by self-report. Smoking status was classified as never, past, or current smoker. The educational level was self-reported and classified as no formal education, 1 to 7 years of formal education, and ≥ 8 years of formal education. In some of the analyses, age was categorized using a cutoff of 65 years.

Medical charts and prescriptions were reviewed in order to analyze the frequency of administration, reasons for non-administration, and reasons for the suspension of the following medications: aspirin, clopidogrel, heparins, beta blockers, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARB). The frequency of the administration for statins, nitrates, and morphine was also analyzed.

"Non-administration" was defined as the non-prescription of medications from admission to discharge. "Suspension" was defined as the withdrawal of drugs initially prescribed during the hospitalization period. One exception was the withdrawal of the heparin prescription after the eighth day of hospitalization.[16] The reasons were separated by pharmacological class: (a) aspirin: allergy, bleeding or risk of bleeding, and revascularization surgery; (b) clopidogrel: bleeding or risk of bleeding and coronary artery bypass; (c) heparin: bleeding or risk of bleeding, revascularization surgery, low risk acute coronary syndrome, and coronary angiography; (d) beta blockers: bronchospasm, bradycardia, shock/hypotension, decompensated heart failure, and non-invasive testing for ischemia; and (e) ACEI/ARB: chronic renal failure (CRF), shock/hypotension, acute renal failure (ARF), and hyperkalemia.

These reasons are described in supplementary table 1, along with the most frequently prescribed drugs for each pharmacological class. The non-administration (or suspension) of any medication was defined as the non-administration (or suspension) of one or more of the following: aspirin, clopidogrel, heparin, beta blockers, statins, and/or ACE inhibitors/ARB.

When the reason for drug non-administration or suspension was noted in the medical charts, this information was retrieved and classified according to its explicit reason. Whenever these reasons for non-administration or suspension were not explicit, a doctor and a pharmacist from the study reviewed the

medical chart to verify whether any of the described reasons were implicit. Therefore, the reasons for non-administration or suspension were classified as "not described", "implicit", or "explicit".

Vital status was assessed by telephone interview 30 days after the index event, according to ERICO study protocol.[14,17] Official death records were obtained with the collaboration of the municipal and state's health offices whenever it was verified that the participant had died or if the patient could not be contacted at that time.

Ethical considerations

The study protocol was in accordance with the Declaration of Helsinki. The hospital's institutional review board approved the research protocol (Ethical Committee Approval 866/08). Written informed consent was obtained from all ACS patients admitted to the hospital who agreed to participate in this study, and each subject received a copy of the informed consent form.

Statistical analysis

Categorical variables are presented as absolute counts and proportions, and compared using chi-squared tests. Due to its non-normal distribution (evaluated by density plots and the Shapiro-Wilk test), age is presented as a median and interquartile range and compared among groups using the Kruskal-Wallis test. This study also performed pairwise comparisons (with Holm adjustment) for age distribution in STEMI, NSTEMI, and UA groups. Crude and multiple logistic regression models were built to analyze if sex, being ≥ 65 years of age, educational level, or ACS subtype were associated with (a) the non-administration of any medication and (b) the non-administration or suspension of any medication. As sensitivity analyses, these models were repeated: (a) excluding the non-administration/suspensions due to the scheduled percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG) and (b) excluding those with unstable angina, as some medications may not have been prescribed due to low-risk ACS. Kaplan-Meier curves and the log-rank test were used to determine if 30-day survival was associated with ≥ 1 non-administered or suspended medications. The significance level was set at 5%. The R software, version 3.2.0, was used to conduct these analyses.[18]

Results

Table 1 shows the baseline characteristics of the study sample, according to the ACS subtype. This study's sample had a predominance of males (n=327; 58.1%), with a median of 62 years of age. Individuals with STEMI had a lower age compared to participants with NSTEMI (p=0.002) and UA (p=0.024). Age distribution in participants with NSTEMI and UA is not significantly different (p=0.35). Hypertension (n=421; 76.5%) and sedentarism (n=369; 70.3%) were the most frequent cardiovascular risk factors in the sample. Only 150 (29.1%) of the participants had a CAD diagnosis prior to the ACS event that led to the enrollment in the ERICO study.

Table 2 shows the frequency of the administration of aspirin, clopidogrel, heparins, statins, beta blockers, ACEI or BRA, nitrates, and morphine during in-hospital treatment. Considering the main medications in ACS treatment (aspirin, clopidogrel, heparin, beta blockers, statins, and/or ACE inhibitors/ARB), this study identified 183 (32.5%) participants in whom one or more medications were not administered. Nitrate use was similar according to ACS subtype (p=0.32)

Table 1– Baseline characteristics of the study sample

	STEMI (N=162)	NSTEMI (N=232)	UA (N=169)	Total (N=563)
Age (years; median [IQR])	59.0 [50.0 - 68.0]	64.0 [53.8 - 74.0]	62.0 [53.0 - 73.0]	62.0 [52.0 - 72.0]
Male sex	106 (65.4%)	140 (60.3%)	81 (47.9%)	327 (58.1%)
Educational level				
No formal education	16 (9.9%)	24 (10.3%)	22 (13.0%)	62 (11.0%)
1 to 7 years	69 (42.9%)	107 (46.1%)	62 (36.7%)	238 (42.3%)
≥ 8 years	76 (47.2%)	101 (43.5%)	85 (50.3%)	262 (46.6%)
Hypertension	101 (64.3%)	174 (76.0%)	146 (89.0%)	421 (76.5%)
Diabetes	49 (31.4%)	99 (42.9%)	67 (41.4%)	215 (39.2%)
Dyslipidemia	66 (50.0%)	113 (53.3%)	83 (57.2%)	262 (53.6%)
Sedentarism	98 (66.2%)	156 (70.6%)	115 (73.7%)	369 (70.3%)
Smoking status				
Never	37 (23.7%)	69 (31.7%)	60 (38.5%)	166 (31.3%)
Past	57 (36.5%)	81 (37.2%)	62 (39.7%)	200 (37.7%)
Current	62 (39.7%)	68 (31.2%)	34 (21.8%)	164 (30.9%)
Previous CAD	25 (16.9%)	50 (23.3%)	75 (49.3%)	150 (29.1%)

IQR: interquartile range; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; CAD: coronary artery disease.

Table 2 – Administration of guideline-oriented medications during in-hospital treatment

Drug	STEMI	NSTEMI	UA	Total
Aspirin	158 (97.5%)	229 (98.7%)	165 (97.6%)	552 (98.0%)
Clopidogrel	159 (98.1%)	226 (97.4%)	158 (93.5%)	543 (96.4%)
Heparin	153 (94.4%)	228 (98.3%)	160 (94.7%)	541 (96.1%)
Statins	152 (93.8%)	217 (93.5%)	147 (87.0%)	516 (91.7%)
Beta-blockers	138 (85.2%)	194 (83.6%)	142 (84.0%)	474 (84.2%)
ACEI/ARB	136 (84.0%)	201 (86.6%)	132 (78.1%)	469 (83.3%)
Nitrate	95 (58.6%)	119 (51.3%)	95 (56.2%)	309 (54.9%)
Morphine	37 (22.8%)	30 (12.9%)	9 (5.3%)	76 (13.5%)

STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; ACEI/ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

and, as expected, morphine administration was more frequent in the participants with a STEMI diagnosis ($p<0.001$). In 288 (51.2%) participants, this study observed the non-administration or suspension of one or more of the main medications during in-hospital treatment.

Table 3 presents the reasons for the non-administration or suspension of aspirin, clopidogrel, heparin, beta blockers, and ACEI/ARB. It was observed that the non-administration or suspension of aspirin, clopidogrel, and heparin is a rare event, usually linked to an increased risk of bleeding. The most frequent reason for the non-administration of beta blockers were decompensated heart failure and shock/hypotension. Heart failure was also the most frequent reason for beta blocker suspension. Shock/hypotension was the most frequent reason for the non-administration and suspension of ACEI/ARB. Supplementary Table 2 reports the frequencies for the presence of reasons for the non-administration/suspension of medications in the medical charts. It was observed that the reasons for non-administration were not described in the medical charts in 64.0% of the cases, and the reasons for suspension were not described in 26.4%.

Table 4 shows the odds ratios (from multiple models) for the non-administration and non-administration/suspension of one or more medications (aspirin, clopidogrel, heparin, statins, and/or ACE inhibitors/ARB), associated with age, sex, educational level, and ACS subtype. Analyzing the entire sample, individuals aged 65 or older ($p=0.027$) and those with unstable angina ($p=0.025$) presented a higher probability for the non-administration of one or more medications. When individuals with unstable angina were excluded, being $\geq$ 65 years of age was associated with either the non-administration ($p=0.023$) or the non-administration/suspension ($p=0.035$) of one or more medications. In this subsample, individuals with STEMI or NSTEMI presented a similar probability for the non-administration ($p=0.73$) or the non-administration/suspension ($p=0.85$) of one or more medications.

Sensitivity analyses, considering that participants with programmed PTCA and CABG did not qualify as a reason for the non-administration and/or suspension of clopidogrel and heparins (Supplementary Table 3), led to similar conclusions, except for a significant association between being $\geq$ 65 years of age and the non-administration/suspension of one or more medications (Odds ratio: 1.44; 95% CI: 1.02 – 2.04). Supplementary Tables 4 and 5 show the results obtained from the crude models.

At 30 days, eight (2.9%) individuals who had all medications administered without suspension and 20 (6.9%) individuals with one or more non-administered or suspended medications had died (Figure 1). Survival at 30-days was significantly associated with the presence of one or more non-administered or suspended medications ($p=0.03$).

Discussion

The present study observed that, during the in-hospital treatment of the index ACS event in the ERICO study, the non-administration of one or more medications occurred in approximately one-third of the sample, and the non-administration/suspension of one or more medications occurred in approximately one half of the sample. The reasons for non-administration were not described in the patients' medical charts in 64.0% of the cases, and the reasons for suspension were not described in 26.4%. Individuals aged $\geq$ 65 and those with a diagnosis of unstable angina presented a higher probability of the non-administration of one or more medications. Individuals of 65 years of age also presented a higher probability of the non-administration/suspension of one or more medications.

The frequency of the non-administration or suspension of medication during the treatment of an ACS event has been reported in other settings. Candela et al.[19] analyzed data from 1,134 patients with non-ST segment elevation ACS treated in tertiary hospitals in Spain. These authors analyzed groups according to PTCA and/or CABG treatment options, and found that within the first 24 hours, 96.3% to 99.2% received aspirin, 75.8% to 83.6% received heparin and 67.7% to 77.9% received clopidogrel (this proportion may rise to 78.3% to 99.2% among groups, when the proportion of individuals receiving prasugrel and/or ticagrelor are added). Khedri et al.[20] analyzed a large sample of 75,129 patients with ACS in Sweden using a nationwide web-based system. In that setting, upon hospital discharge, aspirin was not prescribed for 6.8% of the patients, beta blockers for 11.4%, and ACEI/ARBs for 31.9%. Considering the absence of prescription upon hospital

Table 3 – Causes for the non-administration or suspension of medications in the sample

Drug	Cause	Non-administration	Suspension
Aspirin	Allergy	4	0
	Bleeding or risk of bleeding	1	5
	Coronary artery bypass graft	0	5
	Total	5	10
Clopidogrel	Bleeding or risk of bleeding	1	15
	Coronary artery bypass graft	1	2
	Coronary angiography	0	22
	Total	2	39
Heparin	Bleeding or risk of bleeding	2	7
	Coronary artery bypass graft	0	4
	Coronary angiography	0	35
	Low-risk acute coronary syndrome	2	0
	Total	4	46
Beta-blockers	Decompensated heart failure	16	11
	Bronchospasm	14	5
	Shock / hypotension	14	5
	Bradycardia	6	4
	Non-invasive testing for ischemia	0	1
ACEI/ARB	Shock / hypotension	14	9
	Chronic renal failure	6	0
	Hyperkalemia	3	5
	Acute renal failure	1	7
	Total	24	21

ACEI/ARB: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Table 4 – Odds ratios (95% CI) from multiple models for the association between non-administration and non-administration or suspension with age, sex, educational level, and ACS subtype

	All ACS subtypes		Excluding participants with UA	
	Non-administration	Non-administration or suspension	Non-administration	Non-administration or suspension
Male sex	0.96 (0.67 - 1.39)	0.88 (0.62 - 1.24)	0.98 (0.62 - 1.55)	0.93 (0.61 - 1.41)
Age ≥ 65 years	**1.51 (1.05 - 2.19)**	1.36 (0.96 - 1.92)	**1.69 (1.07 - 2.67)**	**1.57 (1.03 - 2.40)**
Educational level				
No formal education	0.58 (0.31 - 1.11)	0.58 (0.32 - 1.03)	0.58 (0.25 - 1.33)	0.55 (0.26 - 1.13)
1 to 7 years	0.90 (0.61 - 1.31)	1.10 (0.77 - 1.58)	0.95 (0.60 - 1.51)	1.16 (0.76 - 1.76)
≥ 8 years	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
ACS subtype				
STEMI	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
NSTEMI	1.10 (0.70 - 1.73)	0.98 (0.65 - 1.48)	1.08 (0.69 - 1.71)	0.96 (0.64 - 1.45)
UA	**1.72 (1.07 - 2.75)**	1.23 (0.79 - 1.91)	-	-

p<0.05 in bold. ACS: Acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina.

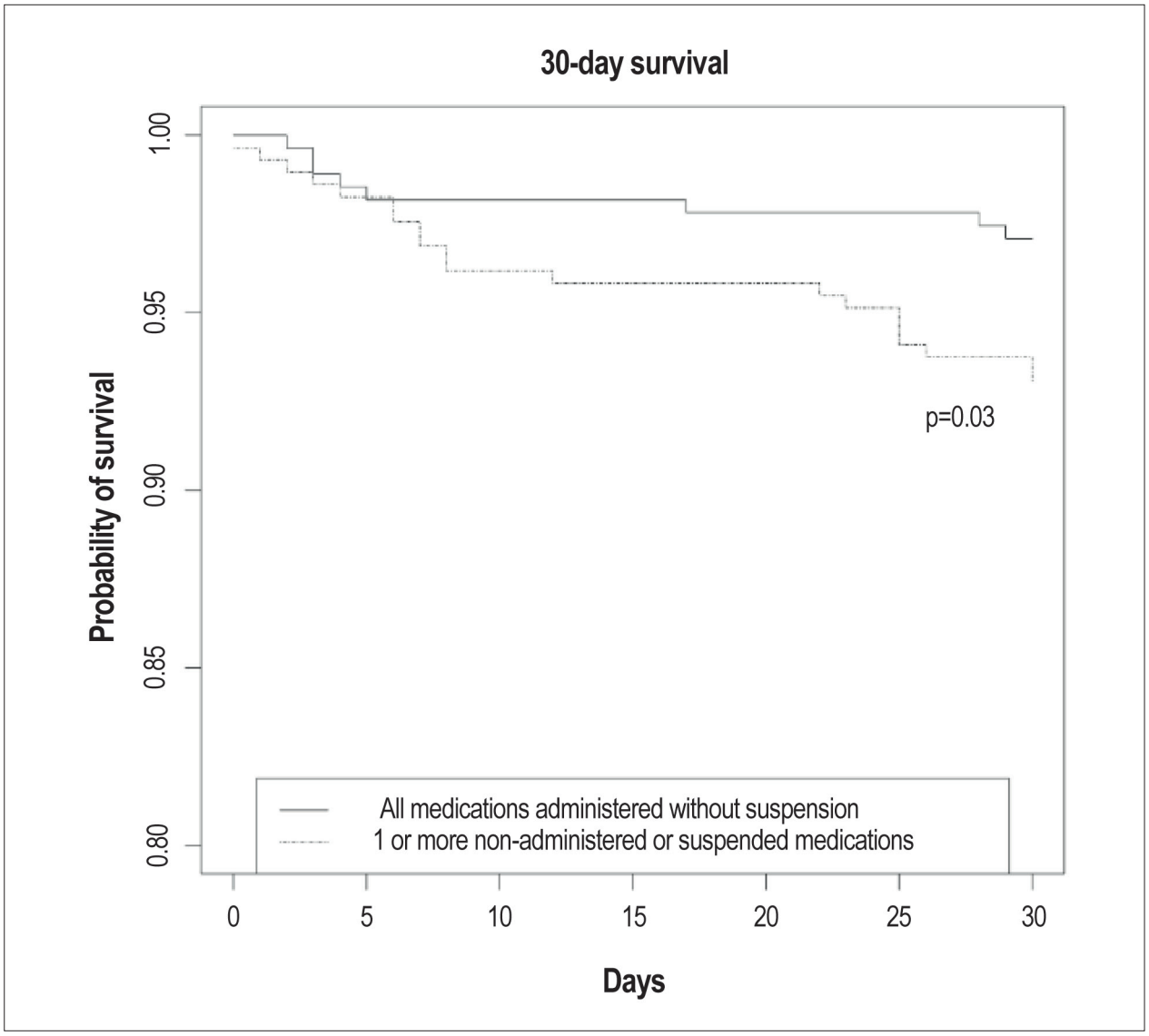

Figure 1 - *Survival at 30 days for individuals who (a) had all medications administered without suspension and (b) had one or more non-administered or suspended medications.*

discharge as the result of the non-administration or suspension of medication during hospital treatment, our study observed lower rates of the non-administration or suspension of aspirin (3.7%) and ACEI/ARBs (21.5%) and higher rates of the non-administration or suspension of beta blockers (23.1%). As specific reasons were not explored in Khedri et al.[20] study, it is impossible to make further inferences concerning the reasons for those differences.

Other authors have explored the reasons for the non-administration or suspension of medication. However, unlike our study, most limit their descriptions to a smaller number of medications, or aim to quantify the frequency of a specific reason for a non-administration or suspension. Consistent with our findings, Marino et al.[12] identified that hemorrhagic complications explained a significant proportion of the non-administration or suspension of aspirin, although our rates of uninterrupted in-hospital prescription were slightly higher than their prescription rates upon hospital discharge (96.3% vs 93.3%). By contrast, Bandara et al.[21] analyzed 81 participants with STEMI and found that 95% received aspirin, clopidogrel, and statin upon hospital admission, while only 88% received these medications upon hospital discharge. They describe that the most common discontinued medication was aspirin, and the most frequent reason was epigastric pain or presumed gastrointestinal hemorrhage. This contrasts with our findings, as aspirin was rarely discontinued during treatment. One possible contributor to these differences is that our sample identified no individuals in whom aspirin treatment was non-prescribed or withheld due exclusively to epigastric pain, as this is not a formal contraindication to aspirin treatment.[22]

Marino et al.[12] also reported data about beta blocker use in their sample. Among 181 (30.5%) patients with ACS who did

not receive a beta blocker in the first 24 hours in their study, 39 (21.5%) had identifiable contraindications to drug use. Although there must be some caution in directly comparing 24-hour patient data with full hospital stay patient data, in the present study, rates for beta blocker non-administration (15.8%) and suspension (4.8%) were lower, while the proportion of individuals in which a contraindication could be retrieved from the medical charts was higher (56.2% and 63.4% for non-administration and suspension, respectively). Some hypotheses may be raised in relation to these differences. First, Marino et al.[12] included individuals who came to the hospital through pre-hospital services or who were transferred by ambulance from other units. As the present study evaluated only individuals who came spontaneously to the hospital, one can speculate that the proportion of individuals with more severe cases (and, potentially, with more contraindications to beta blocker use) is lower in our sample. Mortality data from both studies corroborate this hypothesis. While 17.2% of the STEMI patients in Marino et al.[12] study died before hospital discharge, one-year mortality for STEMI patients in the ERICO study was 9.6%.[14] Second, there may be inequalities in the completeness of the medical chart data. This is further supported by the fact that in Marino et al.[12] study, cardiogenic shock was the most frequent contraindication for beta blocker use. Less severe complications (such as decompensated heart failure and bronchospasm) may be more prone to under-reporting compared to more severe ones. Therefore, it is possible that their lower rates of medical chart-defined reasons for beta blocker non-administration may be partially caused by this under-reporting.

Our study adopted a conservative strategy in some sensitivity analyses, excluding individuals with unstable angina from logistic regression models addressing variables associated with non-administered or suspended medications. However, the finding in main analyses that unstable angina patients presented a higher probability for the non-administration of one or more medications should not be overlooked. It is possible that some of these patients did not receive some medications due to low-risk unstable angina (characterized by the absence of a history of cardiovascular disease, normal ECG, normal troponin, and clinical stability[23]). However, some characteristics of the ERICO cohort suggest this may not fully explain our findings. First, the diagnosis of unstable angina in ERICO requires confirmatory evidence of ACS (for example, by baseline ECG alterations or positive non-invasive testing) or, alternatively, concordance by two independent physicians. Second, individuals with low-risk ACS are more prone to receive early discharge from the emergency clinic. Although these features do not preclude the inclusion of individuals with low-risk unstable angina in the ERICO study, their representation in the sample is probably reduced. Therefore, our results may actually point to an undertreatment of individuals with intermediate- or high-risk unstable angina. The findings from Breuckmann et al.[24] support this interpretation as well. In their study, the authors analyzed data from 1,400 patients with unstable angina in 30 chest pain units in Germany and found that 78% of the high-risk patients were undertreated. Along with our results, available evidence suggests that physicians should be aware to avoid overly conservative approaches (including undertesting and undertreating) in the management of patients with unstable angina.

The completeness of medical chart data is still challenging, and it is important to emphasize that a significant proportion of reasons for non-administration (and, to a lesser extent, suspension) could not be retrieved from medical charts in our study. This information is not usually reported in other articles. Based on our findings, one can speculate that caregivers are fairly likely to register a clinical situation requiring a change in prescription (i.e., suspension) but rarely document the reasons for not introducing an otherwise indicated medication. As medical chart completeness is an important point related to patient safety[25] and decision-making in individual and organizational levels, our data may point to an additional opportunity to improve the quality of care in this regard.

Our results suggest that higher age is an important marker for medication underuse during the treatment of an ACS event. This is to be expected, as the prevalence of some of the contraindications and the incidence of adverse effects may increase with age,[26,27] although conflicting evidence does exist.[28] Roe et al.[29] analyzed data from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial and found that individuals of ≥ 75 years of age had a higher risk for major bleeding during 30 months of follow-up, compared to those of <75 years of age (Hazard ratio, 2.15, 95% CI, 1.44-3.20). Although that study was not intended to analyze the in-hospital phase of ACS treatment, it can be hypothesized that this higher risk may influence the physicians' decision to prescribe a specific medication. However, it is noteworthy that in Roe et al.'s[29] study, the frequency of major bleeding in the subgroup of individuals of ≥75 years of age was still low (1.8%). It is plausible that, even considering a higher frequency of adverse effects and contraindications, individuals with higher ages are possibly being undertreated.

The presence of non-administered or suspended medications was also associated with poorer 30-day survival in our analyses. It is arguable that this finding reflects, at least partially, a detrimental effect of undertreatment on survival. However, in the context of an observational study like ours, this result must also be interpreted with caution. Individuals with more severe disease may be more prone to have contraindications to medical therapy. Therefore, differences in short-term mortality between groups may also be influenced by inequalities in baseline characteristics or in the course of the disease. The low proportion of individuals who died in the first 30 days (5.0%) also limits the strength of conclusions from this analysis.

Our study has some strengths. Few previous studies present a thorough description of reasons for the non-administration and suspension of medications used during an ACS event. In particular, when these data are presented, they are limited to one or a small subset of medications. The ERICO study sample[13,14] is derived from a community hospital, a setting frequently under-represented in ACS cohorts. As this study used a complete review of medical charts, it was able to identify the reasons for the non-administration and suspension of medications even when they were not explicitly stated in

patient diagnoses. Our study should be interpreted within its context. As this is a single-center study conducted in a community hospital, conclusions may be applicable only in contexts similar to ours. Treatment data in our article were collected at the ERICO study baseline, and alterations in the study setting since then could, potentially, change our findings. However, the authors believe that no substantial change in the study setting was made in such a ways as to consider our findings to be no longer valid. Even if this were the case, our descriptions of the causes for the non-administration and suspension of medication, comparative quality of medical chart completeness (between non-administered and suspended medications), and the undertreatment of older individuals are mostly applicable in other settings. Reasons for the non-administration and suspension were not described in the medical charts in 64.0% and 26.4% of the cases, respectively. As discussed above, medical chart completeness in the emergency clinic is rarely described in articles. Missing chart data in our study is comparable to the description found in Marino et al.'s study[12]. On the other hand, in comparison to tertiary centers, patients in community hospitals (like ours) have less severe disease and comorbidities. It is reasonable to consider that milder contraindications are more prone to underreporting, and, therefore, this may reflect on the relative frequency of causes for the non-administration or suspension of medications in our sample. We could not retrieve complete data from approximately one-fifth of the potentially eligible participants. Due to the design and objectives of this study, only individuals with complete inpatient data could be included. Some of these losses were due to transfers to other hospitals for specialized treatment (PTCA or surgery), and it is possible that this subset of patients is under-represented in our sample. ERICO is an observational study and does not influence medical treatment by protocol. Therefore, the decision not to administer, or to suspend medications, was under the discretion of the emergency ward's physician. Finally, as most of the medical chart information was in physical (non-electronic) files, our results for medical chart records regarding the reasons for the non-administration and/or suspension of medications may not be transposable to settings using mainly electronic medical records.

Conclusions

In this ERICO study, the non-administration or suspension of one or more medications occurred in 51.2% of the sample. Individuals aged 65 or older and those with unstable angina diagnosis presented a higher probability of the non-administration of one or more medications. Adequate medical chart registry is still challenging and may present an additional opportunity to improve the quality of care.

Author contributions

Conception and design of the research and Obtaining financing: Bensenor IM, Goulart AC, Lotufo PA, Santos IS; Data acquisition, Statistical analysis and Writing of the manuscript: Santos RCO, Santos IS; Analysis and interpretation of the data: Santos RCO, Santos IS; Critical revision of the manuscript for intellectual content: Bensenor IM, Goulart AC, Lotufo PA.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Study Association

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*Supplemental Materials

For additional information, please click here.

Neck Circumference and 10-Year Cardiovascular Risk at the Baseline of the ELSA-Brasil Study: Difference by Sex

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Abstract

Background: **Neck circumference (NC), an indirect measure of upper-body subcutaneous adipose tissue, has been pointed out as an independent predictor of cardiometabolic diseases.**

Objectives: **To assess the association between NC and 10-year cardiovascular risk in men and in women.**

Methods: **Cross-sectional analysis of 13,920 participants of the (baseline) Longitudinal Study of Adult Health (ELSA-Brasil). The association between NC (used as continuous variable and grouped into quartiles) and the 10-year cardiovascular risk was estimated by the Framingham Global Risk Score and analyzed by generalized linear models after adjustments for sociodemographic characteristics, health behaviors, body mass index and waist circumference. The significance level adopted was 5%.**

Results: **Mean NC was 39.5 cm (SD± 3.6) in men and 34.0 cm (SD±2.9) in women. After adjustments, a one-centimeter increase in NC was associated with an increment of 3% (95%CI1.02-1.03) and 5% (95% 1.04-1.05) in the arithmetic mean of the 10-year CVD risk in men and women, respectively. Men and women in the last quartile showed an increment of 18% (95%CI 1.13-1.24) and 35% (95%CI 1.28-1.43), respectively in the arithmetic mean of the 10-year CVD risk, after adjustments.**

Conclusions: **We found a positive, independent association between NC and the 10-year cardiovascular disease risk. NC may contribute to the prediction of cardiovascular risk, over and above traditional anthropometric measures. (Arq Bras Cardiol. 2020; 115(5):840-848)**

Keywords: **Cardiovascular Diseases; Risk Factors; Gender; Adiposity; Cardiovacular Risk.**

Introduction

Evidence has shown that the localization of adipose tissue is important to determine health risk.[1] It is known that upper-body adiposity is more strongly associated with cardiovascular disease (CVD), insulin resistance and type 2 diabetes as compared with lower-body adiposity.[2] In addition, independently of other measures of adiposity, abdominal visceral fat seems to be associated with increased cardiometabolic risk,[3] and this association is stronger than abdominal subcutaneous fat.[4]

However, the presence of abdominal visceral fat does not explain all the variation between cardiometabolic risk models, suggesting that fat deposition in other compartments may be also relevant.[5] The interest in the study of the metabolic risk associated with upper-body subcutaneous fat, in particular with subcutaneous neck fat, has grown.[6]

Neck circumference (NC), a simple and practical anthropometric measure, is consider an indirect indicator of subcutaneous adipose tissue accumulation in the upper part of the body.[7] It has been suggested that NC represents an additional cardiometabolic risk, independently of other adiposity measures.[5] Results of sectional analysis showed that NC was positively associated with metabolic syndrome,[8] hyperinsulinemia,[9] elevated blood pressure[10] and many cardiometabolic risk factors,[11] after adjustment for abdominal and total body fat. Baseline results of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) also confirmed the positive association between NC and cardiometabolic risk factors.[12] For this reason, an elevated NC has been considered a cardiovascular risk factor[13] and proposed as an additional non-invasive measure in cardiovascular risk prediction.[14]

The Framingham Global Risk Score (FGRS), designed to predict the 10-year[15] CVD risk, has been used to identify

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individuals at greater cardiovascular risk and guide the clinical practice.[16] Considering that NC has been shown to be more strongly associated with metabolic syndrome in men and with arterial hypertension in women,[17] the present study investigated whether NC is associated with 10-year CVD risk, estimated by the FGRS, in men and in women separately. We investigated the hypothesis that the higher the NC the greater the 10-year CVD risk, and that this association, with different magnitude to men and women, is independent of body mass index (BMI) and waist circumference (WC)..

Methods

This was a cross-sectional analysis of baseline data obtained from the ELSA-Brasil. ELSA-Brasil is a multicenter cohort study of active and retired civil servants, aged from 35 to 74 years, from education and research institutions located in six capital cities of Brazil – Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo and Vitoria. The ELSA-Brasil aims to investigate the factors associated with the development and progression of CVD and diabetes. The cohort was composed of both volunteers (76%) and participants actively recruited (24%). Efforts have been made to recruit similar proportions of men and women, as well as predefined proportions of age groups and occupational categories. Exclusion criteria were willingness to leave the institution, pregnant women, or pregnancy in the last four months, severe cognitive or communication impairment, and retired individuals living outside the metropolitan area.[18] At baseline (2008-2010), a total of 15,105 participants were included, 54.4% of them were women, 52.2% self-reported as white race, and 52.7% had university education.[19] Details of design and cohort characteristics of the ELSA-Brasil study can be found in previous publications.[18,19]

Data were obtained by face-to-face interview, anthropometric measurements and tests performed by trained experts, using standardized instruments and procedures. The ELSA-Brasil was approved by the ethics committees of the institutions involved, and all participants signed and informed consent form.

For the purpose of this study, patients with previous CVD (acute myocardial infarction, heart failure, stroke and cardiac revascularization surgery, n=26), and patients with missing data regarding CVD (n=26), NC (n=11), FGRS (n=28) and covariables (n=382) were excluded. The final analytical sample included 13,920 individuals.

Response Variable

The (continuous) response variable was the 10-year risk of developing one of the following cardiovascular events – coronary artery disease, cerebrovascular events, peripheral artery disease and heart failure – estimated by the FGRS.[15] This score is sex-specific and composed of: age (years), current smoking, total serum cholesterol level, HDL-cholesterol, systolic arterial pressure, diabetes and use of anti-hypertensive drugs.[15]

Individuals who ever smoked at least 100 cigarettes (or five packs of cigarettes) and current smokers were classified as "smokers", and the others as "non-smokers". Blood pressure was measured using an Omron® automated blood pressure monitor following standard procedures. Three measures were taken and the mean of the second and third readings was considered for analysis.[20] Diabetes was defined as self-reported diagnosis of diabetes, use of hypoglycemic agents in the last two weeks, fasting blood glucose pressure ≥7.0 mmol/L, plasma glucose of 11.1 mmol/L two hours after a standard oral glucose load, or glycated hemoglobin (HbA1c) level ≥ 6,5%. Blood glucose level was determined by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA), and HbA1c was measured by liquid chromatography (Bio-Rad Laboratories, Hercules, California, USA). The use of antihypertensive and antidiabetic agents was assessed by patients' self-report, and information in drug prescriptions and drug labels. Total cholesterol and HDL cholesterol levels were measured using the ADVIA 1200 Siemens®. All laboratory parameters were determined in the same laboratory, after a median fasting time of 12 hours (10h – 14h).[21]

Explanatory Variable

NC was measured using an inelastic tape (mm) above the cricothyroid cartilage, perpendicular to the long axis of the neck, with participant in sitting position. NC was used as continuous variable (cm) and categorized into quartiles.

Covariables

The covariables included were sociodemographic data – age range (35-44, 45-54, 55-64, 65-74 years), used in the population description and as continuous variable in the regression models; self-reported race/skin color (white, *pardo*, black, yellow, indigenous) and educational attainment (undergraduate degree, high school, completed elementary school, some elementary school).

Health-related behaviors were also analyzed as covariables. Self-reported weekly use of alcohol was assessed considering number of doses and types of beverages and classified into 'no consumption', 'moderate' and 'heavy drinking'. High consumption was defined as ≥ 210g for men and ≥ 140g for women, and any consumption below these values was considered moderate. Leisure-time physical activity was assessed using the long version of the International Physical Activity Questionnaire (IPAQ), and categorized by the sum of the time spent in each activity, weighed by the activity intensity (high: ≥ 3000 MET-min/week, moderate: 600-3000 MET-min/week, low: <600 MET-min/week).[22]

Body mass index (BMI) (kg/m^2) and waist circumference (WC) (cm) were also assessed and described as categorical variables. BMI values were categorized into normal weight (BMI<25), overweight (BMI ≥25 and <30) and obesity (BMI≥30). WC was measured at the midpoint between the lowest rib and the iliac crest[24] and classified as adequate or inadequate (≥88 cm for women and ≥102 cm for men).[23] Both measures were used as continuous variables in the regression models. Measures were taken in fasting conditions using standard procedures.

Statistical Analysis

Characteristics of the study population and components of the FGRS were described as absolute and relative frequencies (categorical variables), and mean and standard deviation (SD)

(continuous variables with normal distribution) or median and interquartile range (continuous variables without normal distribution). Normality of data distribution was tested by the Shapiro-Wilk test. The Pearson's chi-square test was used for comparison of frequencies, the unpaired t-test used for comparison of means and the Mann-Whitney test used for comparison of medians. The one-way ANOVA test followed by the Bonferroni post-hoc test was performed to detect significant differences in NC values by 10-year cardiovascular risk (low risk <6%, intermediate ≥ 6% and ≤ 20% and high >20%). The level of significance adopted was 5%.

The magnitude of the association between NC and 10-year CVD risk was estimated using generalized linear models (GLM), which are a flexible generalization of ordinary linear regression models, that allow for non-normal errors and default link function.[25] The GLM for the gamma distribution and logarithmic function was used. The results represent the arithmetic mean ratio (AMR), obtained by the exponentiation of the regression coefficients.

First, the gross association between NC (continuous) and the 10-year risk for CVD (model 0) was estimated. Then, the multivariate models were calculated, with successive adjustments for age, race/skin color, and educational attainment (Model 1), physical activity and alcohol consumption (model 2), BMI (model 3) and WC (model 4). In addition, in the estimation of the magnitude of the association of NC and the 10-year cardiovascular risk, NC was categorized in quartiles, and the multivariate analysis performed using the same sequence of adjustments. All analyses were stratified by sex.

Sensitivity analysis was performed by exclusion of those participants who were taking hypolipemic agents, corticoids, contraceptive pills, or women in hormone replacement therapy. The use of medications was assessed by self-report, drug prescriptions and drug labels on the day of the interview.

Statistical analysis was performed using the Stata software version 13 (Stata Corporation, College Station, USA).

Results

Data of 13,920 participants were analyzed. Mean age was 51.7 years (SD ± 7.6), and 55% were women. Most participants reported a white race/skin color and completed higher education. The prevalence of overweight was higher in men, whereas the prevalence of obesity higher in women. An inadequate WC was more frequent in women than men (44.3% vs, 25.5%). Mean NC was 39.5 ± 3.6 cm in men and 34 ±2.9 cm in women (Table 1).

Results of the FGRS components are described in Table 2. Mean NC, grouped in risk categories (low risk <6%, intermediate ≥6% and ≤20%, and high risk >20%), increased with the increment of the 10-year CVD risk in both sexes (Figure 1).

Table 3 shows the results of the regression models with the variable NC. A one-centimeter increase in NC was associated with an increment of 5% (95% 1.04-1.05) in the mean 10-year CVD risk (Model 0). This association remained statistically significant after all adjustments (AMR: 1.03; 95%CI:1.02-1.03) (Model 4). Among women, the increase of one centimeter in NC was associated with an increment of 11% in the mean 10-year CVD risk (95%CI: 1.10-1.12) (Model 0). After all adjustments (Model 4), the one-centimeter increase in NC was associated with an increment of 5% (95%CI: 1.04 – 1.06) in the mean 10-year CVD risk (Table 3).

Results of the regression models using the NC grouped into quartiles are presented in Table 4. In all models, there was a gradual increase in the arithmetic mean of the 10-year CVD risk from the first to the fourth quartile, achieving an increase of 18% in those located in the last quartile (95%CI: 1.13-1.24) among men and of 35% (95%CI: 1.28-1.43) among women (Model 4).

Analyses of sensitivity showed that the exclusion of participants using hypolipemic agents, corticoids, and of women taking contraceptive agents or in hormone replacement therapy did not change the results.

Discussion

The findings of the present study indicate a direct association between NC and 10-year CVD risk, independently of others potential cofounding factors and body adiposity measures, particularly BMI and WC, in individuals free of CVD. This was corroborated by the results of the analysis of NC grouped into quartiles, which indicated a dose-response gradient. The magnitude of the associations between NC (both continuous and in quartiles) and the 10-year CVD risk was higher in women than men.

Our results pointed to a direct association between NC and the 10-year CVD risk. We found only one study that investigated the relationship between NC and the risk for CVD in 10 years estimated by the Framingham coronary heart disease risk score. This study, that included only 100 individuals free of CVD, pointed out a positive correlation between NC and the 10-year CVD risk.[14] However, previous studies have indicated a positive independent association between NC and intima-media thickening (IMT),[26] a marker of subclinical atherosclerosis, predictive of cardiovascular risk. The baseline analysis of the ELSA-Brasil study also showed an association between NC and IMT, but did not find an association between NC and coronary artery calcification, another measure of subclinical atherosclerosis.[27,28]

The mechanisms of how neck adipose tissue can contribute to the occurrence of cardiovascular outcomes are not well established.[29] Neck adipose tissue is considered an ectopic fat depot,[1] which may explain part of the systemic effect. The formation of ectopic fat depots in several organs, including subcutaneous fat in neck, result from deposition of triglycerides in non-adipose tissue cells that normally contain small amounts of fat and seem relevant for cardiovascular risk,[30,31] especially ectopic fat depositions in the pericardium and liver.[32] Dysfunctional activity of ectopic fat is associated with oxidative stress, endothelial dysfunction, increased secretion of pro-inflammatory cytokines and reduced release of the anti-inflammatory adiponectin, leading to chronic inflammation and altered lipid metabolism[33] involved in the atherosclerotic process. Evidence has supported the association of greater NC and inflammatory markers, notably plasma proteins of the complement pathway, (C3 and C4), C-reactive protein, interleukin-6 and tumor necrosis factor alpha (TNF-α),[34] and markers of endothelial dysfunction such as E-selectin.[9] Also, ectopic fat seems to be a key element that differs metabolically healthy from metabolically non-healthy obese subjects.[26]

Table 1 – Characteristics of the study population by sex, ELSA-Brasil, 2008-2010

Characteristics	Men (n=6,261)		Women (n=7,659)		p value
	n	%	n	%	
Age (years)					
35-44	1,481	23.7	1,708	22.3	0.009*
45-54	2,518	40.2	3,086	40.3	
55-64	1,634	26.1	2,165	28.3	
65-75	628	10.0	700	9.1	
Self-reported race/skin color					
White	3,299	52.7	3,981	52	<0.001*
Pardo	1,888	30.2	2,041	26.7	
Black	870	13.9	1,351	17.6	
Yellow	120	1.9	225	2.9	
Indigenous	84	1.3	61	0.8	
Educational attainment					
Completed higher school	3,162	50.5	4,245	55.4	<0.001*
Completed high school	2,094	33.5	2,744	35.8	
Completed elementary school	516	8.2	396	5.2	
Some elementary school	489	7.8	274	3.6	
Alcohol consumption					
Moderate	3,994	63.8	4,673	61.0	<0.001*
None/former user	1,486	23.7	2,718	35.5	
Heavy drinking	781	12.5	268	3.5	
Leisure-time physical activity					
Mild	4,596	73.4	6,100	79.7	<0.001*
Moderate	1086	17.4	1,143	14.9	
High	579	9.2	416	5.4	
Body mass index (BMI) (Kg/m^2)					
Normal weight	2,179	34.8	3,040	39.7	<0.001*
Overweight	2,819	45.0	2,756	36.0	
Obesity	1,263	20.2	1,863	24.3	
Waist circumference (cm)					
Adequate	4,662	74.5	4,270	55.7	<0.001*
Inadequate	1,599	25.5	3,389	44.3	
Neck circumference (cm), mean (±SD)	39,5	(±3.6)	34,0	(±2.9)	<0.001†
10-year cardiovascular risk score (%), median (1st/3rd quartile)	11,3	(6.2- 19.9)	4,4	(2.4-8.3)	<0.001‡

BMI: normal weight < 24.9 kg/m²; overweight: 25.0 – 29.9 kg/m²; Obesity: ≥ 30 kg/m².
*Waist circumference: Inadequate: ≥ 88 cm (women) and ≥ 102 cm (men). Adequate < 88 cm (women) and < 102 cm (men). *Pearson's chi-square test, † unpaired t-test, ‡ Mann-Whitney test.*

Table 2 – Components of the Framingham Global Risk Score in men and women, ELSA-Brasil, 2008-2010

Risk factors	Men (n=6.261)		Women (n=7.659)		p value
Age (years), mean (±SD)	51.7	±11.5	51.8	±10.0	0.53†
Total cholesterol (mg/dL), median (1st and 3rd quartiles)	210	(185-239)	214	(189-241)	<0.001‡
HDL cholesterol (mg/dL), median (1st and 3rd quartiles)	49	(43-57)	60	(51-70)	<0.001‡
Use of antihypertensive agents, n (%)	1.687	26.9	2.071	27.0	0.90*
Systemic arterial pressure, mean (±SD)	125.3	±20.9	117.2	±18.9	<0.001†
Diabetics, n (%)	1.200	19.2	1.068	14.0	<0.001*
Smokers, n (%)	889	14.4	927	12.1	<0.001*

**Pearson chi-square test, † unpaired t-test, ‡ Mann-Whitney test.*

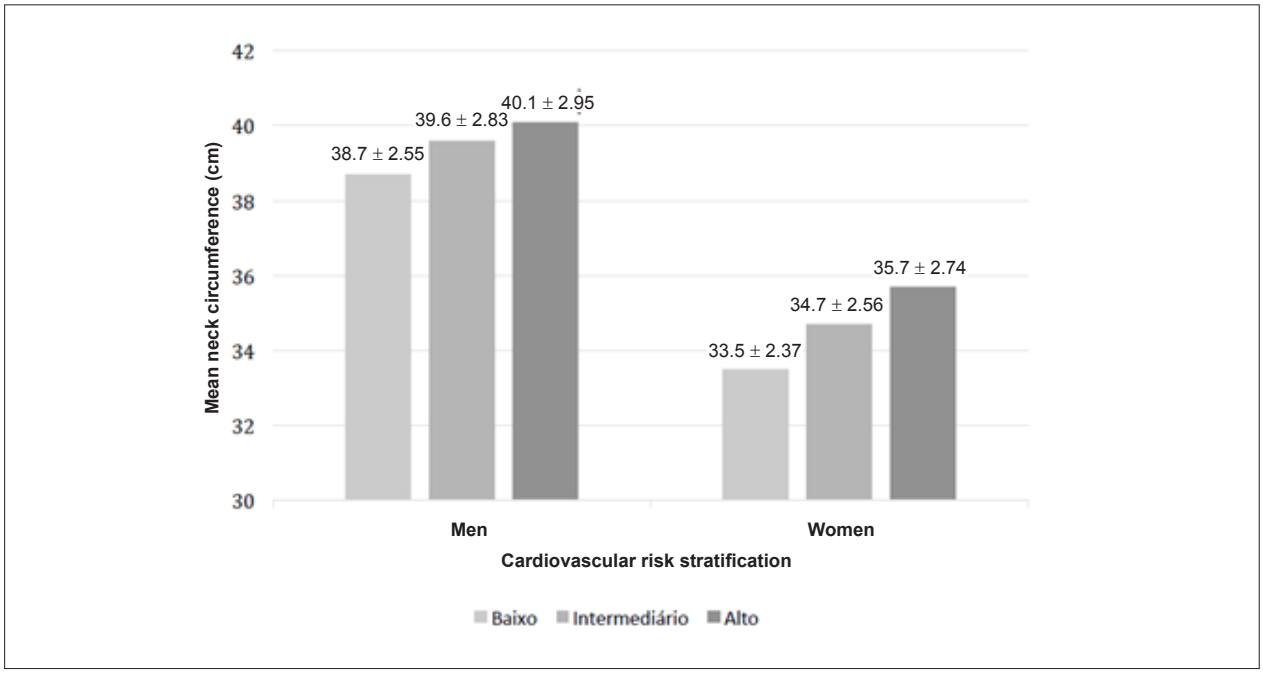

Figure 1 – *Mean (cm) neck circumference by 10-year cardiovascular disease risk stratification in men and women, ELSA-Brasil, 2008-2010. Low risk: <6%; intermediate risk: ≥ 6% and ≤ 20%, high risk: > 20%. One-way ANOVA and Bonferroni post-hoc test.*

In addition, most of blood vessels, including carotid arteries, are involved by the perivascular adipose tissue, which helps in the vascular tone and endothelial function regulation.[35] As this tissue increases and becomes dysfunctional, there seems to be a direct pro-inflammatory effect on the carotid arteries, which may explain the increased cardiovascular risk related to the increment in NC.30[30] It is worth pointing out that NC is a renowned risk factor for sleep obstructive apnea, which, in turn, is associated with increased risk for CVD and type 2 diabetes.[36]

Our findings revealed stronger associations between NC and 10-year CVD risk in women compared with men. In agreement with this, results of the Framingham Heart Study showed a strong association between elevated NC and dyslipidemia and hypertension among women,[11] and an increased risk of developing diabetes associated with increased NC was reported in women.[37] On the other hand, NC was more strongly associated with the risk for coronary artery disease in 10 years, estimated by the Framingham Coronary Artery Disease Risk Score in men than women.[14] A similar association between NC and cardiometabolic changes between men and women has also been reported. [10]

It is possible that differents patterns of neck fat accumulation,[38] subcutaneous fat distribution,[39] and metabolism of free fatty acids[11] explain the differences between genders in the present study and in others. In addition, while women are more likely to develop subcutaneous fat, Men have a higher tendency to accumulate abdominal visceral fat.[40] Upper-body subcutaneous fat delivers more free acids to the systemic circulation as compared with visceral fat,[41] and

Table 3 – Multivariate analysis of the association between neck circumference and the risk of developing cardiovascular disease in 10 years in men and women, ELSA-Brasil, 2008-2010

	Men	Women
	AMR (95%CI)	AMR (95%CI)
Model 0	1.05 (1.04 – 1.05)	1.11 (1.10 – 1.12)
Model 1	1.06 (1.05 – 1.06)	1.09 (1.08 – 1.10)
Model 2	1.06 (1.05 – 1.06)	1.09 (1.08 – 1.10)
Model 3	1.03 (1.02 – 1.04)	1.07 (1.06 – 1.08)
Model 4	1.03 (1.02 – 1.03)	1.05 (1.04– 1.06)

AMR (95%CI): arithmetic mean ratio obtained by generalized linear models and respective 95% confidence intervals. Model 0: unadjusted arithmetic mean ratio; Model 1: Adjusted for age, self-reported race/skin color and schooling; Model 2: Model 1 + adjusted for alcohol consumption and leisure-time physical activity; Model 3: Model 2 + adjusted for body mass index; Model 4: Model 3 + waist circumference.

Table 4 – Multivariate analysis of the association between neck circumference grouped into quartiles and the 10-year cardiovascular disease risk in men and women, ELSA-Brasil, 2008-2010

	Men AMR (95%CI)				Women AMR (95%CI)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Model 0	1.00	1.14(1.08-1.21)	1.21(1.14-1.28)	1.42(1.34-1.51)	1.00	1.23(1.16-1.31)	1.59(1.49-1.70)	2.04(1.91-2.18)
Model 1	1.00	1.14(1.10-1.19)	1.30(1.25-1.35)	1.52(1.47-1.58)	1.00	1.16(1.11-1.21)	1.37(1.31-1.43)	1.78(1.71-1.86)
Model 2	1.00	1.14(1.10-1.18)	1.28(1.24-1.33)	1.49(1.43-1.54)	1.00	1.16(1.11-1.20)	1.36(1.30-1.41)	1.76(1.69-1.84)
Model 3	1.00	1.07(1.04-1.11)	1.16(1.11-1.21)	1.24(1.18-1.30)	1.00	1.10 (1.06-1.15)	1.25(1.19-1.31)	1.50(1.42-1.58)
Model 4	1.00	1.05(1.02-1.09)	1.12(1.08-1.17)	1.18(1.13-1.24)	1.00	1.06(1.02-1.11)	1.17(1.12-1.23)	1.35(1.28-1.43)

AMR (95%CI): arithmetic mean ratio obtained by generalized linear models and respective 95% confidence intervals Q1, Q2, Q3, Q4: Interquartile range. Model 0: unadjusted arithmetic mean ratio; Model 1: Adjusted for age, self-reported race/skin color and schooling; Model 2: Model 1 + adjusted for alcohol consumption and leisure-time physical activity; Model 3: Model 2 + adjusted for body mass index; Model 4: Model 3 + waist circumference.

increased levels of free fatty acids in plasma contribute to higher insulin resistance, increased secretion of very low density lipoprotein and triglycerides, and induction of oxidative stress and blood pressure elevation.[11,41] It is also known that neck adipose tissue is distributed into three different compartments – posterior, subcutaneous, and perivertebral compartments – that contribute differently to metabolic risk.[38] While women tend to accumulate subcutaneous neck fat, greater neck fat accumulation in the other compartments has been observed in men.[30] Posterior and subcutaneous neck adipose tissue seem to be more associated with metabolic syndrome in women.[38]

In the present study, calculation of the 10-year CVD risk showed a lower median score in women than men, which may be explained by higher HDL cholesterol levels, lower systolic blood pressure, and lower prevalence of diabetes and smoking habits. This result corroborates the differences between gender in the exposure to cardiovascular disease risk factors,[30,38,40,41] and greater likelihood of women to seek out health care than men.[42]

Results of the present study indicate that increased NC may contribute to the prediction of the 10-year CVD risk, independently of BMI and WC, which are the most studied measures of adiposity. Some authors have suggested advantages of NC over WC, since the former is simple, easy-to-perform and less likely to measuring errors.[43] It is interesting to note that our findings suggest that NC may be more strongly associated with 10-year CVD risk, since after all adjustments, the increase of 1 cm in NC was associated with a greater increment in the arithmetic mean of CVD risk as compared with the increase of 1cm in WC [women: 5% (AMR:1.05; 95%CI:1.04-1.06) versus 3% (AMR:1.03; 95%CI:1.01-1.02) and men: 3% (AMR:1.03; 95CI%:1.02-1.03) versus 1% (AMR: 1.01; 95%CI:1.01-1.02), respectively]. This is reinforced by a recent meta-analysis showing an association of NC with coronary artery disease.[44]

Strengths of our study include the sample size, the methodological rigor, adjustment for potential cofounding factors, and the investigation of the association between NC and 10-year CVD risk, measured by the FGRS, which is a known cardiovascular risk predictor already used in clinical practice and, similar to NC, does not include invasive measurements.

Limitations of the study include the cross-sectional nature of the analysis, the lack of validation of the FGRS for the Brazilian population, and the fact that NC was measured only once. The presence of residual confounding cannot be excluded.

Conclusion

Increased NC was positively associated with the 10-year CVD risk, regardless of measures of total and visceral adiposity. These findings suggest that NC may contribute to the prediction of cardiovascular risk, over and above traditional anthropometric parameters, such as BMI and WC. Longitudinal analysis will contribute to clarify the causal role of NC in the cardiovascular risk.

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Author contributions

Conception and design of the research: Silva AAGO, Araujo LF, Diniz MFHS, Barreto SM, Giatti L; Acquisition of data: Diniz MFHS, Lotufo P, Bensenor I, Barreto SM, Giatti L; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Silva AAGO, Araujo LF, Giatti L; Obtaining financing: Diniz MFHS, Lotufo P, Bensenor I, Barreto SM; Critical revision of the manuscript for intellectual content: Diniz MFHS, Lotufo P, Bensenor I, Barreto SM, Giatti L.

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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Mortality Due to Acute Myocardial Infarction in Brazil from 1996 to 2016: 21 Years of Disparities in Brazilian Regions

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Abstract

Background: Acute myocardial infarction (AMI), the leading cause of death in Brazil, has presented regional disparities in mortality rate time trends in recent years. Previous time trend studies did not correct for cause-of-death garbage codes, which may have skewed the estimates.

Objective: To analyze regional and gender-based inequalities in the AMI mortality trend in Brazil from 1996-2016.

Methods: A 21-year time series study (1996-2016). Data are from the Mortality Information System and population estimates from the Brazilian Institute of Geography and Statistics. Corrections of deaths due to ill-defined causes of death, garbage codes, and underreporting were made. The time series broken down by major geographic regions, gender, capital cities, and other municipalities was analyzed using the linear regression technique segmented by Jointpoint. Statistical significance level was set at 5%.

Results: In the period, mortality decreased more sharply in women (-2.2%; 95% CI: -2.5; -1.9) than in men (-1.7%; 95% CI: - 1.9; -1.4) and more in the capital cities (-3.8%; 95% CI: - 4.3; -3.3) than in other municipalities (-1.5%; 95% CI: - 1.8; -1.3). Regional inequalities were observed, with an increase for men living in other municipalities of the North (3.3; 95% CI: 1.3; 5.4) and Northeast (1.3%; 95% CI: 1.0; 1.6). Statistical significance level was set at 5%. Mortality rates after corrections showed a significant difference in relation to the estimates without corrections, mainly due to the redistribution of garbage codes.

Conclusions: Although AMI-related mortality has decreased in Brazil in recent years, this trend is uneven by region and gender. Correcting the numbers of deaths is essential to obtaining more reliable estimates. (Arq Bras Cardiol. 2020; 115(5):849-859)

Keywords: Myocardial Infarction; Epidemiology; Mortality; Time Series Studies; Myocardial Ischemia.

Introduction

In recent decades, cardiovascular diseases (CVD), and specifically ischemic heart disease (IHD) have become the primary causes of death worldwide, although age-standardized mortality rates have dropped.[1]

When conducting mortality studies, one must to pay attention to the quality of death records which, in Brazil, differs between geographic regions and between municipalities, with it being better in the capital cities. Some indirect indicators of standard data quality are the proportion of deaths from ill-defined causes of death, use of garbage codes, underreporting, and ignored age and gender. They reflect difficulties in diagnosing the diseases that caused death, accessing health services, filling out the death certificate, and/or entering data into the system.[2] One way to solve this problem and properly estimate mortality rates is to make corrections that will allow greater comparability between regions over time.[1,3,4]

This study aims to analyze regional and gender inequalities in the AMI-related mortality trend in Brazil from 1996-2016, correcting deaths from ill-defined causes, garbage codes, and underreporting.

Methods

Time series (21 years: 1996 to 2016) of AMI-related mortality in the capital cities and cities and towns in the countryside (other municipalities) of large Brazilian regions were analyzed. Annual data on AMI-related deaths (code I21. ICD 10) were obtained from the Mortality Information System (SIM in Portuguese) on the DATASUS website - Department of Informatics of the Unified Health System (http://datasus.saude.gov.br) and population estimates from the Brazilian Institute of Geography and Statistics. As publicly available secondary data, the study was exempted from approval by a research ethics committee in accordance with CONEP Resolution

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510 of April 7, 2016. The SIM has national coverage and, in recent years, it has greatly improved the quality of its database between Brazilian regions and municipalities. To make a more meaningful comparison between regions and over the time period covered by this study, we corrected the numbers obtained from the SIM regarding ill-defined causes of death, use of garbage codes, and underreporting using procedures adopted in other studies.[1,3,5]

Figure 1 outlines the procedures used to correct AMI-related deaths for ill-defined causes, use of garbage codes, and underreporting.

The ill-defined causes of death are those in which the cause of death has not been established and have therefore been classified in codes R00-R99 from Chapter XVIII of ICD-10: "Unclassified Symptoms, Signs, and Abnormal Clinical and Laboratory Findings Not Elsewhere Classified".[2,5,6] The redistribution of ill-defined causes of death (Correction 1) was conducted in the following manner: for each year and region, correction factors (CF1) were calculated using equation (1) for each gender and for each five-year age range. To calculate the redistribution of deaths, the number of deaths was multiplied by the CF1.[3,7]

$$(FC1) = \frac{Total\ deaths - \ deaths\ by\ external\ causes}{(total\ deaths - deaths\ by\ external\ causes) - deaths\ by\ ill - defined\ causes}$$

Deaths with garbage codes are those in which ICD 10 codes are used that are nonspecific and do not precisely identify the underlying cause of death.[5] The following garbage codes are used in cardiology: I50, I46, I47.0, I47.1, I47.2, I47.9, I48, I49.0, I49.9, I51.4, I51.5, I51.6, I51.9 and I70.0. To proceed with Correction 2 for garbage codes, deaths with cardiologic garbage codes were added to deaths recorded as being caused by AMI in the following proportion: 70% of deaths per 150 in people between 30-60 years of age and 80% for people over 80 years of age, along with other causes 75% (30-60 years of age) and 60% (older than 60 years of age).[5]

To correct for underreported death (Correction 3), meaning deaths that were neither recorded in the Civil Registry System nor in the SIM, the correction factors estimated for Brazil, region, and states,[7] which are readily available in DATASUS, were used.[6] Correction 3 was made by multiplying the underreporting correction factor for deaths in other municipalities. This correction was not carried out in the state capitals, as studies have shown that death records in these cities are reliable.[2,3,5] With respect to the periods from 1996 to 1999 and from 2014 to 2016, for which correction factors were not available, values for the next closest years were used.

Corrections due to ignored gender and age were not conducted in this study, since both categories presented reliable numbers during the studied period.[4]

Mortality rates were calculated and standardized by five-year age groups for adults (20 years of age and over) using the new standard world population as a reference.[8] The standard world population was proposed by the WHO as a way to compare mortality rates between populations with different age groups. Estimates were prepared for each five-year period from 1950 to 2025 based on population censuses and other demographic sources, then adjusted for enumeration errors. From there, an average age structure of the world population was constructed. The specific mortality rates by age groups were applied to the respective population contingents of the standard population. Consequently, the number of deaths expected to occur in each age group was obtained, provided the population studied had the same age composition as the standard population. The standardized mortality rate was obtained by dividing the total number of deaths expected for the standard population. which can then be compared to other populations, and any differences found are not due to variations in the age structure.[8,9]

The time trend analysis of the corrected mortality rates as standardized by region, capital cities and other municipalities, and gender was performed by segmented linear regression using Joinpoint version 4.6.0.0,[10,11] a method used in other AMI time trend studies.[12,13] Models were adjusted with change points in the temporal evolution of the death rates (joint points) ranging from zero (trend represented by a single line segment) to three. Annual percentage changes (APC) were calculated for the period under analysis. Statistical significance level was set at 5%.

Results

A comparison of AMI-related mortality rates in all regions of Brazil, with and without corrections for ill-defined causes of death (Correction 1), garbage codes (Correction 2), and underreporting (Correction 3) by female and male is shown in Tables 1 and 2. respectively. Larger increases were noted after correction for garbage codes, reaching a 92% increase in 1996 among women living in other municipalities of the Central West. The proportional difference in mortality rates with and without corrections, between 1996 and 2016, showed little discrepancy between estimates in the capital cities. However, relative to other municipalities, an important disparity could be seen between them (Table 2). Figure 2 shows that not only does the magnitude of mortality rates increase after corrections, but the time trend slope also changes and percentages of correction are higher at the beginning of the period than at the end. Table 3 shows an increase in the frequency of garbage codes in Brazilian regions.

In general, trends in corrected AMI-related mortality rates are declining. Capital cities, with higher mortality rates at the beginning of the period, showed a more pronounced decline and, consequently, lower rates in recent years. Mortality rates in men were higher than those in women throughout the analyzed period, with both falling. Only mortality rates of men living in other municipalities of the North and Northeast showed an upward trend. At the beginning of the series, mortality rates were higher in the Southeast and South and, due to the more pronounced decline in these regions, their values began to be lower at the end of the period than in the North and Northeast (Figure 3). A percentage difference of -43.6% was observed between 1996 and 2016 in Brazil, with it being higher in the South (-85.1%). The Northeast and North, which in 1996 had the lowest rates, began to reflect the highest rates in 2016 (Table 4).

The segmented regression analysis indicated a decline in mortality rates in all regions except the Northeast (Table 5). The South (APC = -3.4%; 95% CI: - 3.8; -3.0) and Southeast (APC = -3.3%; 95% CI: - 3.9; -2.7) showed the highest percentage

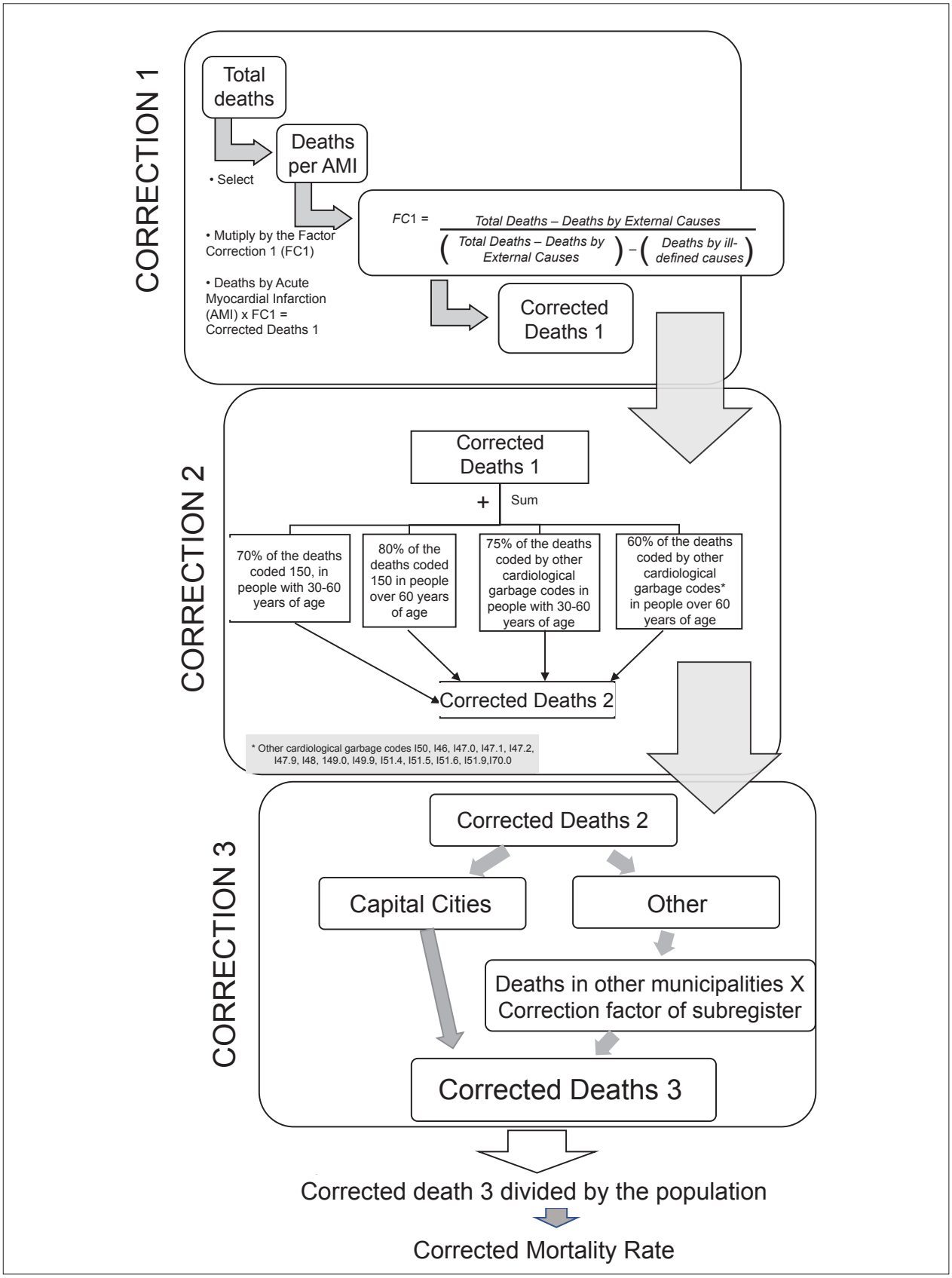

Figure 1 – *Procedures for the correction of the number of deaths regarding ill-defined causes, use of garbage codes, and subregisters.*

Table 1 – Comparison of AMI-related mortality rates in Brazilian regions with and without corrections for ill-defined causes of death, garbage codes, and underreporting in women

Region	Location	Year	Standardized rates				% Changes			
			Not corrected	Correction 1	Correction 2	Correction 3	% Change 1	% Change 2	% Change 3	Total % change
Brazil	Capital cities	1996	79.1	82.9	127.1	127.1	5	53	0	61
		2016	42.7	43.7	65.2	65.2	2	49	0	53
		Dif%	-46	-47	-49	-49				
	Other municipalities	1996	52.9	64.3	105.4	116.5	21	64	11	120
		2016	53.6	56.2	85.6	89.4	5	52	4	67
		Dif%	1	-12	-19	-23				
North	Capital cities	1996	50.1	57.6	98.7	98.7	15	71	0	97
		2016	38.1	40.9	62.7	62.7	7	53	0	64
		Dif%	-24	-29	-36	-36				
	Other municipalities	1996	22.5	37.6	57.7	83.4	67	54	45	271
		2016	51.4	55.4	83.1	97.7	8	50	18	90
		Dif%	129	47	44	17				
Northeast	Capital cities	1996	56.0	59.1	105.5	105.5	6	79	0	88
		2016	42.5	43.8	63.8	63.8	3	46	0	50
		Dif%	-24	-26	-40	-40				
	Other municipalities	1996	25.4	47.5	68.4	87.9	87	44	28	246
		2016	60.2	64.6	95.7	104.2	7	48	9	73
		Dif%	137	36	40	19				
Central West	Capital cities	1996	52.4	55.2	99.5	99.5	5	80	0	90
		2016	38.5	38.8	54.1	54.1	1	39	0	41
		Dif%	-27	-30	-46	-46				
	Other municipalities	1996	46.6	54.8	105.2	120.4	18	92	14	158
		2016	54.4	55.6	83.1	90.0	2	49	8	66
		Dif%	17	2	-21	-25				
Southeast	Capital cities	1996	91.7	95.7	140.1	140.1	4	46	0	53
		2016	46.4	47.2	72.5	72.5	2	54	0	56
		Dif%	-49	-51	-48	-48				
	Other municipalities	1996	66.4	74.0	128.0	134.0	11	73	5	102
		2016	47.9	50.4	79.7	81.8	5	58	3	71
		Dif%	-28	-32	-38	-39				
South	Capital cities	1996	91.9	92.2	130.3	130.3	0	41	0	42
		2016	32.3	32.8	44.1	44.1	2	34	0	37
		Dif%	-65	-64	-66	-66				
	Other municipalities	1996	78.4	86.7	136.4	141.9	11	57	4	81
		2016	44.1	45.4	74.2	76.9	3	63	4	74
		Dif%	-44	-48	-46	-46				

Correction 1: AMI-related mortality rates corrected for ill-defined causes of death. Correction 2: AMI-related mortality rates corrected for garbage codes. Correction 3: AMI-related mortality rates corrected for underreporting.

Table 2 – Comparison of AMI-related mortality rates in Brazilian regions with and without corrections for ill-defined causes of death, garbage codes, and underreporting in men

Region	Location	Year	Standardized rates				% Changes			
			Not corrected	Correction 1	Correction 2	Correction 3	% Changes 1	% Changes 2	% Changes3	Total % changes
Brazil	Capital cities	1996	145.4	153.0	205.1	205.1	5	34	0	41
		2016	86.0	88.9	117.5	117.5	3	32	0	37
		Dif%	-41	-42	-43	-43				
	Other municipalities	1996	86.5	105.2	150.2	167.3	22	43	11	93
		2016	89.4	95.8	131.7	138.4	7	37	5	55
		Dif%	3	-9	-12	-17				
North	Capital	1996	88.6	105.5	154.5	154.5	19	46	0	74
		2016	85.3	92.7	123.3	123.3	9	33	0	44
		Dif%	-4	-12	-20	-20				
	Other municipalities	1996	37.5	62.8	85.9	122.8	68	37	43	228
		2016	88.3	96.7	131.2	153.6	10	36	17	74
		Dif%	136	54	53	25				
Northeast	Capital	1996	101.2	107.1	160.6	160.6	6	50	0	59
		2016	84.9	88.0	119.3	119.3	4	36	0	41
		Dif%	-16	-18	-26	-26				
	Other municipalities	1996	39.9	71.8	95.8	123.9	80	33	29	210
		2016	104.2	113.7	152.6	166.4	9	34	9	60
		Dif%	161	58	59	34				
Central West	Capital	1996	79.0	84.6	136.6	136.6	7	61	0	73
		2016	79.5	80.9	99.9	99.9	2	23	0	26
		Dif%	1	-4	-27	-27				
	Other municipalities	1996	82.9	99.8	154.1	172.8	20	54	12	109
		2016	95.8	99.7	134.5	146.0	4	35	8	52
		Dif%	16	0	-13	-16				
Southeast	Capital	1996	174.7	182.5	235.9	235.9	4	29	0	35
		2016	92.9	95.8	128.0	128.0	3	34	0	38
		Dif%	-47	-48	-46	-46				
	Other municipalities	1996	118.5	134.1	195.1	206.1	13	46	6	74
		2016	88.5	94.7	129.9	133.2	7	37	3	50
		Dif%	-25	-29	-33	-35				
South	Capital	1996	164.6	165.6	208.9	208.9	1	26	0	27
		2016	67.1	68.5	82.3	82.3	2	20	0	23
		Dif%	-59	-59	-61	-61				
	Other municipalities	1996	134.4	149.4	203.7	204.8	11	36	1	52
		2016	83.4	86.7	120.7	121.3	4	39	0	45
		Dif%	-38	-42	-41	-41				

Correction 1: AMI-related mortality rates corrected for ill-defined causes of death. Correction 2: AMI-related mortality rates corrected for garbage codes. Correction 3: AMI-related mortality rates corrected for underreporting.

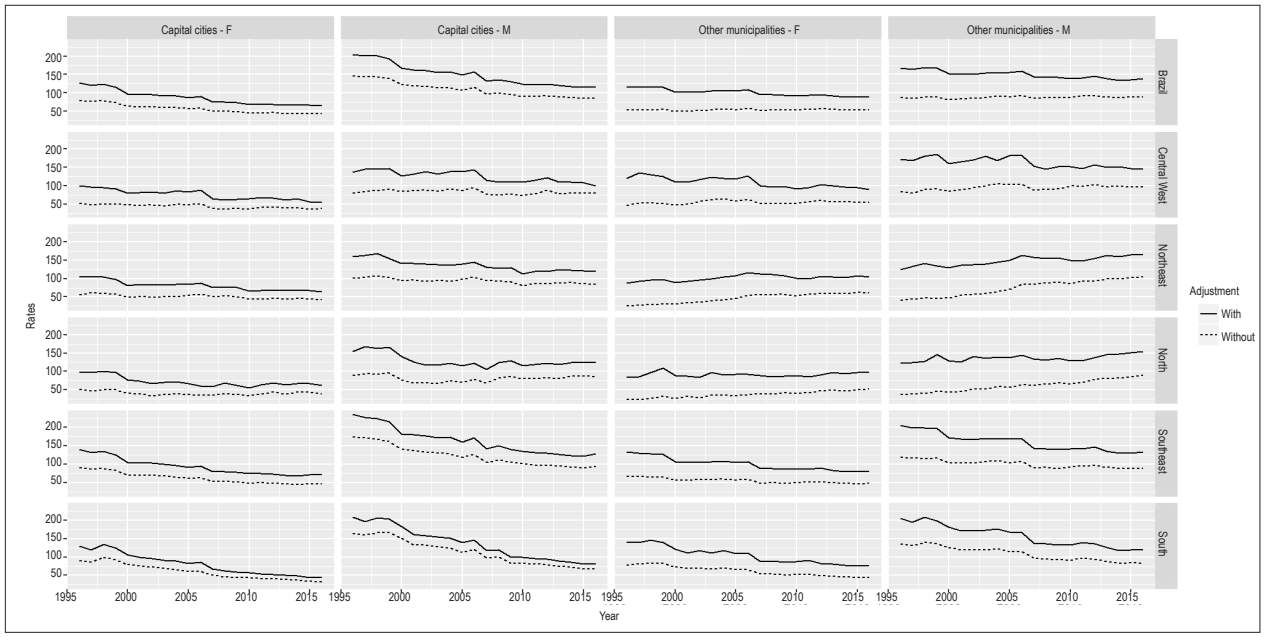

Figure 2 – *Time trends in mortality rates from acute myocardial infarction before (dashed line) and after corrections for ill-defined causes of death, underreporting, and garbage codes (continuous line) in Brazil, regions, capital cities, and other municipalities by gender from 1996 to 2016.*

Table 3 – Frequency of deaths classified with garbage codes for AMI by year/gender/region in Brazil from 1996 to 2016

	North		Northeast		Central West		Southeast		South		Total		
Year	M	F	M	F	M	F	M	F	M	F	M	F	General
1996	883	813	4865	5117	1670	1501	14198	15996	4429	5140	26045	28567	54612
1997	911	797	5056	5175	1816	1696	13429	15240	4181	4881	25393	27789	53182
1998	972	898	5547	5540	1758	1594	13342	15350	4507	5221	26126	28603	54729
1999	1043	863	5379	5367	1827	1492	12632	14569	4098	4691	24979	26982	51961
2000	1046	821	5402	5431	1674	1511	12138	13859	4157	4837	24417	26459	50876
2001	1194	919	5677	5678	1770	1566	11931	13603	3926	4563	24498	26329	50827
2002	1103	900	5783	6109	1963	1668	11649	13821	3915	4784	24413	27282	51695
2003	1184	1002	5871	6141	1974	1623	12100	14002	4047	4703	25176	27471	52647
2004	1183	935	6484	6644	1967	1700	12798	14552	4196	4864	26628	28695	55323
2005	1248	1051	6915	7299	2092	1649	12642	14131	4019	4712	26916	28842	55758
2006	1329	1008	8210	8463	2104	1870	13354	15142	4009	4939	29006	31422	60428
2007	1420	1111	8469	8733	2129	1830	13486	15326	4316	5161	29820	32161	61981
2008	1454	1205	8541	8888	2125	1849	13784	15670	4379	5207	30283	32819	63102
2009	1464	1182	8538	9017	2107	1868	13588	15727	4464	5223	30161	33017	63178
2010	1551	1237	8300	8616	2179	1965	14372	16825	4464	5394	30866	34037	64903
2011	1587	1405	8784	9292	2128	1907	14522	17280	4649	5834	31670	35718	67388
2012	1611	1369	8583	9038	2155	2072	14340	16909	4514	5302	31203	34690	65893
2013	1699	1428	8923	9437	2199	1994	14720	16875	4873	5556	32414	35290	67704
2014	1737	1458	8609	9238	2197	2085	14589	17028	4709	5564	31841	35373	67214
2015	1843	1506	9006	9925	2191	2045	15143	18112	4810	5615	32993	37203	70196
2016	1866	1586	9200	9829	2013	1770	16496	18841	5260	6063	34835	38089	72924

F: Female; M: Male.

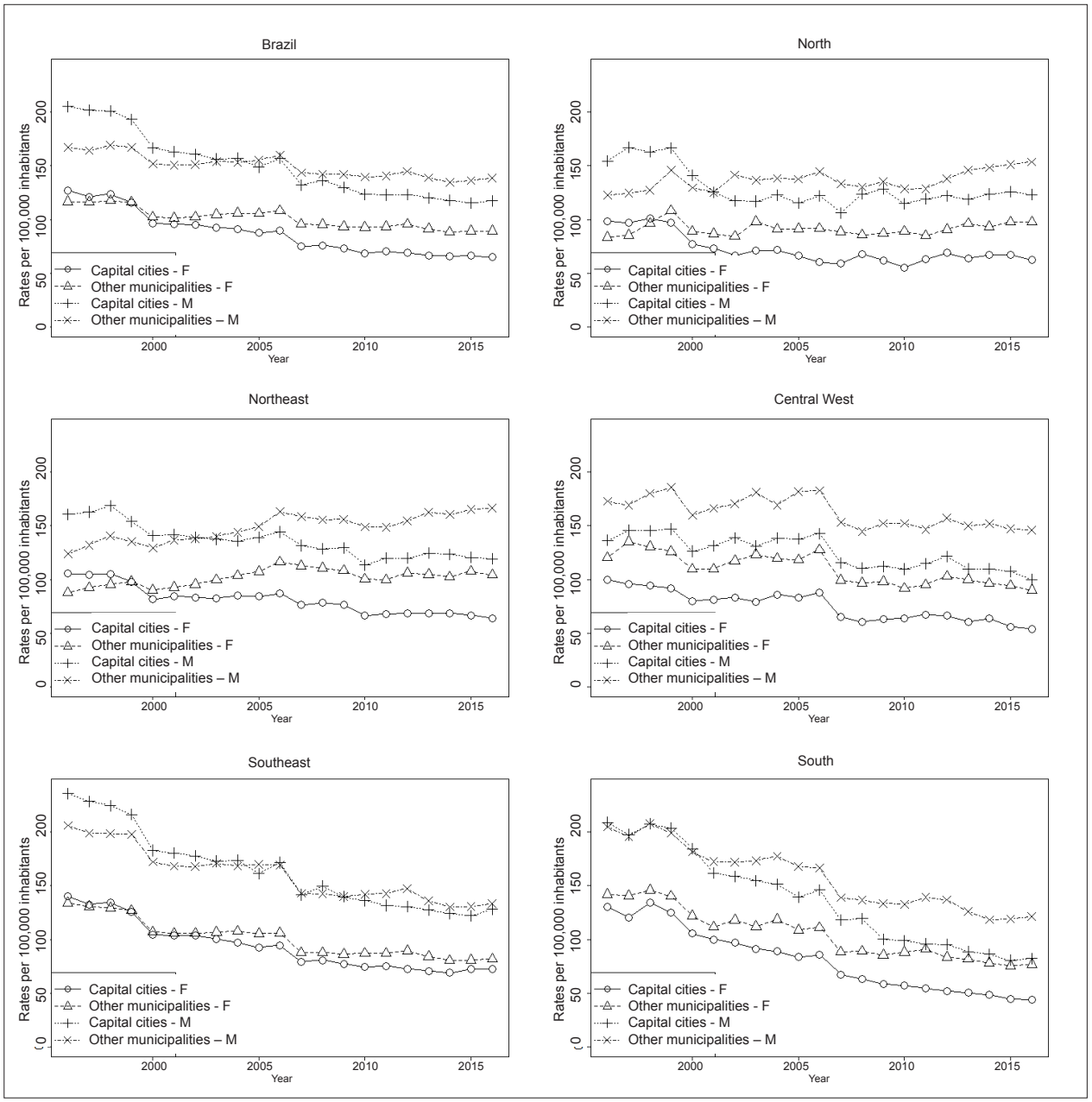

Figure 3 – *Time series after mortality corrections for acute myocardial infarction in Brazil, regions, capital cities, and other municipalities by gender from 1996 to 2016.*

of decrease and the North, the lowest (APC = -0.8%; 95% CI: - 1.3; -0.2).

A markedly different pattern was observed between the capital cities and other municipalities and between genders. There was a decrease in AMI-related mortality rates in all capitals, as well as in other municipalities of the Southeast, South, and Mid-West (Table 5). Conversely, the same rates increased in other municipalities of the North and Northeast, with the highest percentage of increase among women living in the Northeast between 2002 to 2006 (APC = 5.2%; 95% CI: 0.2%; 10.5%) (Table 5).

More significant declines in AMI-related mortality rates were observed among women living in the capital cities, except for the Southeast, where it was higher among men. The greatest decrease was observed among women living in the capital cities of the South from 1996 to 2016 (APC = -5.80%; 95% CI: - 6.2%; -5.4%). Smaller decreases were found among men living in other municipalities, except in the North (APC = 1.3%; 95% CI: 0.3; 2.3) and Northeast (APC = 1.3%; 95% CI: 1.0; 1.6), where an increase was observed (Table 5).

Table 4 – AMI-related mortality rates * standardized by the new world population by Brazilian region in 1996 and 2016

Region	1996	2016	% Difference
Brazil	149.86	104.35	-43.6
North	107.05	112.48	4.8
Northeast	107.42	121.30	11.4
Central West	135.32	100.47	-34.7
Southeast	172.93	102.92	-68.0
South	168.74	91.14	-85.1

**per 100,000 inhabitants.*

Discussion

Few nationally-based studies using data from the SIM system have attempted to estimate standardized mortality rates by means of the standard world population and with corrections for the proportion of deaths from ill-defined causes of death, the use of garbage codes, and underreporting.[4] These corrections are used by studies worldwide.[2,3,14] It was observed in this study that the number of ill-defined and underreported causes declined over the years studied, thus indicating improvements in data quality.[3] This decrease occurred differently between regions and between capital cities and other municipalities. It was more recent in the North and Northeast and in other municipalities than in other regions and capital cities. In contrast, the use of garbage codes showed no signs of significant reduction, remaining very high in number in all regions.

The decline in trends in AMI-related mortality rates has been observed worldwide and in most Brazilian regions,[1,3,14–17] which is being studied for the first time in this study by capital cities and other municipalities. Time series studies of mortality from cardiovascular diseases developed in Brazil analyzed large regions and found differences in mortality from chronic non-communicable diseases (NCDs) in those regions.[3,16-19] This difference is partly justified by the increase in mortality rates among men living there.

Discrepancies found in the analysis by capital cities and other municipalities can be explained by demographic and epidemiological transitions, as well as the implementation of public health policies that occurred differently in these regions.[16,20] Areas with greater socioeconomic development had earlier demographic and epidemiological transitions through urbanization, greater access to services, and the presence of an aging population. This led to a rise in chronic noncommunicable diseases and AMI-related mortality rates. Subsequently, they began to drop as new public policies were implemented.[21] This transition occurred at different times in different cities and regions. The South and Southeast experienced it before the North and Northeast, even as capital cities preceded other municipalities.[16,19] Capital cities generally offer more healthcare resources, better socioeconomic conditions, better health indicators, and better death records. Access to medium- and high-complexity services is also greater. Therefore, AMI-related mortality rates in the capital cities were lower than those in other municipalities, primarily in the final studied period. The time series in the 1990s revealed that mortality rates in other municipalities were lower in some regions and underwent an inversion in the middle of the period.[14,16,17] The issue of underreporting also needs to be taken into account, along with the lack of access to health services for diagnosis and the proper completion of death certificates in other municipalities, which may explain the smaller number of cases recorded in this period[20] and justifies, in part, the need for the corrections made.

It is interesting to highlight the turning point that these rates have undergone in all regions since 2000. A greater drop was observed in the Southeast, South, and Central West starting that year, whereas an increase in mortality rates was noted in other municipalities in the North and Northeast. This was a time when public policies in the healthcare area began to expand with increased funding, such as the National Primary Care Policy (PNAB in Portuguese) and the National Emergency Care Policy (PNAU in Portuguese). The Mobile Emergency Care Service (SAMU in Portuguese) was the first component of the PNAU to be implemented in the country in the early 2000s.[22] Later came incentives for the implementation of Emergency Care Units (UPA).[22] Concomitantly, primary care services wound up with an expanded structure through the implementation of the Family Health Strategy.[21]

Two movements led to a decline in mortality rates: one in relation to the prevention, control, and treatment of risk factors for IHD, with greater access to quality primary care, and another in the transportation, early diagnosis, and treatment of IHD through SAMU and emergency care units (UPA in Portuguese). However, in the North and Northeast, mortality rates rose in other municipalities. Historically, these have been the regions with the highest numbers of underreporting and the most difficulties in accessing healthcare services, especially in other municipalities.[2,3] Federal financial incentives aimed at organizing primary care and urgent and emergency services provided them with much-needed expansion in healthcare services and, with that, improvements in diagnoses and records of the causes of deaths, which, when added to changes arising from an aging population, could explain why mortality rates have risen.[22]

IHD mortality rates in women were lower than in men and the reduction in female deaths was also greater, which is in line with data found in the literature.[15,16] The cardiac protection promoted by female hormones (estrogen) may contribute to it. The presence of estrogen in the cardiovascular endothelium triggers the release of nitric oxide, leading to vasodilation; regulates prostaglandin production; and inhibits smooth muscle proliferation, factors related to AMI.[23]

The limitations of this study are inherent to the use of secondary data, although the quality of death records did improve during the analyzed period. Moreover, corrections were made that enhanced its validity. The factors associated with AMI-related mortality, such as obesity, smoking, and arterial hypertension, were not the object of this study.[24] Permeating all of these factors are socioeconomic and cultural conditions that strongly influence the mortality rates identified in regional differences.[15]

Table 5 – Analysis of the segmented regression of the AMI-related mortality trend by gender, capital cities, and other municipalities of the Brazilian regions, 1996-2016

Region	Municipality	Gender	Trend 1			Trend 2			Trend 3			Trend 4		
			Period	APC	IC95%	Period	APC	IC95%	Period	APC	IC 95%	Period	APC	IC95%
Brazil	Capital cities	F	1996 to 2010	-4.1	-4.7; -3.6	2010 to 2016	-1.1	-3.2; + 1.0						
		M	1996 to 2010	-3.5	-4.0; -3.1	2010 to 2016	-1.2	-3.0; +0.6						
	Other municipalities	F	1996 to 2016	-1.4	-1.7; -1.1									
		M	1996 to 2016	-1	-1.3; -0.8									
	All	Both	1996 to 2016	-1.9	-1.7; -2.2									
North	Capital cities	F	1996 to 2006	-5.1	-6.6; -3.6	2006 to 2016	0.9	-0.7; 2.5						
		M	1996 to 1999	0.6	-5.6; 7.2	1999 to 2002	-10.8	-23.0; 3.4	2002 to 2016	0.5	0.0; 1.0			
	Other municipalities	F	1996 to 2016	0.20	-0.3; 0.7									
		M	1996 to 2005	1.3	0.3; 2.3	2005 to 2010	-1.8	-5.5; 2.0	2010 to 2016	3.3	1.3;5.4			
	All	Both	1996 to 2010	-0.8	-1.3; -0.2	2010 to 2016	2.4	0.2; 4.7						
Northeast	Capital cities	F	1996 to 2000	-5.3	-9.1; -1.2	2000 to 2016	-2.0	-2.5; -1.6						
		M	1996 to 2016	-1.6	-2.0; -1.3									
	Other municipalities	F	1996 to 2002	0.60	-1.0; +2.2	2002 to 2006	5.20	0.2;10.5	2006 to 2010	-3.0	-7.6; +1.8	2010 to 2016	0.5	-1.1 ;2.1
		M	1996 to 2016	1.30	1.0; 1.6									
	All	Both	1996 to 2003	0.0	-1.2; 1.3	2003 to 2006	5.2	-4.0; 15.3	2006 to 2010	-2.8	-7.2; 1.8	2010 to 2016	1.0	-0.6; 2.6
Central West	Capital cities	F	1996 to 2016	-2.8	-3.3; -2.2									
		M	1996 to 2016	-1.7	-2.1; -1.2									
	Other municipalities	F	1996 to 2016	-1.8	-2.2; -1.3									
		M	1996 a 2016	-1.0	-1.4; -0.6									
	All	Both	1996 to 2016	-1.7	-2.1; -1.2									
Southeast	Capital cities	F	1996 to 2010	-4	-5.0; -3.8	2010 to 2016	-0.6	-2.8;1.6						
		M	1996 to 2001	-5.7	-8.1; -3.2	2001 to 2016	-2.9	-2.5; -3.3						
	Other municipalities	F	1996 to 2001	-5.2	-7.5 -2.8	2001 to 2005	0.10	-5.5; 6.2	2005 to 2008	-6.4	-17.5 6.1	2008 to 2016	-0.9	0.2; -2.1
		M	1996 to 2016	-2.3	-2.6; -1.9									
	All	Both	1996 to 2009	-3.3	-3.9; -2.7	2009 to 2016	-1.3	-2.9; 0.4						
South	Capital cities	F	1996 to 2016	-5.8	-6.2; -5.4									
		M	1996 to 2016	-5.2	-5.5; -4.8									
	Other municipalities	F	1996 to 2016	-3.4	-3.8; -3.0									
		M	1996 to 2016	-2.9	-3.3; -2.5									
	All	Both	1996 to 2016	-3.4	-3.8; -3.0									

F: female; M: male; Both=Male+Female. All=entire region. APC: annual percentage changes. 95% CI: confidence interval. Statistical significance level: 5%.

Conclusions

The evolution of AMI-related mortality in Brazil from 1996 to 2016 showed a downward trend, characterized by important inequalities and disparities between genders, capital cities and other municipalities and regions. The importance of correcting causes of death (due to ill-defined causes, garbage codes, and underreporting) was emphasized to encourage the construction of more reliable indicators that would allow a proper assessment of mortality trends to be made.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Ferreira LCM, Nogueira MC, Carvalho MS, Teixeira MTB; Critical revision of the manuscript for intellectual content: Nogueira MC, Carvalho MS, Teixeira MTB.

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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Evolving Outcome of Acute Myocardial Infarctions in Five Brazilian Geographic Regions Over Two Decades

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Short Editorial related to the article: Mortality Due to Acute Myocardial Infarction in Brazil from 1996 to 2016: 21 Years of Disparities in Brazilian Regions

It is a current research method to evaluate the outcome of diseases over decades, mainly in most prevalent diseases such as myocardial infarction, a public health issue with a significant toll in morbidity and mortality of the population. In addition to evolving over time, local conditions may also contribute to differences in outcome, mainly in countries with continental dimensions as Brazil is, as well as with large populations (206.081.432 habitants in 2016; 210.147.125 habitants in 2019).[1] Other epidemiologic variables, such as age, sex, access to treatment, co-morbidities, etc. – are part of the continuous spectrum of health care and risk factors for cardiovascular diseases.

In the current study[2] authors evaluated mortality data from a National Database System on Mortality in five geographic Brazilian regions between 1996 and 2016. Researchers corrected obtained from death certificates adjusting for: a) ill defined causes of death; b) codes-garbage without meaning for a causality study; c) correction for under registry or notification. The analysis was made in time series with segmented linear regression.

Inconsistencies would reflect limitations in treatment facilities and resources, in diagnosis and operational details in data collecting, processing and reporting in the deaths certificates. Efforts for better qualifying health data is a constant drive in health care and is continuously stimulated at the different levels of organization of the system,[3] data collection and analysis.[4,5]

The results of the study demonstrated differences in the quality of examined data between State capitals and some cities in the countryside. There was a tendency to decrease in mortality due to myocardial infarction. However, such a decrease was not homogeneous in every region of the country in the study period. In the Northeast region that was not the case.

In addition to the regional differences, an additional difference emerged relative to sex: there was an increase in mortality in women in the Northeast region between 2002 to 2006. Pathophysiological, clinical presentations, and outcome may have specific characteristic in women relative to men.[6,7] In some studies, it was suggested that access to treatment might be optimizes.[8,9]

Some other variables related to outcome are out of the scope of this investigations as the authors recognized such as hypertension, obesity, diabetes, smoking, hypercholesterolemia, family history of cardiovascular disease and myocardial infarction. However, they are not to the point of learning with the contribution of the findings of this study.

The authors concluded that in spite of a tendency in decrease in mortality due to myocardial infarction in different regions of Brazil, such a decrease was heterogeneous in the time course of this research and relative to sex. It means that there is progress to be worked out in this field of health care.

Keywords

Cardiovascular Diseases/complications; Myocardial Infarction; Mortality; Morbidity; Epidemiology; Public Health Administration.

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Repercussions of the COVID-19 Pandemic on the Care Practices of a Tertiary Hospital

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Abstract

Background: **We still do not have information regarding the impact of the COVID-19 pandemic on medical care activity in Brazil.**

Objective: **To describe the repercussions of the COVID-19 pandemic on the care routine of a tertiary hospital, which is a regional reference in cardiology and oncology.**

Methods: **Cross-sectional cohort study. We conducted a survey of medical visits from March 23, 2020 (when local commerce was closed) to April 23, 2020 (P20), in comparison with the same period in 2019 (P19).**

Results: **We found decreases in the number of cardiology consultations, exercise tests, Holter, ambulatory blood pressure monitoring, electrocardiogram, and echocardiogram (90%, 84%, 94%, 92%, 94%, and 81%, respectively). In relation to cardiac surgery and cardiac catheterization, there were 48% and 60% decreases, respectively. There was an increase in the number of percutaneous transluminal coronary angioplasties (33%) and definitive pacemaker implantations (29%). There were 97 admissions to the ICU during P19, in contrast with 78 during P20, a 20% decrease. Visits to the cardiac emergency room (45%) and admissions to the cardiology ward (36%) also decreased. The decrease in oncology consultations was 30%. Chemotherapy sessions decreased from 1,944 to 1,066 (45%), and radiotherapy sessions decreased by 19%.**

Conclusion: **COVID-19 has led to a considerable decrease in the number of consultations in outpatient clinics for cardiology, oncology, and other specialties. There was a concerning decrease in the number of cardiac surgeries, chemotherapy sessions, and radiotherapy sessions during the initial weeks of the pandemic. The number of people seeking care in the cardiac emergency room and the number of admissions to the cardiology ward and ICU also decreased, generating concern regarding the evolution and prognosis of these patients with pathologies other than COVID-19 during this pandemic time. (Arq Bras Cardiol. 2020; 115(5):862-870)**

Keywords: **COVID-19; Pandemics; Coronavirus, Betacoronavirus, Oncology; Hospitalization; Emergency Medical services.**

Introduction

In December 2019, the first cases of individuals infected with the new coronavirus (SARS-COV 2) were reported in Wuhan, China; the virus rapidly spread throughout the country, leading to a large number of deaths and hospitalizations.[1] Within a short period of time, coronavirus disease 2019 (COVID-19) went beyond the limits of China, reaching other countries in Asia, Europe, and the Americas. By the middle of 2020, approximately 8.5 million people had tested positive for the new coronavirus in more than 187 countries and 200 territories, with 960,000 positive tests in Brazil. During this time, there were close to 450,000 deaths in the world attributed to COVID-19 (47,000 in Brazil).[2] The first case of COVID-19 in Brazil was confirmed in São Paulo, on February 26, 2020.[3] On March 6, 2020, the Secretary of Health of the State of Bahia confirmed the diagnosis of the first case of COVID-19 in Bahia, specifically, in the city of Feira de Santana. The patient was a 34-year-old woman, who had returned from Italy on February 25, having visited Milan and

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Rome, where contamination occurred. On March 11, 2020, the World Health Organization classified COVID-19 as a pandemic, and, on March 20, 2020, the Brazilian Ministry of Health declared community transmission of the disease throughout the national territory.[4] This means that the virus was already circulating throughout the country. On the same date, the local public administrator of Feira de Santana issued a decree closing all wholesale and retail trade in the municipality, starting on March 23, 2020.

Scientific investigations are underway worldwide, and, as this is still a new incident, many efforts are being made to support health professionals and administrators. In Brazil in particular, any and all health conditions need to take into consideration the size of the country and its regional differences. During a pandemic like this one, the tripartite management structure of the Brazilian Unified Health System (SUS, acronym in Portuguese) becomes even more important, given that decisions must be shared between federal, state, and municipal governments.

During the pandemic, some authors have reported changes in the structures of healthcare systems in Europe and the USA, with an important decrease in the number of medical visits and procedures that are associated with COVID-19, including those of high complexity.[5-12] As a collateral effect, these changes may lead to delayed diagnosis and/or therapy, with a consequent increase in the risk of decompensation of chronic diseases.

We still do not have information regarding the impact of the pandemic and subsequent government actions on medical care activity in Brazil. The objective of this study was to describe the repercussions of the COVID-19 pandemic on the number of consultations, tests, hospitalizations, and medical procedures carried out in a tertiary hospital, which is a regional reference for cardiology and oncology.

Methods

This was a cross-sectional cohort study carried out in a tertiary hospital with 110 ward beds and 12 ICU beds. It is a regional reference unit in cardiology (cardiac surgery, catheterization, angioplasty, implantable electronic devices, echocardiogram, and cardiac emergency room [ER]) and oncology (chemotherapy, radiotherapy, and oncology surgery), and it provides care to both the SUS and the supplementary health system. In order to analyze the repercussions of the COVID-19 pandemic on the hospital's care practices, a survey was carried out regarding the number of visits in the various sectors of the unit during the period from March 23, 2020 (the date when local commerce was closed) to April 23, 2020 (P20), in comparison with the services provided during the same period in 2019 (P19). This was a convenience sample, including all patients with data available from electronic records during the periods mentioned above. Data were collected on care practices and admission to the following sectors of the hospital: ICU (mainly cardiology), cardiac surgery, non-cardiac surgery, cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), pacemaker implantation, cardiology consultations, echocardiography, ambulatory blood pressure monitoring (ABPM), Holter, electrocardiogram, exercise test, cardiac ER, admission to the cardiology unit, clinical laboratory analysis, oncology consultations, chemotherapy sessions, radiotherapy sessions, ultrasound, computerized tomography, endoscopy, colonoscopy, and rectosigmoidoscopy.

Statistical Analysis

We carried out descriptive analysis of the data obtained in the sample. Nominal or categorical variables were described by their absolute values. The differences in events observed between the two study periods were described as absolute and relative ratios. Data analysis and graph construction were performed with the aid of Excel®, Microsoft 365®.

Ethical Aspects

This study received approval from the Research Ethics Committee of the State University of Feira de Santana, under protocol number CAAE: 31056220.0.0000.0053. All of the procedures involved in this study are in accordance with the 1975 Declaration of Helsinki, revised in 2013. The survey was conducted by means of direct research of hospital records, following express authorization from the hospital. The researcher responsible signed an agreement form regarding use of data from hospital records.

Results

During P19, there were 379 consultations at the cardiology outpatient clinic; this number decreased to 38 during P20, representing a 90% drop (Figure 1). Decreases were also observed in the number of exercise tests (84%), Holter (94%), ABPM (92%), and electrocardiogram (94%). In relation to echocardiogram, there were 509 fewer exams during P20, corresponding to an 81% decrease (Figure 1). This number comprised 470 outpatient echocardiograms (88%) and 39 exams carried out in patients who were hospitalized (41%).

In relation to cardiac surgery and cardiac catheterization, there were 48% and 60% decreases, respectively (Figure 2).

There was a 33% increase in the number of PCTA and a 29% increase in definitive pacemaker implantations (Figure 2).

During P19, 97 patients were admitted to the ICU, in comparison to 78 during P20, representing a 20% decrease. A decrease was also observed in the number of visits to the cardiac ER (45%) and in the number of admissions to the hospital's cardiology ward (36%) (Figure 3).

The oncology sector also saw a considerable decrease in visits during the initial phase of the COVID-19 pandemic. Oncologists carried out 1,688 consultations during P19. This number dropped to 1,184 consultations during P20, a 30% decrease. The number of chemotherapy sessions dropped from 1,944 to 1,066, a 45% decrease. Radiotherapy sessions also decreased by 19% (Figure 4).

There was a 42% decrease in the number of clinical analysis exams. This decrease comprises both outpatients and hospitalized patients; it was greater among the former (Figure 5). There were 337 troponin assays in 2019, in contrast with only 59 in 2020, a 82% decrease.

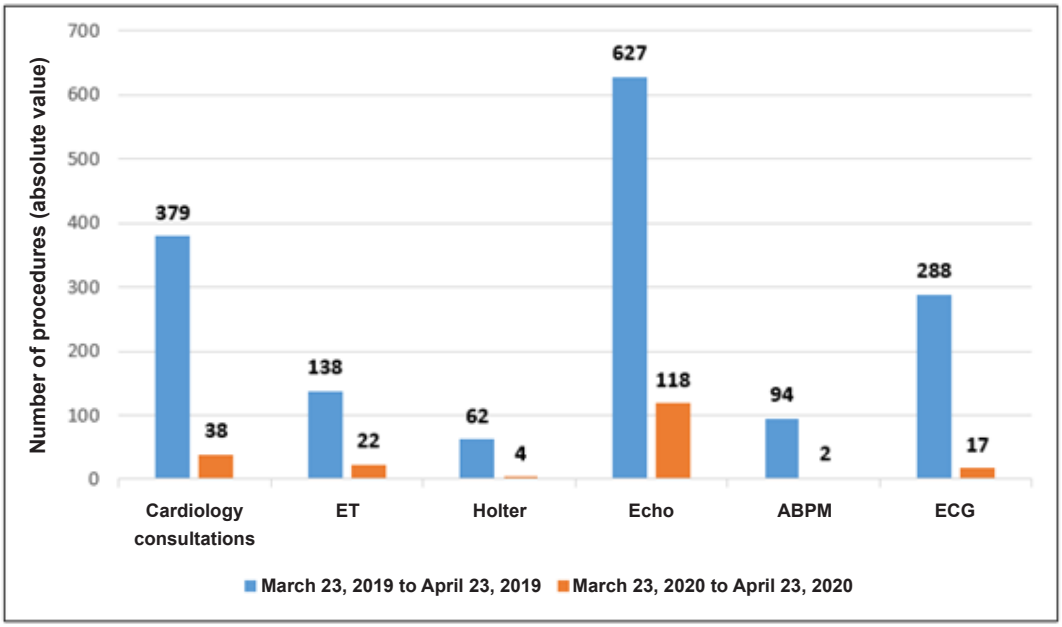

Figure 1 – *Number of cardiology consultations and exams. ABPM: ambulatory blood pressure monitoring; ECG: electrocardiogram; Echo: echocardiogram; ET: exercise test*

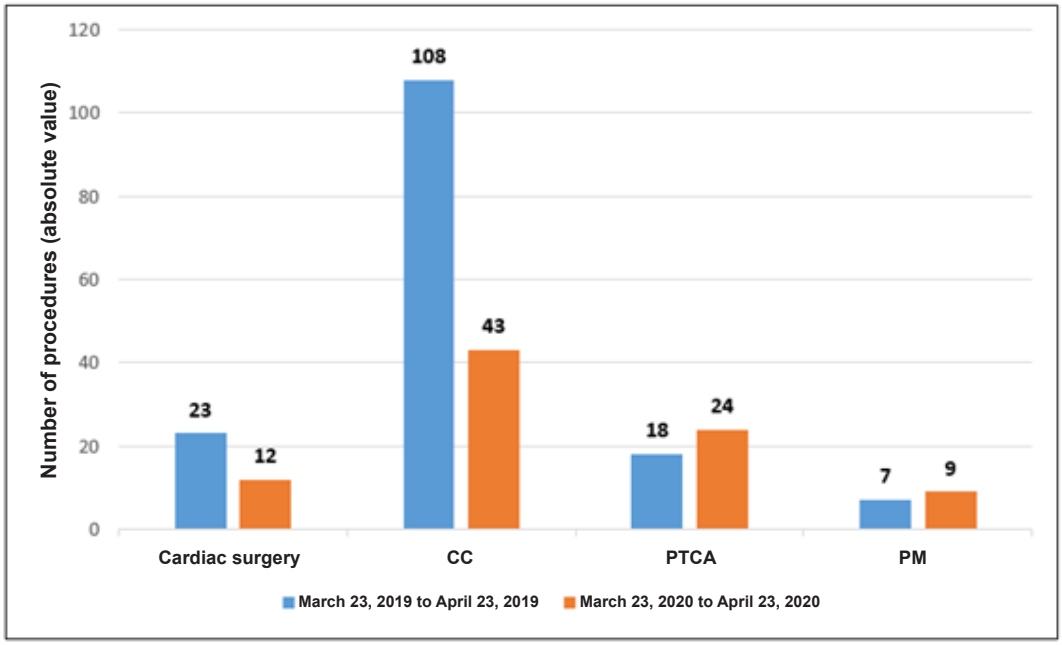

Figure 2 – *Movement in the interventional cardiology sector. CC: cardiac catheterization; PM: pacemaker; PTCA: percutaneous transluminal coronary angioplasty*

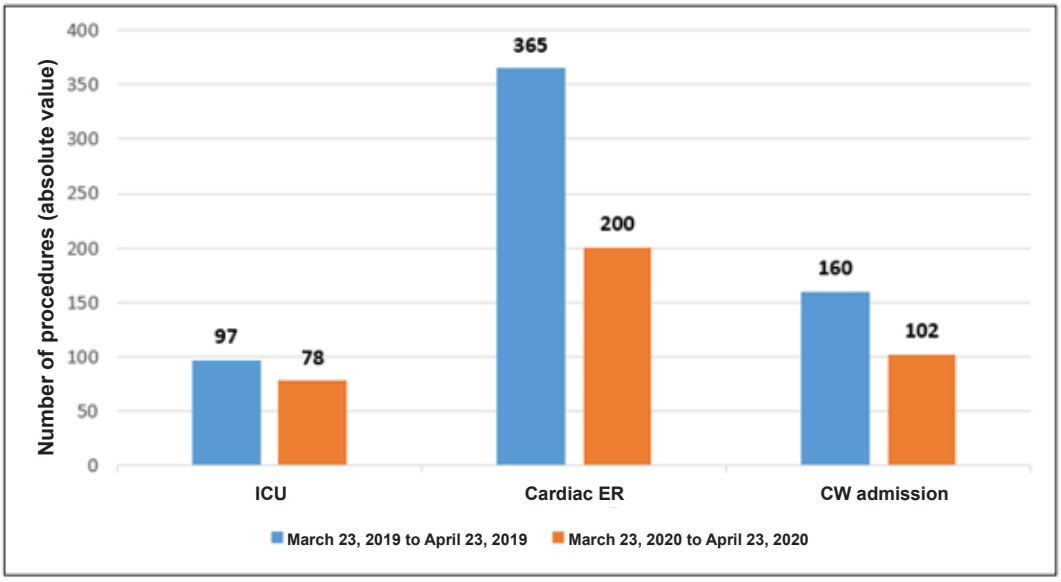

Figure 3 – *Number of admissions to the cardiology unit. CW: cardiology ward; ER: emergency room; ICU: intensive care unit*

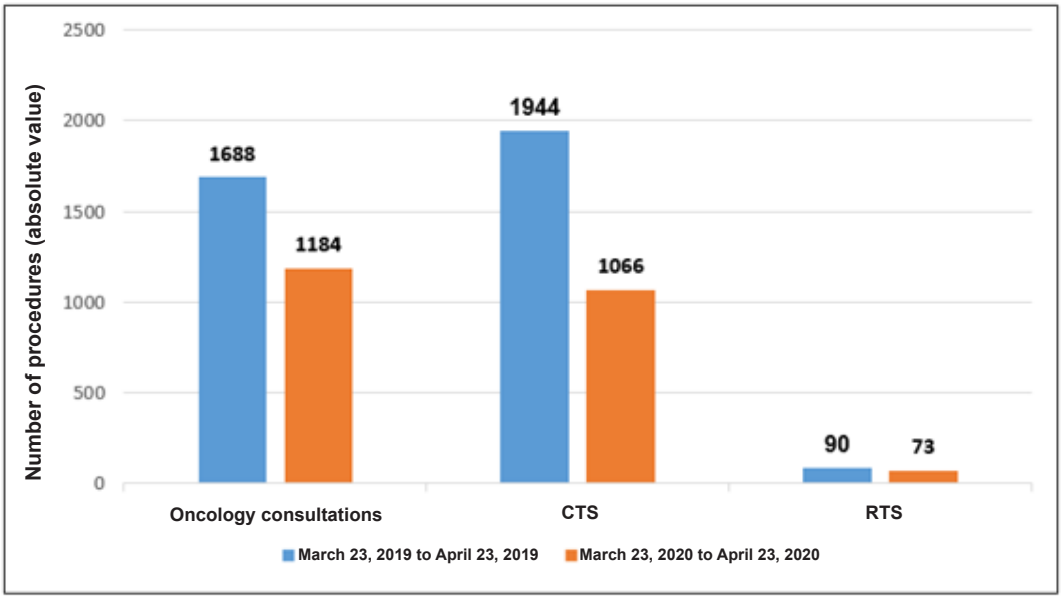

Figure 4 – *Movement in the oncology sector. CTS: chemotherapy sessions; RTS: radiotherapy sessions*

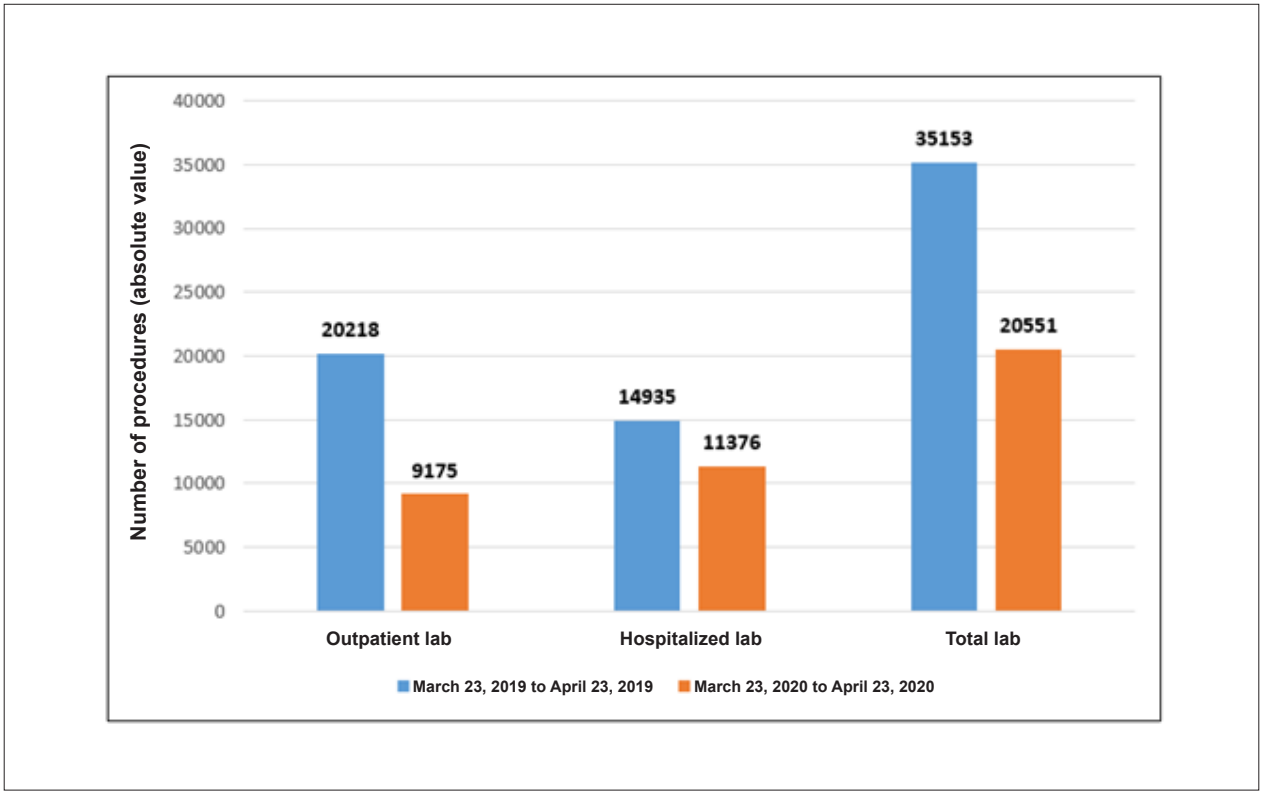

Figure 5 – *Movement of clinical laboratory analyses. Lab: laboratory exams*

There was also a decrease in the number of the following procedures: endoscopy/colonoscopy/rectosigmoidoscopy (52%), ultrasound (94%), and computerized tomography (35%) (Figure 6).

Non-cardiac surgeries (general, oncology, head and neck, orthopedic, among others) saw a 40% reduction during the first month when social distancing was recommended due to the COVID-19 pandemic in the study region. The number of oncology surgeries related to urology decreased from 82 to 57 (30%). Non-cardiology and non-oncology consultations decreased by 92% (Figure 7).

The hospital where data were collected is not a reference center for providing care for patients with COVID-19. Up to the moment when data collection was completed, no patients with COVID-19 had been admitted to the unit.

Discussion

This study has shown that the COVID-19 pandemic led to a considerable decrease in the number of consultations at our hospital's outpatient clinics in cardiology, oncology, and other specialties. Furthermore, we observed a concerning decrease in the number of cardiac surgeries, chemotherapy sessions, and radiotherapy sessions during the initial weeks of the pandemic. These decreases can lead to disastrous consequences for the patients who need these treatments. The number of people seeking care in the cardiac ER and the number of admissions to the cardiology ward and ICU also saw an important decline, leaving cardiologists and other healthcare professionals with a concerning question during this initial moment, namely: Where are patients with cardiac complications, whether or not they are associated with the COVID-19 pandemic, going?

We observed a 45% decrease in the number of visits to the cardiac ER in our hospital, with a 82% decrease in troponin assays. This was accompanied by 20% and 36% decreases in the rates of admission to the cardiology ICU and the cardiology ward, respectively. Similarly, Metzler B et al.[10] demonstrated a 39.4% decrease in the admission of patients with acute coronary syndrome during the first month of the COVID-19 outbreak in Austria. In the USA, there was a 38% drop in coronary angiography in cases of acute ST-elevation myocardial infarction (STEMI) during the first month of the pandemic.[8] In our study sample, we observed a 60% decrease in the number of cardiac catheterization procedures and a 48% decrease in the number of cardiac surgeries. In Spain, during the first week of quarantine due to COVID-19, researchers observed a 56% decrease in diagnostic cardiovascular procedures, a 48% decrease in coronary therapy procedures, an 81% decrease in structural therapy procedures (transcatheter aortic valve implantation, patent ductus arteriosus closure, and interatrial communication closure), and a 40% decrease in cases treated for STEMI.[8] The decrease that we observed in individuals seeking medical attention for cardiac reasons during the pandemic, which has also been seen in other countries, goes against what we usually see during periods

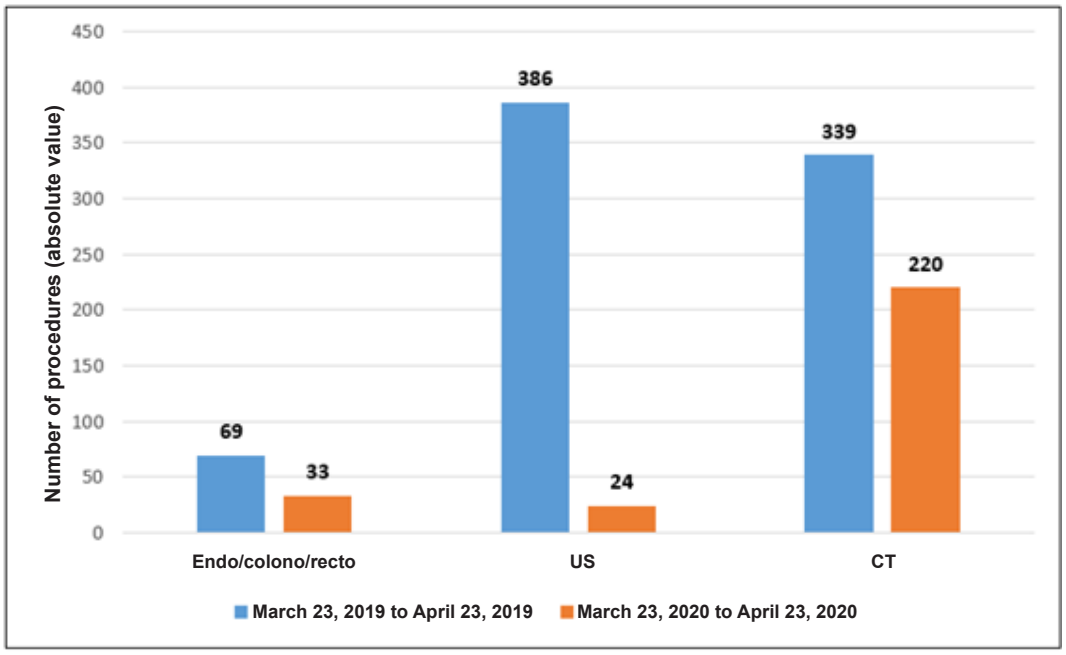

Figure 6 – *Movement of imaging exams. Colono: colonoscopy; CT: computerized tomography; endo: upper digestive endoscopy; recto: rectosigmoidoscopy; US: ultrasound*

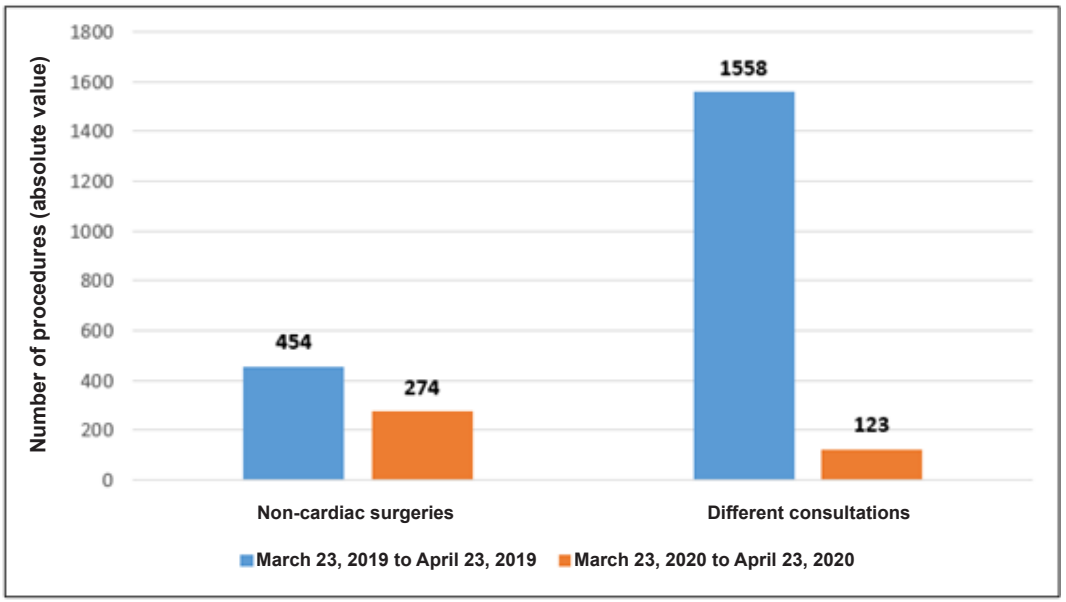

Figure 7 – *Number of non-cardiac consultations and surgeries.*

of tragedy. It is known that there is a considerable increase in the incidence of acute myocardial infarction and stroke following earthquakes and tsunamis.[13,14] Perhaps, as a result of this decrease in spontaneous demand for medical care in cases that not related to COVID-19, the region of Lombardy, Italy, showed a 58% increase in the occurrence of cardiac arrest outside the hospital during the period that included the first 40 days of the COVID-19 outbreak.[12] This finding showed a strong association with the cumulative incidence of COVID-19 in the region studied. Similarly, data published on Angioplasty.Org report an 800% increase in the incidence of sudden deaths occurring at home in the city of New York when it was the epicenter of the pandemic.[15] Many of these patients may have avoided going to the hospital due to fear of becoming infected with COVID-19.[16]

In contrast with the data obtained in Spain,[8] we observed a 33% increase in PCTA. We attribute this increase to the greater availability of beds in our hospital's ICU during the initial phase of the COVID-19 pandemic. This made it possible for us to carry out the procedure and transfer patients to the ICU for observation, which is a different scenario from the pre-COVID phase, when the ICU, invariably, had no beds available.

The decrease which we observed in the number of oncology consultations (30%), chemotherapy sessions (45%), and radiotherapy sessions (19%) is a different case. A recent study, carried out in England and North Ireland, observed that the majority of patients with cancer or suspicion of cancer were not accessing health services during the COVID-19 pandemic.[17] As a consequence, it is estimated that this COVID-19 outbreak has the potential to increase mortality by approximately 20%, over the coming 12 months, in patients with recent diagnosis of cancer, in England alone.[17] Moreover, patients with cancer have an almost four-fold risk of presenting severe complications secondary to COVID-19, when compared to individuals without cancer.[18] Therefore, monitoring of patients in oncology should be doubled, rather than decreased, during the pandemic. The challenge in identifying and treating complications associated with some chemotherapy drugs, such as severe myocarditis and/or pneumonitis, is another issue which specialists need to face during the COVID-19 pandemic.[19]

Our results are of great assistance to patients, healthcare professionals, and hospital managers. They shine a light on a serious problem, which is occurring in parallel to the COVID-19 pandemic, namely, a considerable decrease in the number of consultations, cardiac and oncological surgeries, visits to the cardiac ER, cardiac catheterization, chemotherapy and radiotherapy sessions, laboratory tests, and other medical procedures that are important and necessary for patients who do not have COVID-19. Decreased access to medical care is associated with a decline in the population's health status.[20] Delayed diagnosis and treatment of myocardial infarction or stroke increase the risk of death.[21] Interrupting the use of anti-hypertensive medication, even for short periods of time, may lead to severe cardiovascular complications.[22] Withdrawal of statins increases rates of events in patients with acute coronary syndromes.[22] Undiagnosed decompensation of diabetes has severe consequences. Delayed performance of oncological surgery can lead to disease progression and worsened prognosis. The same applies to adjuvant or neoadjuvant chemotherapy sessions. The fact that patients are abstaining from going to the hospital does mean that other diseases have disappeared. By any means! They continue affecting patients, but patients are not seeking medical care to the appropriate extent. The question is: Why? Among other reasons, they are probably afraid of going to the hospital on account of the risk of contracting COVID-19. It is also possible that some patients with cardiovascular problems are seeking medical attention, but the symptoms they present may be confused with those of COVID-19. Express recommendations for people to stay home, in addition to restrictions on traffic and movement, also contribute to the scenario that we have detected in our hospital. It would not be an exaggeration to say that these individuals have also become victims of COVID-19, even without having contracted the disease.

Regardless of the cause, the results of our study reflect what is happening in several other places. These facts have the potential to generate a worrying collateral effect, namely, a substantial increase in morbidity and mortality, both short and medium term, due to causes other than the infection caused by SARS-COV 2.[16] This would be the other side of the COVID-19 tragedy. It is possible that, soon, we will face an ascending, post-pandemic curve composed of patients with serious complications secondary to pathologies that could have been adequately treated, had they been previously attended at a time which would have, theoretically, been more favorable.

Our results open perspectives for other researchers to investigate the real outcomes of patients who are not attending elective medical consultations, chemotherapy sessions, radiotherapy sessions, and the cardiac ER, as well as those who are not undergoing routine examinations and/or oncological or cardiac surgeries during the COVID-19 pandemic. This would complement our findings and bring important information to the medical community and to patients themselves.

There are some limitations to this study. It was a single center study, and the observation period was relatively short. We did not follow up the outcomes of patients who stopped coming to consultations and/or procedures in our hospital. We observed the repercussions of the COVID-19 pandemic on the care practice of a tertiary hospital as a whole, but we did not characterize the pathologies that brought patients to the hospital.

Conclusion

The COVID-19 pandemic caused an important reduction in the number of consultations in the cardiology, oncology and other specialties outpatient clinics at our hospital. We also noticed a considerable decrease in the number of cardiac surgeries and in chemotherapy and radiotherapy sessions in the initial weeks of the pandemic. The demand for care in the cardiac ER, as well as the number of hospitalizations in the ICU and cardiology ward, also reduced, generating concern about the evolution and prognosis of these patients with other pathologies, other than COVID-19, in these pandemic times.

Author Contributions

Conception and design of the research: Almeida ALC, Santo TME, Santos Jr. EG; Acquisition of data: Almeida ALC, Santo TME, Mello MSS, Cedro AV, Lopes NL, Ribeiro APMR, Mota JGC, Mendes RS, Ferreira MA, Arruda DM, Santos AAP, Rios VG, Dantas MRN, Silva VA, Silva MG, Sampaio PHS, Guimarães AR, Santos Jr. EG; Analysis and interpretation of the data: Almeida ALC, Santos Jr. EG; Statistical analysis: Almeida ALC; Writing of the manuscript: Almeida ALC, Almeida PAA, Santos Jr. EG; Critical revision of the manuscript for intellectual content: Almeida ALC, Santo TME, Mello MSS, Cedro AV, Sampaio PHS, Guimarães AR, Santos Jr. EG.

Potential Conflict of Interest

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

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The Unapparent Non-COVID Consequences of the COVID-19 Pandemic

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Short Editorial related to the article: Repercussions of the COVID-19 Pandemic on the Care Practices of a Tertiary Hospital

The world has been facing a COVID-19 pandemics of enormous proportion. Most places were unprepared to cope with this situation[1] and considering its occurrence in the current scenario of fast, widespread and occasionally unfiltered information, the considerable growth of fear has affected most people worldwide. Mainly considering the rapid contamination of people in the hospitals and in the communities, as announced by the news, and potentialized by pictures of unassisted patients waiting outside the medical facilities, due to the lack of adequate support.

This apocalyptic scenario was seen in many places that were considered as adequately equipped for the regular treatment of ordinary health problems. All attention was diverted to provide installations and equipment to take care of the COVID-19 affected patients and their relatives.[2]

However, an unseen problem was emerging in the middle of all this. The care for the patients in need of attention for non-COVID and yet, severe conditions.

Almeida et al.,[3] in this issue of *Arquivos Brasileiros de Cardiologia*, demonstrate an accurate view of the problem, as they were among the first to document such a problem in their municipality of Feira de Santana in Bahia, Brazil, by analyzing a considerable reduction in the treatment of heart disease, oncologic disease and other potentially incapacitating conditions. Others have identified such problems in many parts of the world, with severe consequences of out-of-the-hospital sudden death, untreated myocardial infarction (MI), late hospital arrival for MI and as a consequence, ventricular rupture, as it had not been seen for a long time, and cardiogenic shock, heart failure[4] cardiac surgery,[5,6] and other consequences, not mentioning the loss of opportunity for early diagnosis of cancer, as well as appropriate chemotherapy and radiotherapy. Suppurative appendicitis and perforated gastric ulcers have also been documented.

As the hospital facilities progressively acquired the necessary support and the transmission stabilized, and in many cases declined, the awareness brought on by observations such as the one reported in this issue of the *Arquivos Brasileiros de Cardiologia* prompted immediate attitudes toward facilitating the treatment of non-COVID cases in need of such care.[7,8]

This is not always a simple task[9] and the protection of the patients and their relatives have to be guaranteed by means of questionnaires, COVID testing for the patients, relatives and medical personnel, adequate hygienization of the environment and whenever possible, with distinct flows for these patients.

Until the arrival of a much expected effective vaccine, one must remember that humanity hopes for a post-pandemic situation but must be reminded that, in populational terms, there will not be a Post-COVID 19 era. This threat will accompany us for many years and, therefore, there will always be a need for precautions against contamination and the adoption of better sanitation conditions.

Keywords

Pandemics; COVID-19; Betacoronavirus; Cardiology; Oncology; Hospitalization; Emergency Medical Services.

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Association of Cardiovascular Risk Factors and APOE Polymorphism with Mortality in the Oldest Old: A 21-Year Cohort Study

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Abstract

Background: Knowledge of environmental and genetic factors for healthy aging in elderly people is controversial. In addition to this evidence, few studies have been designed for this population.

Objectives: To investigate the relationship between the most frequent apolipoprotein E (APOE) genotypes and mortality in very elderly individuals living in a community and to evaluate survival according to cardiovascular risk factors.

Methods: A sample of 74 elderly individuals aged ≥ 80 years, from the Veranópolis Project cohort, was selected for APOE genotyping. At baseline, anthropometric variables, glucose and lipid levels, blood pressure, and lifestyle variables (smoking, alcohol consumption, and physical activity) were collected. The Bayer Activities of Daily Living Scale was applied to their caregivers. Total study follow-up was 21 years. Two-sided $p < 0.05$ was considered statistically significant.

Results: There was no association between APOE genotypes and mortality. However, the risk of death in elderly smokers was 2.30 times higher (hazard ratio [HR], 95% CI 1.01 to 5.24); in individuals with diabetes, it was 3.95 times higher (HR, 95% CI 1.27 to 12.30) than in individuals without diabetes. Subjects who practiced vigorous physical activity had a 51% reduction in risk of death (HR = 0.49, 95% CI 0.27 to 0.88). For an increase of 1 mmHg in systolic blood pressure, there was a 2% reduction (HR = 0.98, 95% CI 0.97 to 0.99) in risk of death.

Conclusion: In this sample population, APOE genotypes were not associated with mortality. However, classic cardiovascular risk factors may be important for overall mortality in the very elderly. (Arq Bras Cardiol. 2020; 115(5):873-881)

Keywords: Cardiovascular Diseases; Risk Factors; Mortality; Apoliprotein E4; Aged, 80 and over.

Introduction

The rapid growth in the elderly population worldwide has brought an increased interest in and need for studies on factors related to longevity with quality of life. Mortality data about elderly individuals aged 80 and over show that cardiovascular diseases (CVD) represent half of the causes of death.[1] Despite the high frequency of chronic diseases, such as CVD and dementia, in this age range, they are usually excluded from well controlled studies or only analyzed as subgroups. Results from studies in the very elderly (aged 80 and over) are different from those in the young elderly (aged 60 to 74), for instance, higher mortality associated with reduction in diastolic pressure[2] or systolic pressure[3,4] and reduction in cholesterol,[5] or a protective effect related to body mass index (BMI) above 30 kg/m².[6] However, other risk factors such as smoking[7] and diabetes mellitus (DM)[8] have been similarly associated, even at more advanced ages. Otherwise, a widely studied genetic factor, apolipoprotein E (APOE) polymorphism, more specifically the ε4 allele, appears as a risk factor for Alzheimer's disease (AD) in adults and young elderly.[9,10] However, results from a specific cohort with very elderly identified a paradoxical effect of APOE ε2 allele associated with an increase in AD through post-mortem neuropathological criteria.[11] Meta-analysis studies have shown that carriers of the APOE ε4 allele present a higher risk of early CVD.[12,13] However, there are no studies to indicate whether this association is maintained in the oldest old. From this perspective, the objective of this study was to investigate the relationship between the most frequent

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APOE genotypes and mortality in very elderly individuals and to describe survival according to genotypes and exposure to classical cardiovascular risk factors.

Methods

Design

Prospective cohort study

Study Population

The Veranópolis Project cohort started in 1994 following two comprehensive eligibility criteria: (1) age equal to or older than 80 years and (2) residing within the territorial domain of the municipality of Veranópolis, Rio Grande do Sul, Brazil. Recruitment of eligible individuals took place in 1994, 1996, and 1998. Summarily, the first recruitment happened during the month of July 1994 through an informal invitation by the research coordinator to participants in a religious service. Those present registered spontaneously and informed their intention to participate. During three weeks in July 1994, the researchers visited 100 elderly individuals at their residences or in community centers. In 1996, recruitment occurred through broadcasting in a local radio station; another 129 consented to take part in the study, and those who had participated in 1994 were reassessed. In 1998, a simple random sample of the participants in the previous years and another 13 new volunteers underwent APOE genotyping, and the main tests from the previous assessments. Thus, the Veranópolis Project cohort comprised 242 individuals, representing 87.4% of elderly individuals aged 80 and over who resided in the municipality between 1994 and 1998.[14]

During 2011 and 2012, vital status of the elderly individuals sampled for APOE genotyping (74 volunteers) was checked once more through home visits and, at that time, the Bayer Activities of Daily Living Scale (B-ADL) questionnaire was applied to their caregivers.

In December 2012, 18 years after the start of the cohort, 11 of the 242 members of were still living. The results presented in this manuscript refer to a period after verification of vital status from 2011 to 2012, that is, after the occurrence of the mortality outcome in all participants of the cohort of the oldest old, which occurred in 2015.

This study received approval from the Research Ethics Committee of the Federal University of Rio Grande do Sul, Brazil. All participants and/or their relatives signed an informed consent form.

Variables

The APOE genotypes (rs7412 and rs429358) were used as a predictor variable, and the genetic factor was analyzed in two different periods during follow-up, the first in 1998[15] and the second in 2011, including all living individuals who had not been sampled in 1998, namely, another 9 elderly individuals (methodology described in Alvim et al.[16] (See Flowchart in Annex)

The outcome defined in this study was mortality from chronic CVD included in codes I00-I99 or from dementia included in codes F00-F03 of the International Classification of Diseases, 10th revision. To define cause of death in elderly individuals, copies of their death certificates were presented to two medical professionals, one geriatrician and one cardiologist, who were blinded to one another's assessments and to the genotypes of the deceased. In case of any divergence between the professionals concerning the cause of death, assessment was requested from a third professional. The final diagnosis, in case of an impasse, was defined by consensus between the three professionals. When cause of death could not be defined by the document alone, medical records were surveyed, and interviews were carried out with the family doctors or next of kin of the deceased.

The Veranópolis Project cohort is a broad study which seeks answers for the peculiar longevity of this population. Among the variables investigated in the cohort for this study, we selected those that are described as classical risk factors for CVD and those that could be independently associated with the outcome studied, namely, arterial hypertension, obesity, DM, dyslipidemia, smoking, alcohol abuse, and physical inactivity. Data from these variables were collected at the baseline of the year of inclusion of the elderly individual in the cohort (1994, 1996, or 1998). The baseline data collected in 1994 were re-evaluated in 1996. In 1998, data collection was repeated from a random sample from 1994 to 1996 and 13 additional individuals included in the cohort. For this study's data analysis, we used the information collected in the year of entry of the elderly individual in the cohort.

The methods used to measure cardiovascular risk factors and the justifications for the categorization, when applicable, are described succinctly below. Blood pressure (BP) was obtained using a mercury sphygmomanometer (Erka, Germany). Two or three measurements were taken according to variability, following the measurement intervals recommended by the guidelines, and the weighted average was calculated. To analyze data, BP was used as a quantitative, categorized variable, and individuals were considered hypertensive when BP ≥ 140/90 mmHg or when they were taking antihypertensive medication.[17] Furthermore, pulse pressure, the result of subtracting diastolic blood pressure (DBP) from systolic blood pressure (SBP), was evaluated.

Obesity was defined by BMI; weight was measured with participants dressed lightly, without shoes, using mechanical scales (Filizolla, São Paulo). Height was determined standing upright, without shoes, using a measuring tape with shoulders in a normal position. To analyze the data, BMI was used as a continuous, categorical variable, with obesity[18] and overweight[19] being defined by the cut off points ≥ 30 kg/m^2 (World Health Organization [WHO] and > 27 kg/m^2 (Lipschitz), respectively.

For glycemia and lipid profile biochemical evaluations, venous blood samples were collected after 12 hours of fasting. A blood sampling system with disposable vacuum device (Vacutainer) in tubes with no anticoagulant was used. Plasmatic dosages were obtained through the manual technique of colorimetric enzymatic reaction with calibration standards and samples in duplicate. DM was defined as fasting

glycemia ≥ 126 mg/dL or use of hypoglycemia medication.[20] Dyslipidemia was evaluated through plasmatic dosages of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) calculation, which were used as quantitative, categorized variables according to the following criteria from the V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis[21] and the American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis,[22] TG ≥ 150 mg/dL; TC ≥ 200 mg/dL; HDL-C < 50 mg/dL for women and < 40 mg/dL for men; LDL-C ≥ 160 mg/dL. LDL-C was obtained using Friedewald's formula for TG values below 400 mg/dL.

The lifestyle variables smoking, alcohol abuse, and physical inactivity were obtained using a standardized questionnaire applied at baseline. Smoking was evaluated through statements on consumption or non-consumption of tobacco (cigarette, corn straw cigarette, pipe). Two groups were considered: 1) non-smokers: individuals who never smoked; 2) smokers or ex-smokers. Alcohol abuse was evaluated through statements on the amount of alcohol consumed per week, and abuse was considered at values of > 210 g/week for men and > 105 g/week for women.[23] Physical inactivity was evaluated through statements on daily activities during a normal week of work and leisure. Two different cut-off points were used, < 2,000 kcal/week[24,25] and < 4,000 kcal/week,[26] which are the minimum amounts of physical activity to attain major cardiovascular benefits such as attenuated thickening of the inner-middle layer of carotid arteries,[24] increase in HDL-C[25] and reduction of mortality in patients with coronary arterial disease.[26] The instrument used to report different physical activities comprised a list of 27 habitual activities in the routine of people who live in the city and in the country, and one further open question about any other activity besides the pre-selected ones. Participants in the study were asked to report time spent in minutes and the weekly frequency practicing these activities. Therefore, following the same rationale for other studies on the very elderly, we chose to use energy expenditure calculated in kilocalories per week (kcal/week), considering participants' weight, the reported time duration of the activity, the metabolic equivalents (MET) for the specific activity[27] and the weekly frequency of the activities: Energy expenditure (kcal/week) = MET X weight (kg) X time duration of activity (minutes) / 60 X weekly frequency. We thus deem that this measurement better reflects the very elderly energy expenditure in the community studied (rural and urban) than the simply measurement of MET that is usually described in current works.

B-ADL was applied by a researcher, who was trained and blinded in relation to participants' genotypes, to their caregivers in the period from August 2011 to December 2012. The instrument was employed as a way of identifying cases of dementia and the result used as a potentially confounding variable, as it has been well described that the APOE ε4 allele is a risk factor for the development of AD.[9,10] The score obtained from the B-ADL ranges from 1.00 to 10.00, and higher scores represent greater difficulty in the activities. To analyze the data, the B-ADL score was used as a quantitative, categorized variable, using a cut-off point of ≥ 3.12 to define cases of dementia.[28]

Statistical Analysis

Quantitative variables were described as average and standard deviation or median and interquartile amplitude. For comparison between groups, we used Student's t test for independent (unpaired) samples (Shapiro-Wilk normality test) and, in case of asymmetry, the Mann-Whitney test. Qualitative variables were described as absolute and relative frequencies. For comparing proportions between groups, the Pearson chi-square test or Fisher exact test were applied. We used the the Kaplan-Meier survival curve estimate method to evaluate survival time and the log-rank chi-square test for comparison between groups.

To control confounding factors in relation to death, Cox proportional hazards model was used. As a measure of effect, the hazard ratio (HR) was calculated, with respective 95% confidence intervals (CI). The criterion for entering a variable in the multivariate model was that it presented p value < 0.20 in univariate analysis.

The level of significance was $p < 0.05$, and the data were analyzed with Statistical Package for the Social Sciences software version 21.0.

Results

In this study, the sample of 74 individuals of the Veranópolis cohort had a median follow-up time of 9 years (P25 – P75: 6 – 14 years), ranging from 0.6 to 21 years. It is worth underscoring that there were no follow-up losses in this sample. Based on statements by the elderly individuals, 94.6% descended from Italian immigrants. The APOE gene (allele) frequency present in the sample was 4.1% ε2; 85.1% ε3, and 10.8% ε4. The genotype frequency was 1.4% E2E2; 5.4% E2E3; 71.6% E3E3, and 21.6% E3E4. The genotype distribution is in Hardy-Weinberg equilibrium ($\chi^2 = 0.07$; degree of freedom = 1; $p = 0.79$). No carriers of the E2E4 and E4E4 genotypes were found in the sample. Therefore, only the E3E4 formed the exposed group, that is, carriers of the APOE ε4 risk allele. Table 1 summarizes the characteristics of the groups of interests. The complete table, including all the described variables, can be found in a quantitative, categorized form in Additional File 1: Complete Table 1.

The causes of death between the E3E3 and E3E4 groups are summarized in Table 2. We point out that average life expectancy for individuals was 92.3 years (95% CI 91.2 to 93.4). For comparison, the table presents the levels of significance without adjustment and adjusted for variables with $p < 0.2$ in univariate analysis.

To evaluate survival of the elderly according to the APOE genotypes, the Kaplan-Meier survival curve estimate method was used, represented in the graph in Figure 1. We observed that there was no association between APOE polymorphisms and survival (logrank = 0.955) in the very elderly in this sample.

Additionally, it is pertinent to analyze cardiovascular risk factors associated with the mortality in very elderly, since this age range usually presents singular and, at the same time, contradictory results. In order to do this, Kaplan-Meier survival estimates were used with Cox regression to control

Table 1 - Characterization of the sample at baseline

Variables	Total sample	E3E3 genotype	E3E4 genotype	p*
	(n = 69)	(n = 53)	(n = 16)	
Age at entry (years)	82.6 2.8	82.2 2.7	84.0 ± 2.8	0.021
Sex				0.267
Male	23 (33.3)	20 (37.7)	3 (18.8)	
Female	46 (66.7)	33 (62.3)	13 (81.3)	
B-ADL†	2.98 (1.44-5.55)	2.95 (1.38-5.46)	3.19 (1.54-7.44)	0.631
Smoking				0.717
Non-smoker	56 (81.2)	42 (79.2)	14 (87.5)	
Smoker/ex-smoker	13 (18.8)	11 (20.8)	2 (12.5)	
Alcohol abuse				0.093
No	17 (24.6)	13 (24.5)	4 (25.0)	
Yes	18 (26.1)	17 (32.1)	1 (6.3)	
Teetotalers	34 (49.3)	23 (43.4)	11 (68.8)	
BMI (kg/m2)†	26.8 ± 5.4	27.6 ± 5.5	23.7 ± 3.6	0.011
Physical activity (kcal/week)	5133 (2386-9846)	5421 (2155-10544)	3580 (2300-6930)	0.216
SBP (mmHg)	161 ± 25.3	162 ± 23.7	158 ± 30.5	0.489
DBP (mmHg)	86.3 ± 13.2	88.6 ± 12.7	78.5 ± 12.4	0.007
Pulse pressure (SBP-DBP)	75.1 ± 22.7	73.9 ± 21.5	79.0 ± 26.8	0.439
Hypertension	62 (89.9)	48 (90.6)	14 (87.5)	0.660
Fasting glycemia (mg/dL)‡	95.4 ± 20.7	96.2 ± 22.7	92.6 ± 12.2	0.539
Total cholesterol (mg/dL)‡	209 ± 48.8	203 ± 43.9	229 ± 59.5	0.066
LDL cholesterol (mg/dL)§	138 ± 42.1	132 ± 36.0	156 ± 55.0	0.055
HDL cholesterol (mg/dL)‡	43.4 ± 11.4	44.0 ± 12.5	41.4 ± 6.6	0.284
Triglycerides (mg/dL)‡	102 (85.8-146)	102 (83.4-144)	107 (88.2-159)	0.806

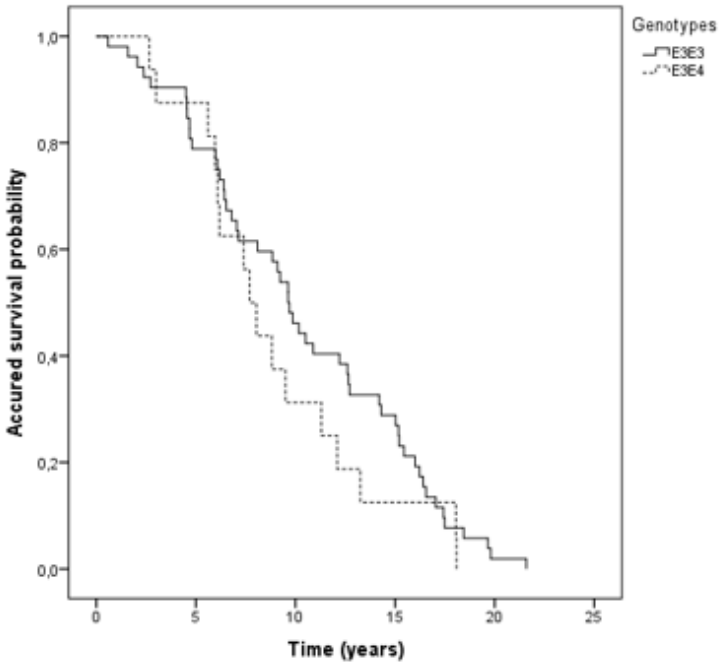
*Results described as average ± standard deviation, median (25 – 75 percentiles) or n (%). * t-student test (comparison of averages), Mann-Whitney test (comparison of medians), Pearson chi-square test (categorical variables) or Fisher exact test (for the variables of smoking and hypertension); † variables analyzed in 15 individuals with the E3E4 genotype; ‡ variables analyzed in 52 individuals with the E3E3 genotype; § variable analyzed in 51 individuals with the E3E3 genotype. B-ADL: The Bayer Activities of Daily Living Scale; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein.*

Table 2 - Comparison of outcomes between genotypes

Outcomes	Sample total (n = 69)	Genotype E3E3 (n = 53)	Genotype E3E4 (n = 16)	p	$p^{adjusted}$†
	n (%)	n (%)	n (%)		
Death	69 (100)	53 (100)	16 (100)	-	-
Cause of death				0.216*	0.302
Cardiovascular	43 (62.3)	36 (67.9)	7 (43.8)		
Dementia	6 (8.7)	4 (7.5)	2 (12.5)		
Other	20 (29.0)	13 (24.5)	7 (43.8)		

** Pearson chi-square test; † adjusted for age of entry in the study, alcohol consumption, body mass index, physical activity ≥ 4,000 kcal/week, diastolic blood pressure, and total and low-density lipoprotein cholesterol*

(A)



(B)

	Survival probability (%)										
Time (years)	1	3	5	7	9	11	13	15	17	19	21
E3E3	98.1	90.4	78.8	63.5	57.7	40.4	32.7	26.9	11.5	5.8	1.9
E3E4	100	93.8	87.5	62.5	37.5	31.3	18.8	12.5	12.5	0.0	0.0

Figure 1 – *(A) Kaplan-Meier survival curve for carriers of the E3E3 and E3E4 genotypes. (B) Survival probability for the groups with a periodicity of 2 years.*

confounding variables. The results are presented in Table 3 (and in Additional File 2: Complete Table 3). The survival curves for the categorical factors associated with death can be viewed in Figure 2.

Considering that the sample for this study comprised elderly individuals selected at two moments of follow-up, there may have been a selection bias. Specifically, the nine elderly individuals that were genotyped in 2011 would form a group of survivors. With the intention of weighing this bias, we performed new analyses without these individuals. In this manner, we obtained very similar results, including in relation to the sample descriptive level, with the exceptions of smoking and diabetes, which lost the association with mortality. In this new analysis, the risk of death in smokers and ex-smokers was 2.14 (95% CI 0.93 to 4.91) in the multivariate model ($p = 0.075$).

Discussion

APOE Polymorphism

Review studies have shown that genetic frequencies related to APOE polymorphism are highly variable, especially in regard to the ε4 allele.[29] The gene frequency observed in the present study is similar to that found in the population in Italy.[30] Since the sample for this work comprised 94.6% Italian immigrant descendants, this similarity was expected, and it indicates that the sampling process was adequate.

Curiously, in our results, individuals with the E3E4 genotype presented an average age significantly older than E3E3 individuals (Table 1). We believe this difference to be casual, since relevant publications indicate that there is no difference in mortality between carriers of the E3E3 and E3E4 genotypes

Table 3 - Univariate and multivariate Cox regression analysis for factors associated with mortality

Variables	Univariate	p	Multivariate*	p
	HR (95% CI)		HR (95% CI)	
Age (years)†	1.19 (1.10 – 1.30)	< 0.001	1.24 (1.12 – 1.39)	< 0.001
Males	1.45 (0.88– 2.39)	0.150	1.04 (0.47 – 2.32)	0.920
E3E4 genotype	1.35 (0.77 – 2.39)	0.299	-	-
B-ADL	0.93 (0.85 – 1.02)	0.119	0.92 (0,82 – 1.02)	0.102
Smoker/ex-smoker	2.37 (1.29 – 4.36)	0.005	2.30 (1.01 – 5.24)	0.047
Alcohol consumption (g/week)	1.00 (0.99 – 1.00)	0.602	-	-
BMI	0.94 (0.90 – 0.99)	0.018	0.96 (0.91 – 1.01)	0.107
Physical activity ≥ 4,000 kcal/week	0.55 (0.34 – 0.89)	0.016	0.49 (0.27 – 0.88)	0.017
SBP	0.99 (0.98 – 1.00)	0.050	0.98 (0.97 – 0.99)	0.018
DBP	0.97 (0.94 – 0.99)	0.016	1.01 (0.98 – 1.04)	0.669
Pulse pressure	0.99 (0.98 – 1.01)	0.392	-	-
Hypertension	0.53 (0.24 – 1.19)	0.123	1.35 (0.54 – 3.38)	0.516
Diabetes mellitus	5.10 (1.70 – 15.3)	0.004	3.95 (1.27 – 12.3)	0.018
Total cholesterol ≥ 200 mg/dL	0.52 (0.32 – 0.86)	0.010	0.74 (0.42 – 1.31)	0.303
LDL ≥ 160 mg/dL	0.69 (0.41 – 1.18)	0.175	1.00 (0.99 – 1.00)	0.410
Low HDL‡	1.46 (0.86 – 2.47)	0.159	1.03 (0.57 – 1.84)	0.932
Triglycerides ≥ 150 mg/dL	1.23 (0.69 – 2.20)	0.489	-	-

** The criterion for entering the variable in the multivariate model was p value < 0.20 in univariate analysis. † Age at the time of cohort recruitment (study entry). ‡ Low HDL refers to HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women. HR: hazard ratio; 95% CI: 95% confidence interval; B-ADL: The Bayer Activities of Daily Living Scale; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein.*

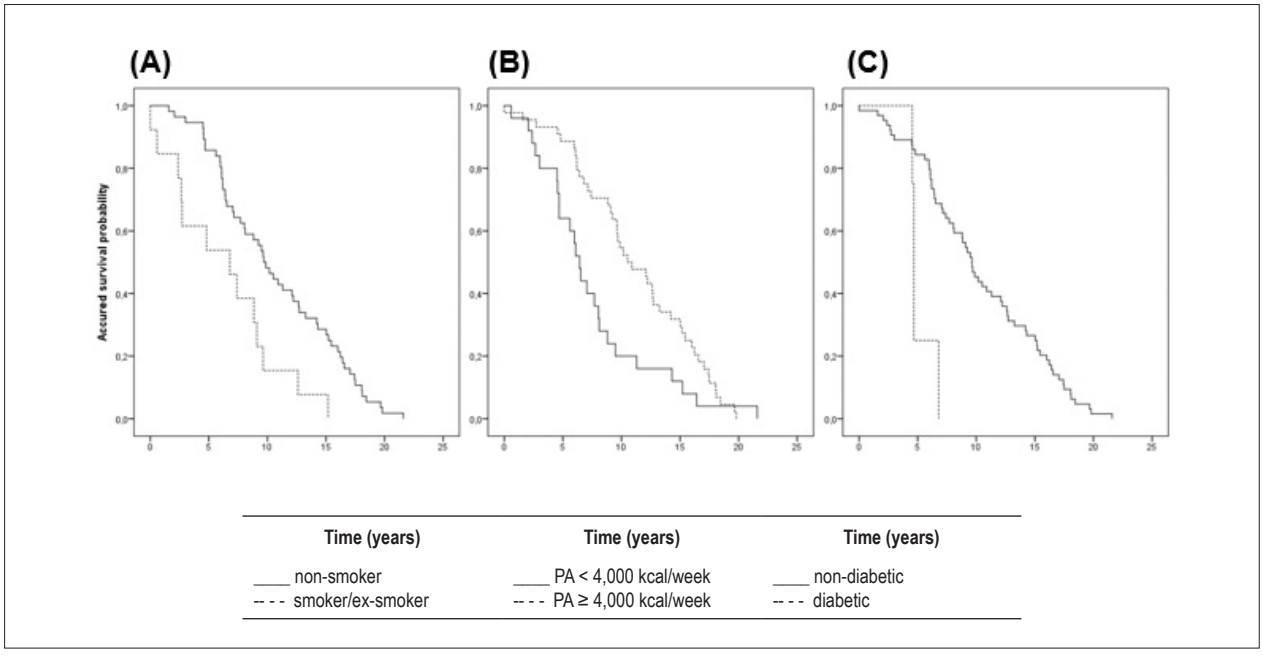


Figure 2 – *Survival curves for factors associated with mortality in the very elderly: (A) smoking, (B) vigorous physical activity [PA] and (C) diabetes mellitus.*

before 80 years of age.[31,32] Among the risk factors for CVD investigated, BMI and DBP presented significant differences between the evaluated genotypes. In those cases, individuals in the E3E3 group presented an average BMI classified as overweight (WHO) or overweight (Lipschitz) and higher DBP. We did not find similar data to these in studies previously published on the community basis, but similar comparisons in larger samples in the adult to young elderly age range suggest that there is no association between obesity[33] or DBP levels[34] and the APOE genotypes.

Classical Cardiovascular Risk Factors

Our results have indicated that some cardiovascular risk factors are associated with general mortality, even in the very elderly age group, in which the majority of these classical factors lose their predictive power for risk. Smoking appeared to be important in this relation. The risk of death in smokers and ex-smokers was 2.30 (95% CI 1.01-5.24) times that of non-smokers. A meta-analysis study[7] brings evidence that smoking remains a strong risk factor for mortality in elderly individuals aged 80 and over as well. In relation to elderly individuals with diabetes, despite the low percentage (6%) present in our sample, this number was enough to attain a significant difference. Very elderly individuals with diabetes had 3.95 (95% CI 1.27-12.3) times higher risk of death in comparison with those without diabetes, showing that this risk factor remains important, even over 80 years of age. A similar result became evident in the very elderly cohort of The Adventist Health Study.[8] Vigorous physical activity appeared as a protective factor against mortality in our study. Individuals who expended more than 4,000 Kcal/week through work and leisure activities had a 51% reduction in the risk of death (95% CI 12% to 73%). Regarding practice of vigorous activities, a study that combined two Australian cohorts, the Australian Longitudinal Study on Women's Health and the Health in Men Study, with more than 18,000 participants with average age over 70, reinforces our findings.[35] In this study, physical activities were categorized according to intensity, and they showed a 40% reduction in mortality for women and a 22% reduction for men who practiced rigorous physical activity.[36]

Finally, in this study, the increase in SBP appeared as a protective factor against general mortality. Thus, an increase of 1 mmHg in SBP reduced the risk of death by 2% (95% CI 1-3%). These findings are in accordance with the results from most studies that identified an inverted reaction between BP and risk of death from cardiovascular or any other causes in persons aged 80 or older.[37,38] However, this subject still generates discussions and propositions in the scientific community. The conflicting results from cohort studies and some clinical trials,[39] such as the results from the Hypertension in the Very Elderly Trial (HYVET) are difficult, but there is a plausible explanation. The HYVET[40] included participants with at least 160 mmHg, and the target for SBP was to attain levels below 150 mmHg. In comparison, our study, which is community based and therefore had no BP restrictions, the risk for individuals with very low BP probably surpassed the risk for those with high BP, which could explain our data showing protection.

Considerations and Limitations

Some limitations in this study must be considered; the small sample size is the main one. External validation is limited, given that the study population is a fraction of a very specific cohort, namely, Italian descendants in a single location, and is not, therefore, representative of the Brazilian elderly population. Another shortcoming that could be considered was the inclusion of elderly patients who were sick, that is, with physical restrictions, in the same group of elderly individuals with weekly energy expenditure below 4,000 kcal. They were considered as sedentary, although this was the situation at the moment they were evaluated and it does not exactly reflect their lifestyle. Nevertheless, only 5% of the sample were sick and unable to practice any physical activity.

The most original aspect of our study is the study population, namely, elderly individuals aged 80 years or older, a group that is not frequently included in observational studies and clinical trials. Furthermore, information on the relationship between APOE genotypes/classic cardiovascular risk factors and mortality in this age group is lacking, especially in Brazil. The results of our study add a relevant contribution to both prevention and management of risk factors in this population.

Conclusions

Considering that the population is getting older and the impact of traditional risk factors on outcomes may not be the same as it is in younger ages, our results add a relevant contribution to the discussion on how to better control risk factors in this population. Our study did not find evidence that very elderly carriers of the APOE ε4 allele were at greater risk of death than carriers of the E3E3 reference genotype. In contrast, exposure to some risk factors was significantly related to general mortality at an advanced age; namely, smoking and DM were characterized as risk factors. However, vigorous physical activity and higher SBP were protective factors.

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Author Contributions

Conception and design of the research, Analysis and interpretation of the data and Statistical analysis: Vivian L, Moriguchi EH; Acquisition of data and Critical revision of the manuscript for intellectual content: Vivian L, Bruscato NM, Werle BM, Carli W, Soares RAG, Santos PCJL, Moriguchi EH; Writing of the manuscript: Vivian L, Bruscato NM.

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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*Supplemental Materials

For additional information, please click here.

Lifestyle in the Very Elderly Matters

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Short Editorial related to the article: Association of Cardiovascular Risk Factors and APOE Polymorphism with Mortality in the Oldest Old: A 21-Year Cohort Study

According to the estimates and projections of the 2019 Revision of World Population Prospects, life expectancy will continue to rise in the following 30 years worldwide, the percentage of the population aged 65 years or over will jump from 9% in 2020 to 16% in 2050, and the number of persons aged 80 years or over will triple up to 2050.[1]

The biology of aging and implicated genes has been studied for a long time as a basis for the search for therapies that may mitigate age-related processes, such as dementia and cardiovascular disease. Among the multitude of aspects that have been explored, the research involving apolipoprotein E (apoE) assumes particular relevance. ApoE is a 299-amino acid protein mainly synthesized by the hepatocytes. Like any other apolipoprotein, apoE is a constituent of lipoproteins and, therefore, has a role in lipid metabolism. In the plasma, apoE is primarily carried by triglyceride-rich lipoproteins and mediates the clearance of their remnants by the low-density lipoprotein receptor. In the brain, *in situ* produced apoE acts on the redistribution of lipids to neurons, as well as in the clearance of β-amyloid, much known for its association with Alzheimer disease.[2,3]

It is well acknowledged that polymorphisms in the APOE gene are associated with pathological processes. Three common APOE alleles are described: the ε2 (the least frequent), ε3 (the most prevalent and considered to be the wild or "neutral" type), and ε4. Based on these alleles, a specific individual can display a homozygous (APOE ε2/ε2, APOE ε3/ε3, or APOE ε4/ε4) or a heterozygous (APOE ε3/ε2, APOE ε4/ε2, or APOE ε4/ε3) genotype. ApoE2 and apoE4 differ from apoE3 by one single amino acid substitution. Nevertheless, these polymorphisms significantly modify the structure and function of apoE.[2,3]

ApoE is the major genetic factor that predisposes to late-onset Alzheimer disease. Compared to apoE3, the presence of apoE4 confers a higher risk of Alzheimer disease, whereas apoE2 is associated with a lower risk. Large cohort studies also showed an association between apoE4 and a higher risk of atherosclerotic cardiovascular disease, cardiovascular mortality, and all-cause mortality.[2,3]

Keywords

Aging; Apolipoproteins E; Life Style.

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In this context, this issue of the *Arquivos Brasileiros de Cardiologia* publishes an article from the Veranópolis prospective cohort, investigating the relationship between APOE genotype and mortality in a population not commonly studied, composed by individuals aged 80 years or older.[4] In a very long follow-up (up to 21 years), the authors did not detect a difference in the hazard of mortality between APOE ε3/ε3 individuals, as compared with APOE ε3/ε4 participants.

The "negative" finding was possibly a consequence of the highly selective sample and the small number of participants (16 with the APOE ε3/ε4 genotype and 53 with the APOE ε3/ε3 genotype), which imposed a lack of power to detect small differences. In a large cohort of the general Danish population, only a minimal difference in the median survival associated with different genotypes was reported (86.4 years in ε33 carriers and 85.9 years in ε43 carriers).[5] Moreover, among the Veranópolis subjects, no one had the APOE ε4/ε4 genotype, which is associated with the highest mortality.[5]

Conversely, even with the limited number of participants, the authors were able to detect an association between traditional risk factors and overall mortality. That was the most striking finding of the study. Adjusted analyses demonstrated clear deleterious effects of smoking and diabetes mellitus, and a powerful protective effect of physical activity.[4]

The results also point to an inverse relationship between blood pressure and mortality: each 1 mmHg rise in systolic blood pressure was associated with a 2% reduction in the risk of death.[4] This finding seems intriguing, since randomized controlled trials support intensive blood pressure lowering in older persons to prevent hard events.[6] The presence of confounders may be responsible for this finding, although a genuinely detrimental effect of excessive blood pressure lowering in this population is also possible.

The increased risk of death associated with diabetes mellitus in the Veranópolis study, although not a surprise, highlights the importance of measures devoted to the prevention of the disease. In this regard, lifestyle interventions with caloric restriction in the diet and physical activity, as well as some pharmacological options (e.g., metformin), have shown to prevent or delay the development of diabetes.[7]

The harmful effects of smoking in the Veranópolis study are consistent with other reports. A large meta-analysis involving subjects aged 60 or older from prospective cohort studies unequivocally showed that smoking is a strong independent risk factor of cardiovascular events, advancing cardiovascular mortality by more than five years.[8] Moreover, a few years of smoking cessation were enough to detect a beneficial effect on cardiovascular mortality, and this benefit increased over time after cessation.[8]

The Veranópolis study showed that older people who exercised (weekly energy expenditure of at least 4000 kcal) had an impressive 51% lower risk of dying. This result is corroborated by several other publications.[9-13] Even light-intensity physical activity has been shown to reduce mortality in older people. In a prospective study from Spain with a follow-up period of 13 years, participants (aged 65 years or older) in the highest-intensity level of physical activity had the lowest mortality risk after adjustment for several covariates. Those with light-intensity physical activity had a better prognosis than sedentary individuals.[10] Similarly, data from the Women's Health Initiative have shown that even light-intensity physical activity reduces cardiovascular events and all-cause mortality in women with a mean age of 79 years.[11,12] Guidelines have recommended multicomponent physical activity for older people, combining aerobic, muscle-strengthening, and balance exercises, to promote comprehensive health benefits, including prevention of falls. If the older adult cannot do moderate-intensity aerobic activity due to a chronic disease, he or she should be encouraged to be as physically active as allowed by his or her condition.[14]

Analyses of observational data suffer from the possibility of bias introduced by lack of adequate adjustments and unknown confounders, as well as reverse causality. Are sedentary individuals more prone to adverse outcomes because of the lack of the beneficial effects of physical activity or because they already have morbid conditions that prevent them from exercising? Nevertheless, considering the multiple studies with appropriate adjustments for comorbidities and functional status, the evidence points to a clear message: lifestyle makes a difference, even in very old persons.

That said, the implications for the medical community and the attending physician are straightforward: age should not be a barrier to the implementation of lifestyle modifications. On the contrary, efforts should be made to create and facilitate the access of older people to programs focused on lifestyle, including those related to smoking cessation, physical activity, dietary habits, and psychological well-being. Guidelines can be developed. Strategies to engage older people in healthy activities should be studied. Novel technologies, such as the use of accelerometer[11,12] and internet platforms,[15] can be used to optimize the results. Caregivers and other personnel should be trained to guide physical activity, recognizing the limits and peculiarities of this specific subgroup. With multifaceted actions, lifestyle modification can be an essential pillar to reduce the burden of age-related diseases in the coming decades.

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Aerobic Exercise and Cardiac Function of Murines Exposed to Doxorubicin: a Meta-Analysis

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Abstract

Background: **Cardiotoxicity may be a consequence of treatments with doxorubicin (DOX).**

Objectives: **To investigate the effect of aerobic exercise on the prevention of cardiac dysfunction in murines exposed to DOX.**

Method: **A comprehensive search was conducted in 9 databases in December 2017. Studies that evaluated the cardiac function of murines exposed to DOX were included. The significance level adopted was 5%.**

Results: **In a comparison between 230 murines that underwent aerobic exercise plus DOX treatment and 222 control murines (DOX treatment only), fractional shortening showed an improvement of 5.33% in favor of the experimental group (p = 0.00001). Left ventricle developed pressure also showed an increase of 24.84 mm Hg in favor of the group of 153 murines that performed exercise in comparison to the control group of 166 murines (p = 0.00001).**

Conclusion: **Preclinical studies included in this meta-analysis indicated that exercise is a good nonpharmacological strategy for preserving post-DOX cardiac function. (Arq Bras Cardiol. 2020; 115(5):885-893)**

Keywords: **Muridae; Exercise; Anti-Bacterial Agents; Doxorubicin; Meta-Analysis.**

Introduction

Chemotherapy exposes a new panorama in oncology, in which the survival of patients has increased along with their vulnerability to acquired cardiotoxicity in advanced treatments.[1] The effects of the toxicity generated by the antineoplastic agents used in the treatment may manifest immediately, during their administration, or even years later.[2,3] Among the organs affected, the heart deserves special attention because heart failure, often acquired after chemical treatment, has an equal or worse prognosis when compared to cancers in the liver, intestine, bladder, prostate, breast, and ovary. Therefore, such complications may interrupt the treatment and compromise the probability of a cure.[4]

Doxorubicin (DOX) is an efficient chemotherapeutic agent in the fight against breast cancer, solid tumors in children, and aggressive lymphomas.[5] However, studies suggest that DOX cardiotoxicity promotes a decrease in left ventricular ejection fraction (LVEF). The incidence of cardiomyopathies in patients previously or currently treated with DOX is 3% to 26%, but data on the prevalence are still scarce.[6] The decrease in LVEF may begin with the first doses of DOX and is related to the cumulative dose. Doses below 550 mg/m^2 may reduce the possibility of cardiomyopathies.[2] Higher doses may cause permanent damage to the myocardium, characterized by apoptosis of the myocytes, resulting in fibrosis and consequent loss of cardiac function.[3]

Oxidative stress potentiated by DOX seems to initiate a series of biochemical processes in cardiac muscle fibers, which result in injury to the sarcoplasmic reticulum and mitochondria, structural and functional modification of myofibrils, and modification of the excitation-contraction coupling and calcium flux. These changes lead to apoptosis and, ultimately, loss of the regeneration capacity of the cardiac muscle.[7]

Improved immune system function, reduced inflammatory activity, and attenuated metabolic effects of immobility and chemotherapy are some of the benefits of exercise, making it an efficient nonpharmacological tool that can reduce the toxic effects of DOX and help improve the quality of life of patients undergoing treatment.[8,9] The cardioprotective potential of exercise against cardiotoxicity seems to be linked to several molecular mechanisms, such as increased antioxidant production, regulation of proapoptotic signaling, limitation of myocyte turnover, modulation of cardiac AMP-activated protein kinase (AMPK) activity, negative regulation of cardiac autophagy, reduction in myocardial accumulation of DOX, and others.[10-12]

Studies on exercise and cardiac dysfunction caused by DOX cardiotoxicity in humans are still limited, but there is a reasonable number of preclinical studies in the literature.

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Therefore, this meta-analysis included preclinical studies and, to the best of our knowledge, is the first on the subject. The aim was to investigate the effects of aerobic exercise on the cardiac function of murines exposed to DOX.

Methods

Inclusion Criteria

Randomized controlled trials (RCTs) of murines that performed aerobic exercise before, during, and after exposure to DOX compared to a control group were included. The cardiac function should have been measured by fractional shortening (FS%) and left ventricular developed pressure (LVDP).

Exclusion Criteria

We excluded studies that used different designs from RCTs, that used concomitant medication in the experimental exercise group, that included humans, or that had no mean and standard deviation for FS% and LVDP results.

Search

The search was conducted in December 2017 using the MEDLINE, LILACS, CENTRAL Cochrane, PEDro, CINAHL, ScienceDirect, SPORTDiscus, Scopus, and Web of Science electronic databases. The descriptors cardiotoxicity, cancer, doxorubicin, exercise, and all synonyms present in the Medical Subject Headings and Descriptors in Health Sciences databases were used in the search.

Data Extracted from the Studies

The types of exercises, training protocols, dosages of DOX infusions, forms of administration, period of exposure to the drug, FS% and LVDP (mm Hg) results, and sample sizes were extracted from the studies selected for review.

For the *in vivo* analysis of cardiac function, left ventricular FS% measured by echocardiography and Doppler was considered. FS% is one of the main parameters to be monitored in patients exposed to cardiotoxic therapies, as this is an indicative measure of left ventricular systolic function.[13,14]

An evaluation of LVDP using a pressure transducer positioned in the left ventricle (LV), based on the Langendorff cardiac isolation model, is common in such studies. Therefore, the *ex vivo* analysis was also considered to examine the contractile capacity of the LV.[15]

Analysis of Methodological Quality

An independent evaluator analyzed the risk of bias in each study included in the meta-analysis using the Cochrane Collaboration tool for assessing risk of bias in randomized trials (2005-2007), available for download at http://www.cochrane-handbook.org. Following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,[16] the GRADE approach via GRADEproGDT, available at https://gradepro.org/, was used to analyze the level of evidence for each outcome (FS% and LVDP).

Statistical analysis

Review Manager v. 5.3, with a continuous outcome, statistical method of inverse variance, random-effects model analysis, measure of effect by mean difference, and 95% confidence interval (CI), was used for the studies and for the meta-analysis and ordering of studies by weight. The significance level adopted was 0.05.

Results

The steps performed in the search of the manuscripts are described in the diagram in Figure 1. Among the 9 studies selected for analysis, 7 had FS% results and 4 had LVDP results. Only 2 studies had both variables analyzed.

The study conducted by Hydock et al.[19] (2012) tested 2 different DOX injection protocols. Therefore, it was divided into two analyses named "a" and "b". To assess the influence of the female hormone on DOX-induced cardiotoxicity, the study performed by Calvé et al.[20] (2012) was divided into "a" with normal rats and "b" with ovariectomized rats. Using 2 different exercise protocols, the study conducted by Jensen et al.[22] (2013) was divided into "a", in which the rats underwent a progressive treadmill protocol, and "b", in which the rats had free access to the running wheel. To better understand the results and their comparisons, Lien et al.[24] (2015) conducted four studies ("a", "b", "c", "d") according to the number of active groups (Tables 1 and 2).

The results for FS% and LVDP as well as I^2 in this meta-analysis are shown in Figures 2 and 3.

The risk of bias in the studies and the level of evidence in the meta-analysis are shown in Tables 3 and 4, respectively.

Discussion

In the present study, cardiac dysfunction resulting from DOX was evaluated using FS% and LVDP (mm Hg), which are related to left ventricular systolic function. A meta-analysis of the results of 230 murines that underwent aerobic exercise plus DOX treatment and 222 control murines (DOX treatment only) showed a FS% improvement of 5.33 ($p = 0.00001$) in those that performed aerobic exercise (Figure 2). Similarly, a meta-analysis of the results of 153 murines that underwent aerobic exercise plus DOX treatment and 166 control murines (DOX treatment only) showed a LVDP increase of 24.84 mm Hg ($p = 0.00001$) in those that performed aerobic exercise (Figure 3). In short, aerobic exercise contributed to improve the systolic function, i.e., to decrease the cardiac dysfunction caused by the use of DOX.

The toxicity of anthracyclines causes severe dysfunction in all muscle tissues. However, the cells in the cardiac muscle appear to accumulate higher amounts of DOX than the cells in the smooth and skeletal muscles.[27] Thus, early detection of cardiovascular risk factors, careful monitoring of parameters of left ventricular systolic and diastolic function, and measurement of LVEF and left ventricular filling pressure should be performed periodically in patients undergoing chemotherapy in order to avoid permanent loss of cardiac muscle function due to cardiotoxicity.[28]

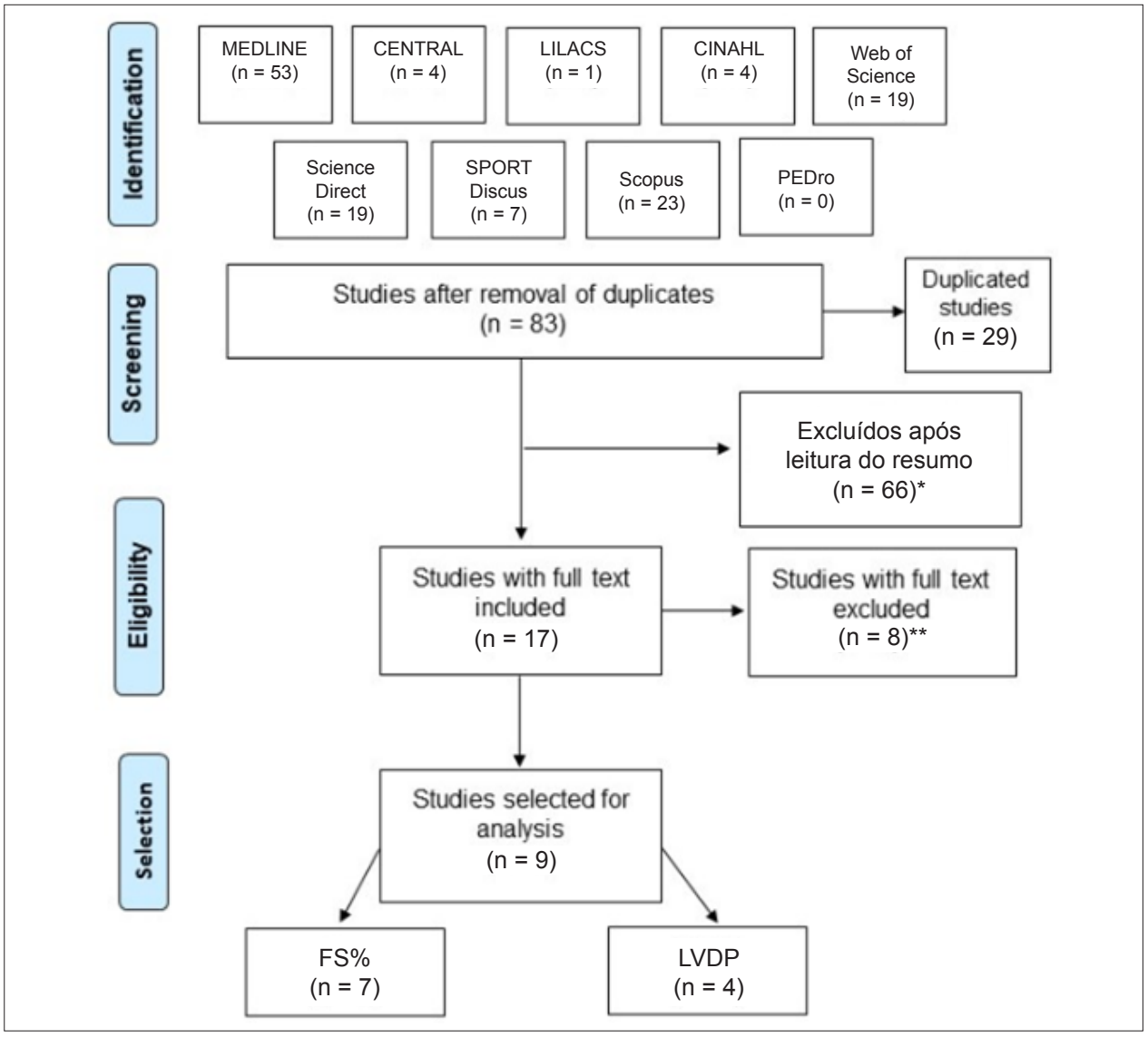

Figure 1 – *Flow diagram of the studies (Prisma, 2009)18. *Studies excluded because they did not fulfill the inclusion criteria; **Studies excluded because of concomitant use of medication in the experimental group, inclusion of humans, and/or absence of mean and standard deviation response for cardiac function. FS%: fractional shortening; LVDP: left ventricular developed pressure.*

Aerobic exercise appears to promote the release of antioxidants, thus protecting the cardiac fiber from damage caused by excessive release of reactive oxygen species after exposure to DOX.[29-32] This oxidative anti-stress effect is noticed when exercise is performed systematically, before or after exposure to the drug.[33] Although the cells are endowed with an endogenous anti-oxidant system, cardiomyocytes have a very low capacity for activation of this system when compared with cells from other tissues.[34,35] Thus, aerobic exercise has proved to be a good nonpharmacological strategy to fight cardiotoxicity.[36]

In humans, regular aerobic exercise 3 to 4 times a week for 40 minutes using moderate-to-extreme intensity activities seems to have a direct effect on the prevention of cardiovascular diseases, regardless of other risk factors, and contributes to lower the rates of cardiac mortality among those who practice it.[37,38] This frequency of exercise also affects the production of free radicals, protecting trained patients from the chronic effects generated by the oxidative stress of daily physical activities.[39]

A metaepidemiological study showed that an aerobic exercise intervention had a similar effect to drugs such as beta-blockers and angiotensin-converting enzyme inhibitors on mortality rates and secondary prevention in patients with coronary diseases, stroke rehabilitation, and treatment of heart failure.[40] Thus, it is important to consider the nonpharmacological treatment with exercise for patients exposed to interventions that accentuate the risk of cardiovascular diseases, such as chemotherapy.

Table 1 – Summary of studies selected for the variable left ventricular fractional shortening (FS%).

Author (year)	Type of exercise	Intervention protocol	DOX injection	Left ventricular fractional shortening (FS%)			
				Control + DOX		Aerobic exercise + DOX	
				n	$\bar{x}$ SD	n	$\bar{x}$ SD
Hayward et al. (2012)[18]	Aerobic Running wheel	Free access 24h/day Total: 10 weeks	2 mg/kg for 7 days Total = 14 mg/kg during exercise	15	52 ± 38	17	61 ± 29
Hydock et al. (2012) (a)[19]	Aerobic Running wheel	Free access 24h/day Total: 10 weeks	1 mg/kg for 15 days Total = 15 mg/kg during exercise	15	45 ± 3	9	46 ± 4
Hydock et al. (2012) (b)[19]	Aerobic Running wheel	Free access 24h/day Total: 10 weeks	2.5 mg/kg weekly for 6 weeks Total = 15 mg/kg during exercise	10	52 ± 5	10	61 ± 4
Calvé et al. (2012) (a)[20]	Aerobic Swimming	1h/day Total: 4 weeks	3 mg/kg on the 26th day of life pre-exercise	8	53.1 ± 3.8	8	49.5 ± 2.2
Calvé et al. (2012) (b)[20]	Aerobic Swimming	1h/day Total: 4 weeks	3 mg/kg on the 26th day of life pre-exercise	8	47 ± 2.1	8	51.6 ± 1.7
Dolinsky et al. (2013)[21]	Aerobic Treadmill	10-18 m/min 5 days/week Total: 8 weeks	8 mg/kg per week for 4 weeks Total = 32 mg/kg pre-exercise	8	23.8 ± 1.0	8	28.0 ± 0.7
Jensen et al. (2013) (a)[22]	Aerobic Treadmill	13-30 min/m 5□-18□ 20-60 min/day 5 days/week Total: 10 weeks	10 mg/kg single dose post exercise	8	50.47 ± 2.77	4	61.60 ± 7.28
Jensen et al. (2013) (b)[22]	Aerobic Running wheel	Free access 24h/day Total: 10 weeks	10 mg/kg single dose post exercise	8	50.47 ± 2.77	7	58.3 ± 4.33
Parry et al. (2015)[23]	Aerobic Running wheel	Free access 24h/day Total: 11 weeks	12 mg/kg single dose post exercise	6	59 ± 6†	4	63 ± 4†
Lien et al. (2015) (a)[24]	Aerobic Treadmill	18-24 m/min Total: 5 days	10 mg/kg single dose post exercise	10	48 ± 4	10	56 ± 4
Lien et al. (2015) (b)[24]	Aerobic Running wheel	Free access 24h/day Total: 5 days	10 mg/kg single dose post exercise	10	48 ± 4	10	51 ± 5
Lien et al. (2015) (c)[24]	Aerobic Treadmill	18-24 m/min Total: 5 days	15 mg/kg single dose post exercise	13	39 ± 6	13	48 ± 5
Lien et al. (2015) (d)[24]	Aerobic Running wheel	Free access 24h/day Total: 5 days	15 mg/kg single dose post exercise	13	39 ± 6	12	45 ± 3

DOX: doxorubicin; x: mean; SD: standard deviation; †: measurement done on the 5th day after DOX injection; (a), (b), (c), (d) are subdivisions of the studies conducted by Hydock et al.[19] (2012), Calvé et al.[20] (2012), Jensen et al.[22] (2013), and Lien et al.[24] (2015).

Table 2 – Summary of studies selected for the variable left ventricular developed pressure (LVDP), mm Hg

Author (year)	Type of exercise	Intervention protocol	DOX injection	Left ventricular developed pressure (LVDP), mm Hg			
				Control + DOX		Aerobic exercise + DOX	
				n	$\bar{x}$ SD	n	$\bar{x}$ SD
Chicco et al. (2005)[25]	Aerobic Running wheel	Free access 24 h/ day Total: 8 weeks	10 µM single dose post exercise	7	30.5 ± 1.4	7	50.1 ± 7.7
Chicco et al. (2006)[26]	Aerobic Treadmill	15-27 m/min 0°-5° 20-60 min/day 5 days/week Total: 12 weeks	15 mg/kg single dose post exercise	15	46 ± 9	15	84 ± 7
Hayward et al. (2012)[18]	Aerobic Running wheel	Free access 24 h/ day Total: 10 weeks	2 mg/kg for 7 days Total = 14 mg/kg during exercise	22	91 ± 15†	22	121 ± 12†
Jensen et al. (2013) (a)[22]	Aerobic Treadmill	13-30 min/m 5°-18 m 20-60 min/day 5 days/week Total: 10 weeks	10 mg/kg single dose post exercise	14	70 ± 3††	10	93 ± 3††
Jensen et al. (2013) (b)[22]	Aerobic Running wheel	Free access 24 h/ day Total: 10 weeks	10 mg/kg single dose post exercise	14	70 ± 3††	10	89 ± 2††

DOX: doxorubicin; x: mean; SD: standard deviation; (a) and (b) are subdivisions of the study conducted by Jensen et al. (2013); †: measurement done with 300 beats per minute; ††: measurement done on the 9th day after DOX injection.

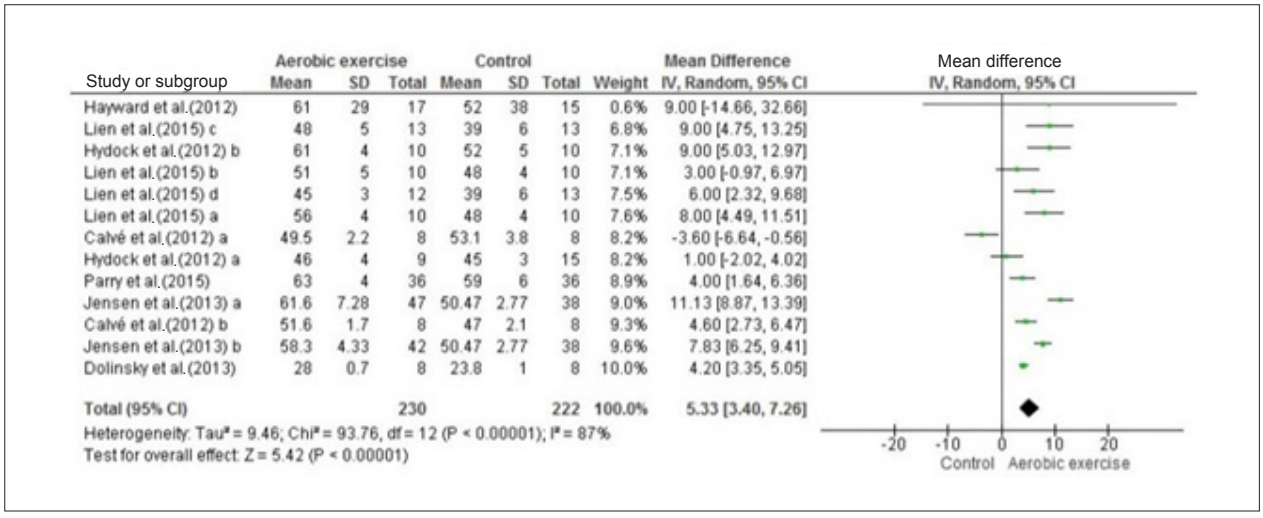

Figure 2 – *Forest plot of the studies of murines exposed to doxorubicin that compared fractional shortening in a group that performed aerobic exercise and a sedentary control group. SD: standard deviation; IV: inverse variance; CI: confidence interval.*

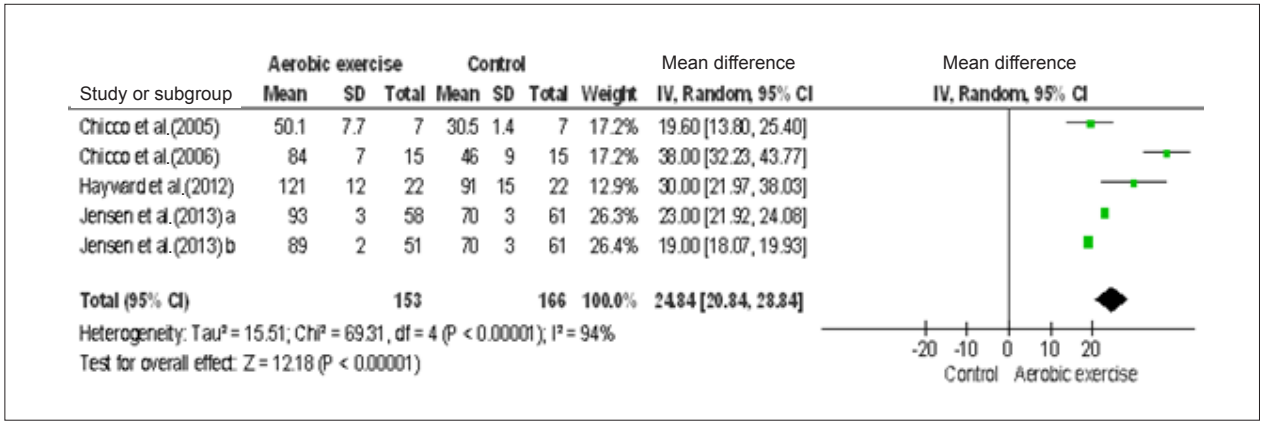

Figure 3 – *Forest plot of the studies of murines that compared left ventricular developed pressure in a group that performed aerobic exercise and a sedentary control group. SD: standard deviation; IV: inverse variance; CI: confidence interval.*

Table 3 – Cochrane collaboration tool for evaluation of the risk of bias

Author (year)	Randomization	Concealment of randomization	Blinding of participants*	Blinding of evaluators*	Incomplete outcomes	Selective outcome reporting	Other sources of bias	Risk of bias
Chicco et al. (2005)	Low	Low	Low	Low	Low	Low	Low	Low
Chicco et al. (2006)	Low	Low	Low	Low	Low	Low	Low	Low
Hayward et al. (2012)	Low	Low	Low	Low	Low	Low	Low	Low
Hydock et al. (2012)	Low	Low	Low	Low	Low	Low	Low	Low
Calvé et al. (2012)	Low	Low	Low	Low	Low	Low	Low	Low
Jensen et al. (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Dolionsky et al. (2013)[21]	Low	Low	Low	Low	Low	Low	Low	Low
Parry et al. (2015)[23]	Low	Low	Low	Low	Low	Low	Low	Low
Lien et al. (2015)[24]	Low	Low	Low	Low	Low	Low	Low	Low

** The items referring to randomization and blinding of the sample were considered as low risk of bias even when not stated in the randomized controlled trial, given that studies of murine models neutralize these biases.*

Table 4 – GRADE tool for analysis of the level of evidence.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	Control	Relative (95% CI)	Absolute (95% CI)		
Fractional shortening (assessed with echocardiography and Doppler)												
13	randomized trials	not serious	not serious	very serious[a]	not serious	none	230	222	-	mean **5.33% higher** (3.4 to 7.26)	⊕⊕◯◯ Low	Critical
Left ventricular developed pressure (assessed with pressure transducer)												
5	randomized trials	not serious	not serious	very serious[a]	not serious	none	153	166	-	mean **24.84 mm Hg higher** (20.84 to 28.84)	⊕⊕◯◯ Low	Critical

CI: confidence interval; a: animal studies are considered indirect evidence.

Another positive aspect of exercise is related to fatigue, which, in addition to being a primary symptom of many cardiac events, is common in patients exposed to chemotherapy. Puetz, Beasman, and O'Connor[41] concluded in a meta-analysis that exercise programs for cardiac rehabilitation are associated with the perception of increased energy and decreased fatigue.[41]

The results found in this meta-analysis in favor of the group that underwent aerobic exercise plus DOX are strengthened by the findings of previous systematic reviews on the subject, which showed that the ability of aerobic exercise to prevent and fight cardiotoxicity generated by DOX exposure appears to be well established in animal studies.[42,43] However, the mechanisms of this effect have not yet been fully clarified.[44,45]

In a review of the effects of physical exercise on cardiovascular response in patients with breast cancer, Sturgeon et al.[46] revealed a lack of studies focused on cardiotoxicity in humans. They showed that although a few preclinical studies indicate a decrease in resting heart rate and blood pressure in patients who practiced aerobic exercise during and after chemotherapy, these parameters are not sufficient to indicate good cardiac function. Kirkham et al.[47] however, in a recent proof-of-concept study of patients with breast cancer, found favorable results when assessing the systolic function of the group that practiced only 1 aerobic exercise session of vigorous-intensity treadmill running up to 24 hours prior to DOX treatment.

Limitations

For both outcomes, the inconsistency between the studies was very high, with $I^2 = 87\%$ ($p = 0.00001$) for FS% and $I^2 = 94\%$ ($p = 0.00001$) for LVDP (Figures 2 and 3). Such inconsistency may be related to the wide variation in types of exercises, intervention protocols, and DOX dosage used (Tables 1 and 2). Thus, a random-effects analysis of the results was chosen. However, the final result does not seem to have been affected by this great heterogeneity. For example, of the 4 studies with the highest weight for FS%, 2 performed exercise before DOX and 2 after DOX, protocols ranged from 4 weeks to 10 weeks, and total DOX dose ranged from 3 mg/kg to 32 mg/kg. Therefore, it was not possible to conclude which protocols were the best.

These findings from preclinical studies provide only indirect evidence regarding clinical practice. Therefore, the GRADE tool had 2 levels lowered in the indirectness item, which resulted in a low level of evidence for the study variables.

Conclusion

This meta-analysis showed that, in studies of murines exposed to DOX, aerobic exercise before, during, or after exposure, performed in a single session or for up to 3 months, is a good strategy for maintenance of left ventricular function. Preclinical studies showed that, at this stage of research, exercise was a good nonpharmacological strategy to preserve cardiac function against damage caused by DOX cardiotoxicity.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Matos MI, Rubini EC, Meireles FO, Silva EB; Acquisition of data: Matos M; Statistical analysis: Silva EB; Writing of the manuscript: Matos MI, Rubini EC, Meireles FO.

Potential Conflict of Interest

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

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Study Association

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

Ethics Approval and Consent to Participate

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

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Pre-Clinical Meta-Analysis: Another Brick in the Wall

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Short Editorial related to the article: Aerobic Exercise and Cardiac Function of Murines Exposed to Doxorubicin: a Meta-Analysis

Currently, systematic review and meta-analysis are considered level 1 of scientific evidence and it is widely used in epidemiology and evidence-based medicine. The term meta-analysis comes from the Greek and means "analysis of analyses", referring to its definition "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" proposed by the statistician Gene V. Glass in 1976.[1]

Despite the similarities, it is important to note that meta-analysis and systematic review are not synonymous. Meta-analysis is often, but not always, preceded by a systematic review, which aim to gather similar studies that meet the strict approach eligibility criteria in order to answer a specific research question, whereas meta-analysis integrates the results of included studies by statistical techniques.[2,3]

Basically, when conducted properly, the major advantage of a meta-analysis is the statistical power substantially increased, which provides a precise estimate of the effect size of a set of studies, being considered the best evidence available.[4] Besides, can be applicable to a broad spectrum of topics, including biomarkers, genetic factors, diagnosis, and treatment.[4,5]

On the other hand, the main criticism regarding meta-analyzes are about heterogeneity among the studies and publication bias, both compromising the robustness and the validation of results.[6] Undoubtedly, it is inevitable a diversity of design, interventions, exposures and outcomes in a collection of studies; however, it is essential to quantify the extent of heterogeneity by performing statistical approaches such as sensitivity, subgroup, or regression analyses.[4] In addition, the "file drawer problem", that is smaller studies or with negative or non-significant results tend to remain unpublished and this might overestimate the actual effect degree leading to publication bias. We can assess publication bias in a meta-analysis using a sample method called funnel plot or another statistical method depending on the case, such as Egger's regression test, trim and fill method, also available for this purpose.[3,7-9]

Keywords

Meta-Analysis; Systematic Review; Scientific Publications; Data Interpretation, Statistical.

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Traditionally, meta-analyzes are performed of data from human studies. However, in the last years, the use of meta-analysis from preclinical studies has become more frequent. Several reasons are related to the lack of clinical studies about a specific issue, especially when dealing with topics that are not possible to investigate in humans, whereas optimal methods on animal models are largely standardized.[10]

In this sense, a recent issue of the *Arquivos Brasileiros de Cardiologia* published an interesting meta-analysis about the effect of aerobic exercise on the prevention of cardiac dysfunction in murines exposed to doxorubicin.[11] New knowledge in this field is always welcome, since doxorubicin-induced cardiotoxicity is one of the main serious consequences of its use and currently therapies to prevent or attenuate cardiotoxicity are scarce and not effective.

In brief, the authors have showed that the practice of aerobic exercise contributed to improve left ventricle fractional shortening and left ventricle developed pressure in murines with cardiac dysfunction caused by doxorubicin treatment. Certainly, it is a very important conclusion because the aerobic exercise can be a good non-pharmacological strategy to prevent, to attenuate or to treat cardiotoxicity, since it has no (or minimum) side effects and could has additional benefits for human healthy.

It is worth to mentioning that animal studies are frequently small and inherently heterogeneous and, therefore, are required to follow all the strict methodological approach.[10] The present meta-analysis was well conducted and followed all the current recommendations for its preparation. However, it brings up some points that should be taken into account, in order to increase the quality of the results and their interpretation.

The important topic to be highlighted is that studies that compound this meta-analysis shown great differences in the dose of doxorubicin, moment that exercise was implemented (pre or post doxorubicin exposure), modality of exercise and intensity of exercise, which attribute a wide heterogeneity between the studies (I^2 = 87 and 94%). It is a frequent problem in meta-analysis carried out experimental studies. It is possible to minimize the heterogeneity including some subgroups analysis or limiting study design aspects during the search strategy. Additionally, as previously described, it is very difficult to publish negative results, mainly in experimental researches, which could attribute publication bias to this study.

In our opinion, the mainly advantage of meta-analysis is provided robust scientific-based evidence for developing guidelines that supports health care professionals to make an optimal clinical decision. Obviously, producing scientific evidence for clinical guidelines should not be the purpose of meta-analysis conducted with pre-clinical studies. They are

classically exploratory and allow us generate hypothesis that can be used to design and conduct future clinical trials. They offer the possibility to include one more brick in the wall of scientific knowledge.

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Microvascular Reactivity in Hypertensive Patients with High Body Adiposity

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Abstract

Background: Several anthropometric indexes have been proposed to determine the association between overweight and cardiovascular risk factors.

Objective: To evaluate the relationship between body adiposity and microvascular reactivity in hypertensive patients under antihypertensive therapy.

Methods: Treated hypertensive patients aged 40 to 70 were submitted to evaluation of anthropometric indexes: conicity (CI), body adiposity (BAI), visceral adiposity (VAI) and waist-to-height ratio (WHtR). Participants were divided by the terciles of fat percentage (%F) obtained by bioelectrical impedance. The patients underwent microvascular reactivity test (Laser Speckle Contrast Image) and pulse wave velocity (PWV) measurement. The p value <0.05 was considered statistically significant.

Results: The variation of the area under the curve (AUC) of the skin perfusion was lower in the upper tercile (97±57% vs. 67±36%; p=0.027). %F showed significant correlation with WHtR (r=0.77; p<0.001), VAI (r=0.41; p=0.018), CI (r=0.60; p<0.001), BAI (r=0.65; p<0.001) in men and only with WHtR (r=0.55; p<0.001) and BAI (r=0.60; p<0.001) in women. In linear regression, AUC was independently associated with %F (β=-3.15; p=0.04) in women and with blood glucose (β=-1.15; p=0.02) in men. There was no difference in PWV measurements.

Conclusion: Anthropometric indices were more associated with %F in men. Higher body adiposity was associated with lower microvascular reactivity, which was more evident in women. There was no difference in arterial stiffness, which may have been influenced by antihypertensive treatment. (Arq Bras Cardiol. 2020; 115(5):896-904)

Keywords: Hypertension/drug effects; Adiposity; Endothelium; Capillary Permeability.

Introduction

The World Health Organization (WHO) considers obesity a major public health problem worldwide. In Brazil, obesity is growing increasingly, and epidemiological evidence shows that more than 50% of the population is overweight and obese.[1,2]

Correct diagnosis of obesity or overweight requires some ways of quantifying body composition. Imaging techniques are alternatives that offer greater precision in the assessment of fat accumulation, but the simplicity of use emphasizes anthropometric methods as good tools for body fat assessment. Several anthropometric indices have been proposed to determine the association between overweight and cardiovascular risk factors.[3]

Body mass index (BMI) is the most widely reported indicator in studies, but it does not correlate with body fat distribution. Waist circumference (WC) and waist-hip ratio (WHR) measurements are the most commonly used markers for central distribution of adipose tissue. Other indicators that have been showing strong correlation with cardiovascular risk factors are: conicity index (CI), waist-to-height ratio (WHtR) and, more recently, body adiposity (BAI) and visceral (VAI) indices.[3]

In obesity, perivascular adipose tissue promotes inflammation and induces vascular dysfunction through increased secretion of vasoconstriction factors, such as the main components of the renin-angiotensin system and proinflammatory adipokines, which are important contributors to endothelial activation and vascular inflammation.[4]

In clinical practice, it is essential to identify parameters that may reflect the distribution of adipose tissue (visceral or subcutaneous) more accurately and feasibly, and its relationship with metabolic and inflammatory changes that lead to impaired vascular health and, consequently, increase cardiovascular risk. Thus, this study aimed to evaluate the relationship between body adiposity and microvascular reactivity in hypertensive patients under

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antihypertensive therapy, and to correlate body fat percentage and sex influence on anthropometric indices of adiposity and cardiovascular risk.

Methods

Study Population

Hypertensive patients aged 40 to 70, of both sexes, using antihypertensive drugs for at least four weeks, were selected from our outpatient clinic and admitted to a cross-sectional study. Exclusion criteria were BMI ≥40 kg/m², diabetes mellitus, hormone replacement therapy, and betablocker or statin use. For analysis of the results, the patients were divided according to terciles of body fat percentage, differentiated by gender. In females, the terciles cutoff points were 36.49 and 39.87%, while in males they were 25.27 and 28.95%. The protocol was approved by the local Ethics Committee (50751314.9.0000.5259), and all participants read and signed the informed consent in accordance with Declaration 466/2012.

Nutritional Assessment

Body weight was measured on a Filizola@ digital scale with maximum capacity of 180 Kg, following the techniques recommended by the WHO.[5] In the same scale, height was verified by the anthropometer. BMI was calculated by dividing body weight (in kilograms) by the square of height (Ht; in meters). The cutoff points adopted for the nutritional classification were based on the criteria proposed by the WHO.[6]

Waist and hip circumferences were obtained with the aid of an inextensible tape measure. Waist circumference was determined at the midpoint between the last rib and the iliac crest. Hip circumference (HC) assessment was performed on the largest diameter of the gluteal region. After obtaining these measurements, the WHR was calculated.[6]

The WHtR was calculated according to the following formula: WHtR = WC/Ht

The CI calculation was performed using the following formula:[7]

CI = WC/0.109 x √ Weight/Ht.

The BAI was calculated from the measurement of hip circumference and height:[8] BAI (%fat) = HC / (Ht x √Ht) - 18

The VAI was calculated considering the variations by gender:[9]

Men: VAI = (WC/39.68 + 1.88 x BMI) x (TG/1.03) x (1.31/HDL)

Women: VAI = (WC/39.68 + 1.89 x BMI) x (TG/0.81) x (1.52/HDL)

Where: TG = Triglyceride (mmol/l); HDL = High-density lipoprotein (mmol/l).

Bioelectrical impedance analysis (BIA) was performed with the Biodynamics model 310e tetrapolar device and was used to evaluate body fat percentage, following previous recommendations.[10]

Laboratory tests

Venous blood samples were collected after an 8-hour fast. Serum glucose, creatinine, total cholesterol, HDL and TG were measured with a self-analysis technique (Technicon DAX96, Miles Inc). C-reactive protein (CRP) was measured by the turbidimetry method. Renal function was assessed using glomerular filtration rate (GFR) estimated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.[11] Insulin was measured by radioimmunoassay, and the Homeostatic Model Assessment Index — Insulin Resistance (HOMA-IR) = [fasting glucose (mmol/L) x fasting insulin (mUI/mL)/22.5] was used to estimate insulin sensitivity.[12]

Blood pressure assessment, vascular and cardiometabolic ages

Systolic (SBP) and diastolic (DBP) blood pressure measurements were obtained with a calibrated digital device (model HEM-705CP, OMRON Healthcare Inc., Illinois), performed with the patient in a sitting position and after five minutes of rest. Vascular age was based on the Framingham Heart Study.[13]

Cardiometabolic age was obtained from https://myhealthcheckup.com, accessing Cardiometabolic Age.[14] Metabolic syndrome was defined according to the criteria established by the National Cholesterol Education and Treatment Program (NCEP ATP III).[15]

Microvascular Reactivity

Microvascular reactivity was assessed using the Laser Speckle Contrast Image (LSCI) method (Pericam PSI System, Perimed, Sweden) in combination with Post Occlusive Reactive Hyperemia (PORH) for continuous analysis of expressed endothelium-dependent microvascular skin perfusion changes in arbitrary perfusion units (APU). Through these analyzes, we obtained the mean perfusion and area under the curve (AUC) at 1-min baseline period, PORH peak mean, and the area under the curve at 1-min after occlusion. Cutaneous vascular conductance (CVC) was obtained by dividing baseline perfusion (or PORH) by mean arterial pressure (MAP).

Central Hemodynamic Parameters

Radial artery pulse wave analysis was performed using a commercially available tonometry device (SphygmoCor; AtCor Medical, Sydney, Australia). Augmentation pressure (AP) is the difference between the second and first systolic peak pressure, and augmentation index (Aix) is defined as the ratio between AP and aortic pulse pressure.

Pulse Wave Velocity (PWV)

Pulse waves were obtained transcutaneously by the Complior Analyses device (Alam Medical, France) using transducers placed over the right carotid artery and the right femoral artery at the same time. The distance between the carotid and

femoral pulses was measured directly with an inextensible tape measure, which was multiplied by 0.8 to calculate the carotid-femoral PWV. This measurement was corrected by calculating normalized carotid-femoral PWV (PWV-N) using the following formula: PWV-N=(PWV/MAP) x 100.[16]

Statistical Analysis

Results were expressed as mean ± standard deviation. To determine the sample size of this study, we considered the equivalence of the change in Flow Mediated Dilatation (FMD) observed in obese subjects. Thus, for a difference of 3.0 (%) in FMD, a standard deviation of 4.0 (%), with 80% study power and 5% significance, a minimum of 22 participants in each group would be required. Considering an estimated loss of 10% of the sample, the minimum number was set at 72 participants. Shapiro-Wilk test was used to evaluate normal distribution. The terciles of fat percentage were compared by One-Way ANOVA test, followed by Tukey post-test. Categorical variables were presented as frequency and percentage, and compared using the chi-square test. Pearson's coefficient was obtained in each correlation test between continuous variables. A confidence interval of 95% was considered, being statistically significant when $p<0.05$. Linear regression was performed respecting the necessary assumptions, including the absence of multicollinearity, considering the UAC as a dependent variable, adjusted for age and SBP, and performed separately in the groups of men and women. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (SPSS, Chicago, IL).

Results

The results presented below are related to 81 patients included in this study, with a mean age of 58±6 years, 59% female (n=48). The average cardiovascular risk (CVR) was 16.8±11.2% and mean blood pressure was 138±11/83±9 mmHg. Clinical parameters of the groups divided by terciles are shown in Table 1. There was no significant difference in mean age and CVR among the groups. Vascular and cardiometabolic ages were significantly higher in the last tercile compared to the first.

The BMI was significantly higher in the third tercile compared to the first and second. WC was significantly higher in the second and third terciles compared to the first in males, and in the third compared to the first in females. The WHR was significantly higher in the third tercile than in the first in women, and no differences were found between men. The WHtR was significantly higher in the last tercile compared to the others in both men and women.

The CI was higher in the last when compared to the first tercile in males, and in the last compared to the second and

Table 1 – Clinical parameters in the groups divided by terciles of fat percentage

	Fat percentage			
Parameters	**1st Tercile (n=27)**	**2nd Tercile (n=27)**	**3rd Tercile (n=27)**	**p value**
Age (years)	57 ± 6	58 ± 7	60 ± 7	0.116
FRS (%)	15.6 ± 10.5	14.2 ± 9.9	20.8 ± 12.9	0.079
Vascular age (years)	70 ±11	68 ± 12	77 ± 10*††	0.007
CM age (years)	55 ± 7	55 ± 8	60 ± 8*	0.025
Systolic BP (mmHg)	136 ± 9	135 ± 13	140 ± 11	0.173
Diastolic BP (mmHg)	84 ± 8	81 ± 10	86 ± 8	0.137
Pulse pressure (mmHg)	52 ± 6	54 ± 9	54 ± 8	0.608
Lifestyle, n (%)				
Alcohol use	11 (41)	12 (44)	13 (48)	0.861
No physical activity	22 (82)	19 (70)	22 (82)	0.526
Antihypertensive use, n (%)				
Diuretics	26 (96)	25 (93)	26 (96)	0.769
RASI	23 (85)	25 (93)	24 (89)	0.687
CCA	8 (30)	5 (19)	5 (19)	0.526
Monotherapy	4 (15)	2 (7)	4 (15)	0.493
With 2 drugs	16 (59)	22 (82)	18 (67)	
With 3 drugs	7 (26)	3 (11)	5 (19)	

*Data expressed as mean ± standard deviation or in proportions where indicated. P value corresponds to chi-square for categorical variables and One-Way Anova for numeric variables with Tukey's post-test, *p <0.05 vs. 1st tercile, †† p <0.01 vs. 2nd tercile. FRS: Framingham risk score; CM: cardiometabolic; BP: blood pressure; RASI: renin-angiotensin system inhibitor; CCA,:calcium channel antagonist.*

first terciles in females. The BAI was significantly higher in the third tercile compared to the other two groups.

The VAI was significantly higher in the third compared to the second tercile. The number of criteria for metabolic syndrome was significantly higher in the last compared to the second tercile (Table 2).

Table 3 presents the laboratory data with no significant difference in creatinine, lipid and glycemic profile, CRP and GFR among the groups. Uric acid and TG/HDL ratio were significantly higher in the last tercile group.

Table 4 shows the vascular test results. Concerning the central hemodynamic parameters, no significant differences were found between the groups. PWV and PWV-N showed no statistical differences among the groups of terciles. Data obtained by LSCI showed no difference among the groups in baseline and PORH perfusion AUC and CVC. The variation in AUC was significantly lower in the third compared to the first tercile.

Fat percentage showed positive and significant correlations with BMI, WC, WHtR and adiposity index in both women and men. In addition to these results, WHR, CI, VAI, and the number of criteria for metabolic syndrome also showed a positive and significant correlation with body fat percentage in men (Table 5). The variation in AUC showed a significant inverse correlation with the percentage of body fat in women and with glycemia in men (Figure 1). Linear regression analysis showed that these associations remained independent even after adjustments for age and SBP (Table 6).

Discussion

This study evaluated the relationship between body adiposity and microvascular reactivity and their associations with different anthropometric and metabolic indexes in a population of treated hypertensive patients. No differences were found between the groups in peripheral and central pressure parameters, showing that the groups were hemodynamically well balanced.

Vascular and cardiometabolic ages were higher in the upper tercile fat percentage group, showing a positive association between body fat accumulation and vascular and metabolic

Table 2 – Body adiposity indexes divided by fat percentage terciles

	Fat percentage			
Parameters	**1st Tercile (n=27)**	**2nd Tercile (n=27)**	**3rd Tercile (n=27)**	**p value**
BMI (kg/m²)	26.1 ± 3.7	28.9 ± 3.1	31.4 ± 2.8***†	< 0.001
Waist circumference (cm):				
♂	88.9 ± 11.7	98.8 ± 6.6*	106.3 ± 8.5***	< 0.001
♀	86.5 ± 8.3	91.5 ± 6.2	97.7 ± 8.8***	< 0.001
WHR:				
♂	0.88 ± 0.08	0.93 ± 0.05	0.95 ± 0.04	0.053
♀	0.80 ± 0.05	0.82 ± 0.05	0.86 ± 0.06*	0.040
WHtR:				
♂	0.53 ± 0.07	0.56 ± 0.03	0.62 ± 0.05**†	0.002
♀	0.54 ± 0.05	0.57 ± 0.04	0.63 ± 0.05***††	< 0.001
Body fat (%):				
♂	20.0 ± 4.6	26.7 ± 1.1***	31.8 ± 2.5***††	< 0.001
♀	31.0 ± 4.5	38.5 ± 1.0**	44.6 ± 8.4***††	< 0.001
Conicity index:				
♂	1.25 ± 0.87	1.30 ± 0.57	1.33 ± 0.62*	0.026
♀	1.21 ± 0.76	1.21 ± 0.53	1.28 ± 0.80*†	0.009
Body adiposity index:				
♂	28.0 ± 3.7	27.4 ± 1.4	31.9 ± 3.7*††	0.004
♀	34.3 ± 3.4	36.4 ± 3.2	40.9 ± 4.6***††	< 0.001
Visceral adiposity index	2.88 ± 1.13	2.51 ± 1.04	3.55 ± 1.98†	0.037
MS criteria	2.3 ± 1.1	2.1 ± 0.9	2.9 ± 0.9†	0.018

*Note: Data expressed as mean ± standard deviation. P value corresponds to chi-square for categorical variables and One-Way Anova for numeric variables with Tukey's post-test, where *p <0.05, **p <0.01, ***p <0.001 vs. 1st tercile; † p <0.05, †† p <0.01 vs. 2nd tercile. BMI: body mass index; WHR: waist to hip ratio; WHtR: waist to height ratio; MS: metabolic syndrome. ♂: male; ♀: female.*

Table 3 – Biochemical parameters divided by fat percentage terciles

Parameters	Fat percentage			p value
	1st Tercile (n=27)	2nd Tercile (n=27)	3rd Tercile (n=27)	
Creatinine (mg/dl)	0.88 ± 0.20	0.89 ± 0.20	0.92 ± 0.25	0.851
Uric acid (mg/dl)	5.29 ± 1.60	5.52 ± 1.49	6.40 ± 1.69*	0.029
Total cholesterol (mg/dl)	209 ± 47	203 ± 28	216 ± 36	0.485
HDL-cholesterol (mg/dl)	56 ± 16	61 ± 20	51 ± 19	0.164
LDL-cholesterol (mg/dl)	126 ±38	123 ± 43	129 ± 34	0.822
TG (mg/dl)	131 ± 49	111 ± 47	130 ± 58	0.061
TG/HDL	2.60 ± 1.43	2.28 ± 1.92	3.59 ± 2.85†	0.050
Glucose (mg/dl)	94 ± 11	93 ± 10	96 ± 11	0.670
Insulin (mcU/ml)	14.4 ± 7.2	13.8 ± 4.8	16.5 ± 7.4	0.317
HOMA-IR	3.38 ± 1.69	3.20 ± 1.29	3.91 ± 1.89	0.270
us-CRP (mg/dl)	0.71 ± 0.50	0.73 ± 0.49	0.83 ± 0.59	0.655
eGFR (ml/min/1.73 m²)	87 ± 13	84 ± 19	79 ± 19	0.544

*Data expressed as mean ± standard deviation. P value corresponds to chi-square for categorical variables and One-Way Anova for numeric variables with Tukey's post-test, where *p<0.05 vs. 1st tercile; † p<0.05 vs. 2nd tercile. HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; HOMA-IR: Homeostatic Model Assessment — Insulin Resistance; us-CRP: ultrasensitive C-reactive protein; eGFR: estimated glomerular filtration rate.*

Table 4 – Vascular parameters divided by fat percentage terciles

Parameters	Fat percentage			p value
	1st Tercile (n=27)	2nd Tercile (n=27)	3rd Tercile (n=27)	
	Central hemodynamics Applanation tonometry			
Aortic SP (mmHg)	131 ± 15	130 ± 17	132 ± 16	0,855
Aortic PP (mmHg)	46 ± 11	47 ± 10	46 ± 12	0,941
AP (mmHg)	17 ± 10	16 ± 7	15 ± 7	0,746
Aix (%)	33 ± 11	32± 10	32 ± 10	0,945
Aix @ HR75 (%)	27 ± 9	27 ± 9	27 ± 9	0,997
ED (%)	34 ± 4	35 ± 3	35 ± 4	0,723
SEVR	167 ± 37	156 ± 27	155 ± 26	0,272
	VOP			
PWV (m/s)	10,0 ± 1,8	9,7 ± 1,9	9,7 ± 2,0	0,803
PWV-N (m/s)	9,9 ± 1,7	9,8 ± 1,7	9,4 ± 1,9	0,468
	LSCI			
Baseline perfusion (APU)	28,4 ± 11,0	32,2 ± 10,7	30,9 ± 9,8	0,410
Baseline CVC (APU/mmHg)	0,28 ± 0,11	0,33 ± 0,12	0,30 ± 0,09	0,303
PORH perfusion (APU)	84,2 ± 26,2	87,2 ± 22,2	90,6 ± 21,0	0,601
PORH CVC (APU/mmHg)	0,84 ± 0,28	0,89 ± 0,25	0,87 ± 0,20	0,743
Baseline AUC (APU)	1800 ± 679	2001 ± 663	1996 ± 579	0,334
PORH AUC (APU)	3360 ± 1190	3257 ± 856	3261 ± 882	0,978
AUC variation (%)	97 ± 57	70 ± 35	67 ± 36*	0,027
CVC variation (%)	218 ± 105	185 ± 73	211 ± 90	0,366

Data expressed as mean ± standard deviation. P value corresponds to One-Way Anova with Tukey's post-test, where * p <0.05 vs. 1st tercile. SP: systolic pressure; PP: pulse pressure; AP: augmentation pressure; Aix: augmentation index; ED: ejection duration; SEVR: subendocardial viability ratio; PWV: pulse wave velocity; PWV-N: normalized pulse wave velocity; LSCI: laser speckle contrast image; APU: arbitrary perfusion unit; CVC: cutaneous vascular conductance; PORH: post-occlusive reactive hyperemia; AUC: area under the curve.

Table 5 – Pearson's correlation (r) of adiposity indexes and cardiovascular risk with fat percentage by sex

Variables	Women (n=48)		Men (n=33)	
	r	p value	r	p value
Body mass index (kg/m²)	0.556	< 0.001	0.738	< 0.001
Waist circumference (cm)	0.476	0.001	0.767	< 0.001
Waist-to-hip ratio	0.215	0.152	0.505	0.003
Waist-to-height ratio	0.550	< 0.001	0.767	< 0.001
Body adiposity index	0.599	< 0.001	0.653	< 0.001
Conicity index	0.264	0.076	0.597	< 0.001
Visceral adiposity index	-0.037	0.809	0.410	0.018
Vascular age (years)	0.062	0.682	-0.005	0.976
Cardiometabolic age (years)	0.242	0.109	-0.044	0.810
Metabolic syndrome criteria	-0.066	0.662	0.464	0.007

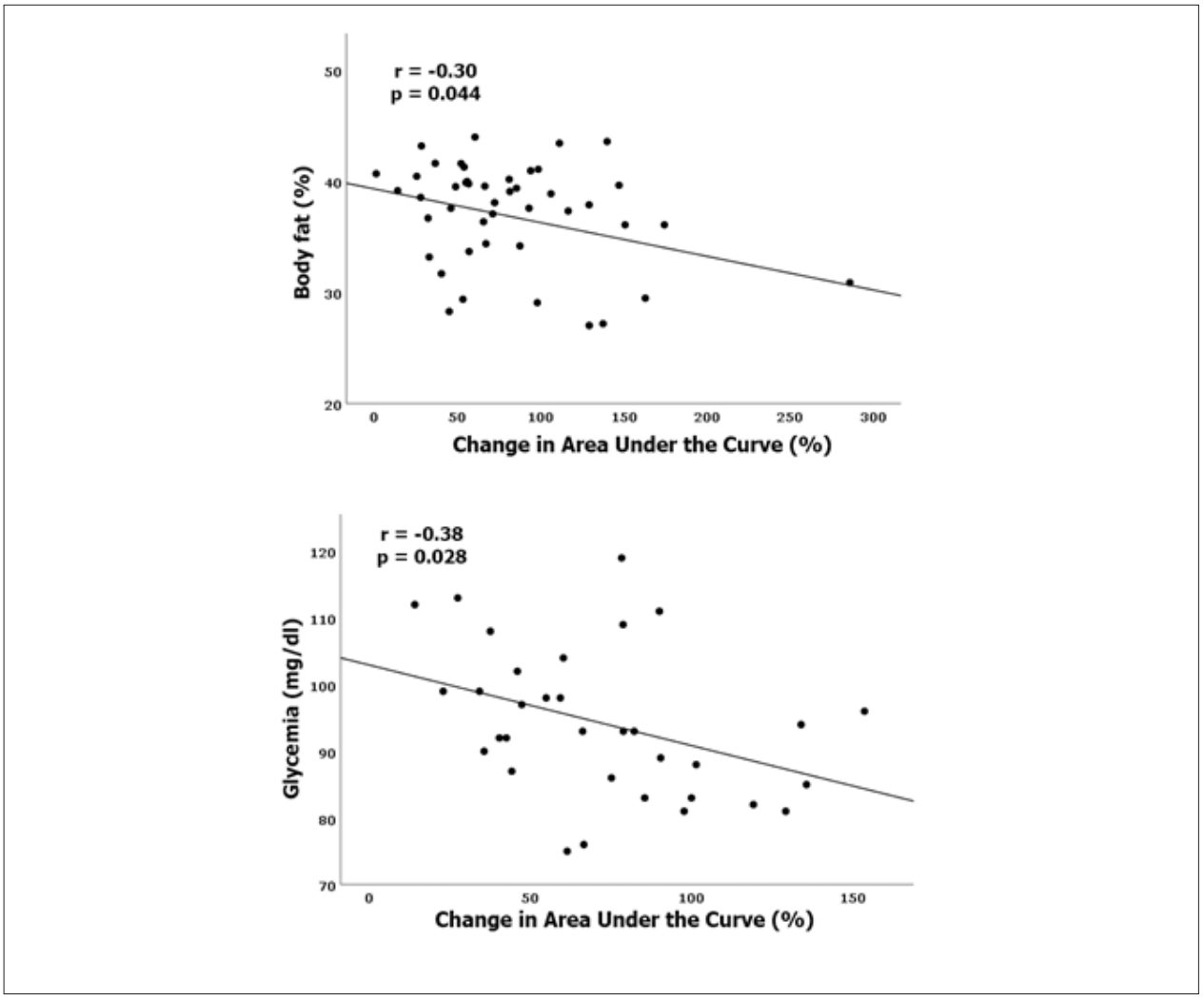

Figure 1 – *Correlation of the change in the area under the curve of skin perfusion by the laser speckle contrast imaging method with body fat in women and with glycemia in*

Table 6 – Linear regression of the change in the area under the curve (dependent variable) of skin perfusion by the laser speckle contrast imaging method with body fat in females and with plasma glucose in males after adjustment for age and systolic blood pressure

Dependent variables		Independent variables	Non-standard coefficient B	CI 95%	Standardized coefficient Beta	p value
AUC (%)	♀	Body fat (%)	-3.15	-6.29 -0.10	-0.32	0.049
	♂	Glycemia (mg/dl)	-1.35	-2.47 -0.22	-0.43	0.020

AUC: area under the curve; ♂: male; ♀: female.

damage. Considering that there was no significant difference in estimated cardiovascular risk, this finding reinforces the importance of assessing these parameters.

Higher values of uric acid and TG/HDL ratio were found in the tercile of higher fat percentage compared with the lower terciles. Elevated uric acid has been associated with metabolic syndrome. Experimental studies have suggested that uric acid can penetrate the smooth muscle and vascular fibers, culminating in increased expression of inflammatory mediators. The consequences are raised blood pressure and vascular smooth muscle cell hypertrophy.[17-19] A recently published study conducted with adults in India demonstrated an association of uric acid levels with anthropometric obesity parameters such as BMI, WHR and WHtR.[18]

The TG/HDL ratio has been proposed as a simple marker of insulin resistance, acting as a biomarker to identify cardiometabolic risk profiles.[20] Pantoja-Torres et al.[21] demonstrated a positive association of TG/HDL ratio with insulin resistance in a eutrophic adult population. This association was also studied by Baez-Duarte et al.[22] who found an association between the TG/HDL ratio with lower insulin sensitivity and the presence of metabolic syndrome in an adult population with an average BMI of 27.8 kg/m^2.

Since endothelial dysfunction is considered a marker of the atherosclerotic process, it is crucial to evaluate its earliest manifestations in micro and macrocirculation.[23] The evaluation of endothelial function by microvascular reactivity through the LSCI method has not been used in clinical trials with an obese population.

In this study, microvascular reactivity was negatively associated with the accumulation of adipose tissue. Suboc et al.[24] demonstrated that obesity was associated with worse endothelial function in non-diabetic adults. These findings only became significant when the groups were divided by gender.[24] Endothelial function, assessed in the present study by the variation in AUC, correlated with plasma glucose in males, suggesting a possible important association between endothelial function and insulin sensitivity in men. In women, this correlation was more evident with body fat percentage, indicating a probable direct relationship between adipose tissue and vascular function in females. These correlations remained significant after adjusting for age and SBP, important factors in the regulation of endothelial function.

Regarding arterial stiffness parameters, no differences were found between the groups in the present study. Desamericq et al.[25] did not find an association between obesity and increased arterial stiffness in adult subjects with associated CVR factors, such as diabetes mellitus. Menezes et al.[26] did not find any association between obesity and insulin resistance with vascular alteration, in either endothelial function or arterial stiffness. In this study, the association of adiposity with arterial stiffness may have been attenuated by the effects of vasoprotective drugs, such as renin angiotensin system inhibitors (RASI).

The fat percentage obtained by BIA in males showed a good correlation with all anthropometric indices of body adiposity assessment, as well as the number of criteria for metabolic syndrome. In women, this correlation remained only for BMI, WC, WHtR and BAI. In 2007, a study conducted in Brazil, aimed at determining the association between the various obesity and coronary risk indicators, showed that the indicators were strongly associated with WHtR, with emphasis on WHR and CI among men, while CI was the best marker for women aged 50 to 74. This difference can be explained by the menopause, in which the loss of protection provided by estrogen occurs, leading to a higher accumulation of abdominal fat, which contributes to cardiovascular complications.[27]

Some limitations were identified in this study. The absence of inflammatory markers and adipokines impaired the analysis of inflammation as a mechanism of endothelial dysfunction associated with increased body adiposity. CRP was the only inflammatory marker evaluated and was not different among the study groups. The effects of some antihypertensive drugs may have influenced this result. No imaging method was used to quantify visceral adipose tissue. However, the main objective of the study was to use simpler methods to assess body adiposity and their association with vascular changes that may characterize a higher cardiovascular risk.

Conclusion

In conclusion, in this sample of treated hypertensive patients, anthropometric obesity indexes were more associated with body fat percentage among men. The highest cardiovascular risk among those with higher body adiposity was more evidenced by the higher vascular and cardiometabolic ages in this group of patients. Higher body adiposity was associated with lower microvascular reactivity, which was more evident among women. There was no difference in arterial stiffness, which can be attributed to the use of antihypertensive medications that maintained similar blood pressure levels in the study groups.

Author Contributions

Conception and design of the research: d´El-Rei J, Oigman W, Neves MF; Acquisition of data: d´El-Rei J, Cunha MR, Mattos SS, Marques BC, Menezes VP, Cunha AR, França EM; Analysis and interpretation of the data: d´El-Rei J, Cunha MR, Mattos SS, Marques BC, Menezes VP, Cunha AR, França EM, Oigman W, Neves MF; Statistical analysis and Writing of the manuscript: d´El-Rei J, Cunha MR, Neves MF; Obtaining financing: Neves MF; Critical revision of the manuscript for intellectual content: d´El-Rei J, Cunha MR, Mattos SS, Marques BC, Menezes VP, Cunha AR, Oigman W, Neves MF.

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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Do Microvascular Reactivity Studies Contribute to Clinical Practice?

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Short Editorial related to the article: Microvascular Reactivity in Hypertensive Patients with High Body Adiposity

We appraise in this publication the article "*Microvascular Reactivity in Hypertensive Patients with High Body Adiposity*", by D'El-Rei et al.[1] This is a complex investigation, assessing patients with Arterial Hypertension undergoing treatment, with the inclusion of several models for obesity assessment and several hemodynamic and circulatory parameters, which are studied in this scenario. Microvascular reactivity was evaluated using the Laser Speckle Contrast Image method in combination with Post-occlusive Reactive Hyperemia, therefore studying the endothelial function in this patient population.

Endothelial cells constitute an organ that is distributed throughout the body, comprising a dynamic interface with all other organs. The endothelium mediates vasomotor tone, regulates cell and nutrient traffic, maintains body fluidity, contributes to the balance between pro- and anti-inflammatory mediators, modulates procoagulant and anticoagulant activity, participates in the formation of new blood vessels, orchestrates organ development, participates in immunity, interacts with circulating blood cells and undergoes programmed cell death.[2]

The endothelial layer has diverse autocrine, paracrine and endocrine characteristics; what is called endothelial function encompasses a series of properties favorable to vascular health, consisting of: relaxed vascular tone, low level of oxidative stress, anti-inflammatory effects, anti-proliferative effects of smooth muscle, inhibition of leukocyte adhesion and migration, platelet aggregation inhibition, anticoagulant and pro-fibrinolytic effects.[3]

Due to the wide distribution of the endothelium in the body and the several activities performed, with extremely complex pathophysiology, it is easy to understand that there are several ways to evaluate the endothelial function, with different stimuli applied to vessels in different sites. Endothelial dysfunction is the initial step towards atherosclerosis and participates in its development, increasing the risk of cardiovascular diseases, so it is clinically important to evaluate endothelial function using a certain technique.[4]

The first demonstration of endothelial dysfunction was performed in the coronary arteries in 1986 by Ludmer et al.,[5] using intra-coronary infusion of acetylcholine.[5] Subsequently, less invasive techniques were developed using mainly the forearm circulation as a replacement for the coronary artery. The basic principle of the several techniques is similar: healthy arteries (coronary, brachial or digital) dilate in response to stimuli, such as reactive hyperemia or intra-arterial infusion of endothelium-dependent vasodilators (acetylcholine, bradykinin or serotonin, via the release of nitric oxide, prostacyclin or other vasodilating substances).[6] The vasodilation response to reactive hyperemia (flow-mediated vasodilation) occurs by a mechanism called shear stress, in which the increased blood flow after a blocking and sudden release, acts as stress force through a vector perpendicular to the vascular axis. The endothelium on this occasion acts as a mechanotransducer, perceives the shear stress and modifies its paracrine constitution, releasing vasoactive factors.[7] In the presence of disease, this endothelium-dependent dilation is reduced or absent.

Following scientific and technological development, several techniques have been described for the study of endothelial function: Plethysmography with strain gauge on the forearm (1990),[8] Flow-mediated vasodilation with high resolution ultrasound on the forearm (1992),[9] Reactive hyperemia on the finger studied with peripheral arterial tonometry (2003),[10] flow-mediated vasodilation assessed by oscillometry (2013)[11] and the perfusion index derived from pulse oximetry (2014).[7,12]

In the investigation reported in this journal,[1] post-occlusive reactive hyperemia was used, and the perfusion was evaluated using the Laser Speckle Contrast Image method. This technique is based on dynamic changes in scattered light due to its interaction with red blood cells when illuminating certain biological tissue and it has been used in several medical areas such as rheumatology, dermatology, burns, ophthalmology, neurology, and gastrointestinal surgery. Its application in cardiovascular analysis is recent.[13]

The study of endothelial function has been the focus of many observations in the last 30 years and has a solid position in the area of medical research. New research horizons have been sought, with many scientists dedicated to the study of the endothelial metabolism, the characterization of genetic variations in atheroprotective genes and the search for new therapeutic strategies aimed at endothelial dysfunction.[14]

The wide range of scientific knowledge on endothelial function, an important physiological concept, seeks its best medical application. Some points that imply in the association with the clinical scenario can be highlighted:

1) Endothelial function contributes as a marker of cardiovascular risk: extensive literature has documented that endothelial dysfunction is associated with almost all conditions predisposing to atherosclerosis and cardiovascular disease (hypertension, smoking, dyslipidemia, aging, diabetes, obesity, hyperhomocysteinemia, inflammatory or infectious diseases).[6,7]

Keywords

Hypertension; Obesity; Adiposity; Biomarkers; Endothelium/function; Oxidative Stress; Cardiovascular Diseases.

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2) Endothelial function provides prognostic information: In the Cardiovascular Health Study[15] and the Multi-Ethnic Study of Atherosclerosis,[16] the evaluation of endothelial function with flow-mediated vasodilation predicted long-term adverse cardiovascular events in addition to the analysis of traditional risk factors. According to Menezes et al.[12] patients with septic shock had prognostic information according to the perfusion index findings during the vascular occlusion test.[12]

3) Endothelial function contributes to the monitoring of therapy: Therapeutic interventions by pharmacological agents (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, some betablockers) or lifestyle changes (physical exercise, weight reduction, smoking cessation, dietary measures) can improve endothelial function, which can be seen with the evolutionary improvement in the indexes that evaluate this parameter.[6] Measurements of endothelial function can help to differentiate responders from non-responders to the researched therapies.

Therefore, the study of endothelial function has many properties that qualify it for clinical use, which, however, has not occurred. The recent Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology[17] does not analyze this possibility of investigation of patients with cardiological diseases, as well as the American or European guidelines. We understand that this occurs precisely because there are dispersed researches, with different applied methodologies. We have sought an ideal test for the analysis of endothelial function. Among its characteristics, it is recommended that: 1) it must reflect the status of the disease; 2) it must be reversible with interventions; 3) it must improve risk stratification; 4) it must be reproducible; 5) it must be operator independent; 6) it must be non-invasive; 7) it must be easy to use; 8) it must be low cost.[6]

It is understood that studies on endothelial function may provide a better assessment of cardiovascular risk than the current scores, leading to an integrated functional analysis. It is believed that the method applies to the better characterization of patients classified as intermediate risk by the scoring systems. There is potential for it to contribute to the choice of therapies and to the follow-up of these patients.

In conclusion, studies with a large number of patients are necessary, with carefully planned designs and meticulous choice of endothelial function test or combination of tests to be included, seeking a standardization of the methodology for further introduction of the technique in clinical practice.

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Original Article

Disease Severity Affects Ventricular Repolarization Parameters in Patients With COVID-19

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Abstract

Background: **There is no study evaluating the T_{peak}-T_{end} (Tpe) interval, Tpe/QT ratio, and Tpe/QTc ratio to assess cardiac arrhythmias in patients with COVID-19.**

Objective: **We aimed to examine whether there is a change in QT, QTc, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio in patients with COVID-19.**

Methods: **The study included 90 patients with COVID-19 infection and 30 age-and-sex-matched healthy controls. QT, QTc, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio were measured. The participants included in the study were divided into the following 4 groups: healthy controls (group I), patients with COVID-19 without pneumonia (group II), patients with COVID-19 and mild pneumonia (group III), and patients with COVID-19 and severe pneumonia (group IV). Statistical significance was set at $p < 0.05$.**

Results: **It was found that baseline heart rate, presence of hypertension and diabetes, white blood cell count, blood urea nitrogen, creatinine, potassium, aspartate aminotransferase, alanine aminotransferase, NT-proBNP, high sensitive C reactive protein, D-dimer, hs-cTnI, Tpe, Tpe/QT, and Tpe/QTc increased from group I to group IV, and they were significantly higher in all patients in group IV ($p < 0.05$). Systolic-diastolic blood pressure, hemoglobin, and calcium levels were found to be lowest in group IV and significantly lower than in other groups (< 0.05). QT and QTc intervals were similar between groups. It was determined that increased heart rate, calcium, D-dimer, NT-proBNP and hs-CRP levels were significantly related to Tpe, Tpe/QT, and Tpe/QTc.**

Conclusions: **In patients with COVID-19 and severe pneumonia, Tpe, Tpe/QT ratio, and Tpe/QTc ratio, which are among ventricular repolarization parameters, were found to be increased, without prolonged QT and QTc intervals. In this study, we cannot definitively conclude that the ECG changes observed are directly related to COVID-19 infection or inflammation, but rather associated with severe COVID-19 scenarios, which might involve other causes of inflammation and comorbidities. (Arq Bras Cardiol. 2020; 115(5):907-913)**

Keywords: **COVID-19/complications; Betacoronavirus, Cardiovascular Diseases; Diabetes Mellitus; Hypertension; Pneumonia; Comparative Study.**

Introduction

In the last months of 2019, a new pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared worldwide, and its effects are still ongoing. This disease, called coronavirus disease 2019 (COVID-19), mainly affects the respiratory tract, but it has a significant rate (12% to 28%) of cardiac involvement.[1-4] Increased levels of cardiac troponin T (cTnT), cardiac troponin I (cTnI), high sensitivity cTnI and cTnT (hs-cTnI and hs-cTnT),[1,2,4] and NT-proBNP[5] have been found in patients with cardiac involvement. Mortality increases in patients with cardiac involvement.[1,6-8] Cardiac involvement is multifactorial in patients with COVID-19.[1,4,9-16] Since cardiac involvement is associated with mortality, an increase in mortality due to arrhythmia can be predicted in these patients. Patients with COVID-19 have been shown to have fatal arrhythmias.[1-3,9] However, no parameter or clear classification has been reported to provide information regarding the frequency of arrhythmia or to predict it these patients. It has only been recommended to measure QT and corrected QT (QTc) in advance, in order to reduce fatal

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arrhythmic events before starting hydroxychloroquine and azithromycin which have been used in COVID-19 prophylaxis and treatment.[17]

Prolonged or impaired ventricular repolarization is associated with life-threatening arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF). There are many electrocardiography (ECG) parameters related to impaired ventricular depolarization and repolarization. The parameters used in clinical practice are the QT and QTc intervals, QT and QTc dispersion, and the T_{peak}-T_{end} (Tpe) interval. The Tpe/QT and Tpe/QTc ratios obtained from these parameters are associated with ventricular transmural dispersion during repolarization.[18] Increased Tpe interval indicates abnormal spread in ventricular repolarization, and it is associated with increased risk of ventricular arrhythmia.[19] To the best of our knowledge, there is no study on QT, QTc, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio regarding the effect of COVID-19 on ventricular repolarization parameters. Therefore, the aim of our study was to investigate whether there is a change in QT, QTc, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio in patients with COVID-19.

Materials and Methods

A total of 120 patients diagnosed with COVID-19, who were admitted to intensive care, inpatient service, and COVID-19 pandemic clinics between March 15 and April 20, 2020 and who underwent admission ECG, were scanned retrospectively. After exclusion criteria were applied, the study included 30 patients with COVID-19 and severe pneumonia (group IV, 20 men and 10 women, mean age 61.2 ± 10.1 years), 30 patients with COVID-19 and mild pneumonia (group III, 18 men and 12 women, mean age 64.8 ± 12.3 years), 30 patients with COVID-19 without pneumonia (group II, 19 men and 11 women, mean age 65.2 ± 14.2 years), and 30 healthy controls (17 men and 13 women, mean age 63.5 ± 13.5 years), who were admitted to the outpatient clinics. In patients with COVID-19 who were scanned in this study, the following factors were considered as exclusion criteria: pediatric age group (< 18 years), failure to perform Tpe and QTc measurements, known coronary artery disease or acute coronary syndrome, mild to advanced valvular heart disease, systolic heart failure, any medical treatment known to prolong or shorten the QT and QTc intervals, and personal or family history of syncope or sudden cardiac arrest. The study was conducted in accordance with the Declaration of Helsinki, and it received approved from the local ethics committee.

Demographic, clinical, and biochemical parameters and 12-lead ECG of all patients were obtained from their files. Demographic data of all patients, sex, baseline heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded from archived files. Using routine biochemistry parameters, white blood cell (WBC) count, hemogram, blood glucose level, kidney function tests, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum calcium level, low density lipoprotein (LDL) cholesterol, high sensitive C reactive protein (hs-CRP), D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP), and hs-cTnI values were recorded.

Twelve Lead Electrocardiographic Evaluation

Twelve-lead ECG, carried out by MAC 2000 ECG Machine (GE medical systems information technologies, Inc., WI, USA) in sinus rhythm, 25 mm/sec speed and 1 mv/10 mm standard calibration, was obtained from files for all individuals. For the QT interval, the time from where QRS started to the point where the T wave merges with the isoelectric line was calculated. *QT c* was calculated using the Bazett Formula ($QTc = QT / \sqrt{R - R}$). Upper limit of normal for QTc was accepted as 450 and 460 ms for men and women, respectively.20 Tpe interval was defined as the time from the peak of the T wave to the point where the T wave joins and ends with the isoelectric line. Measurements were made primarily from V5. In cases where V5 was not suitable for measurement (amplitude < 1.5 mm), measurements were made from V4 or V6.21 *Tpe/QT* and *Tpe/QTc* ratios were calculated according to these measurements. All ECG examinations in sinus rhythm were evaluated by two cardiologists with at least 5 years of electrophysiology experience, who evaluates ≥ 2000 arrhythmia patients annually and who were not aware of the patient or clinic.

Statistical Analysis

Shapiro-Wilk test was used for normal distribution of continuous variables. Continuous variables in group data were indicated with mean ± standard deviation or median and interquartile range. Categorical variables were specified as numbers and percentages. Continuous variables that showed normal distribution were compared using the one-way ANOVA test, whereas the Kruskal-Wallis test was used to compare non-normally distributed samples. For normally distributed data, Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to homogeneity of variances. For non-normally distributed data, Bonferroni adjusted Mann-Whitney U test was used for multiple comparisons of groups. Chi-square test was used to compare categorical variables. Pearson's and Spearman's correlation analyses were performed to determine parameters related to Tpe interval and Tpe/QT and Tpe/QTc ratios. Linear regression analysis was performed for parameters that were more closely to the Tpe interval and Tpe/QT and Tpe/QTc ratios in univariate analysis. In order to avoid multicollinearity problems, each ventricular repolarization parameter was analyzed separately in different models. All models were adjusted by sex, age, and cardiovascular risk factors. The kappa coefficient was used to evaluate interobserver and intraobserver variability of the all ECG measurements. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS 22.0 (Chicago, IL, USA) statistical software package.

Results

As previously stated, the study data were divided into 4 groups and compared. ECG measurements were successfully obtained from all patients included in the study. Cohen kappa values that evaluate interobserver and intraobserver variability were greater than 90% for all ECG criteria.

Demographic and Clinical Data of the Study Groups

When demographic data were compared according to study groups, age and sex distribution were similar between groups. Hypertension and diabetes mellitus were more frequent in group IV. Among clinical parameters, it was demonstrated that the SBP and DBP values were lowest in group IV patients, and they were significantly lower than all other groups (Table 1). It was also demonstrated that the baseline HR value increased from group I to group IV, and they were significantly higher in patients in group IV than in all other groups (Table 1). SBP, DBP, and baseline HR values of groups I, II, and III were similar (Table 1).

Laboratory Data of the Study Groups

Laboratory parameters such as WBC, blood urea nitrogen, creatinine, potassium, AST, ALT, hs-CRP, D-dimer, NT-proBNP, and hs-cTnI levels increased from group I to group IV, and they were significantly higher in patients in group IV than in all groups (Table 1). In addition, WBC, AST, ALT and D-dimer levels were significantly higher than group I and group II. It was determined that hemoglobin and calcium levels decreased from group I to group IV, and they were significantly lower in patients in group IV than in all other groups. They were also lower in group III than in groups I and II (Table 1).

Electrocardiographic Data of Study Groups

When ECG data were compared according to study groups, the QT and QTc intervals were found to be similar across all groups (Table 2). Only 1 patient had QTc > 500 ms, and 1 patient had QTc > 460 ms. The QTc values of all other patients were normal. The Tpe interval and the Tpe/QT and Tpe/QTc ratios increased from group I to group IV, and they were significantly higher in all patients in group IV than in those in all other groups (Table 2).

Determination of Parameters Related to Tpe Interval, Tpe/QT ratio, and Tpe/QTc ratio

Correlation analysis was performed to determine parameters related to Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio. Table 3 summarizes parameters related to Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio in correlation analysis. Linear regression analysis was performed to determine the parameters significantly related to Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio in correlation analysis (Table 4). As a result of this analysis, baseline HR, D-dimer, and hs-cTnI levels were found to be positively and significantly associated with Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio. Serum calcium level was negatively and significantly correlated with Tpe interval and Tpe/QTc ratio. Concomitantly, NT-proBNP and Tpe/QTc ratio were positively and significantly related. Statistically, the most significant relationship was found between Tpe/QTc and D-dimer (Table 4)

Discussion

The main finding of our study is that, in patients with COVID-19 and severe pneumonia, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio are increased, without prolonged QT and QTc intervals. To the best of our knowledge, this is the first study in the literature to show increased Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio, which are among ventricular repolarization parameters, in patients with COVID-19.

COVID-19 infection mainly involves the airways, but significant cardiovascular complications can also occur.[1-3,9,10] It is not correct to explain the cardiac involvement or complications occurring in this disease as a single mechanism, and cardiac injury is considered to be multifactorial.[4] Possible mechanisms for cardiac involvement can be summarized as follows: i) direct viral myocarditis as the most commonly considered mechanism,[1,9-11] ii) hypotension and increased HR,[3] iii) hypoxia,[14] iv) increased inflammation and cytokine release,[14] v) down regulation of ACE-2 receptors,[13] vi) drug toxicity (chloroqiune, hydroxychloroqiune, erythromicin, etc.),[15-16] and vii) increased endogenous catecholamine release.[12] Although all these parameters were not observed in our study, there were shown to be increases in hs-cTnI and NT-proBNP levels, which suggests myocardial involvement; increases in WBC and hs-CRP, showing the inflammation process; an increase in HR with a decrease in SBP and DBP, showing hemodynamic status, progressing from the control group to the group with severe pneumonia, in accordance with the literature. In addition, in our study, an increase in D-dimer level was found in patients with increased disease severity.

Mortality increases with increased cardiac involvement in patients with COVID-19.[1,6-8] As with cardiovascular diseases, the most common cause of cardiac mortality in COVID-19 patients is arrhythmic events. In many studies, it has been reported that patients with COVID-19 and cardiac involvement have different frequencies and types of cardiac arrhythmias.[1-3,9] There is still no clear arrhythmia mechanism and classification for this disease. Guo et al.[2] reported that the rate of cardiac involvement in 187 patients was 27.8% and VT or VF were present in 5.9% of these patients. Zhou et al.[3] reported that the rate of cardiac involvement was 17% in 191 patients, and 1% of these patients had HR > 125 bpm. Shi et al.[1] reported that the rate of cardiac involvement was 19.7% in 416 patients, and ST depression was found in 0.7% of these patients. Wang et al.[9] reported a 16.7% frequency of arrhythmic events in 118 patients.

The most important mechanism in the physiopathology of ventricular arrhythmia in patients with COVID-19 infection is similar to that of arrhythmias in patients with acute myocarditis.[1,9-11] As in acute myocarditis, the most important reasons of arrhythmias are increased hs-cTnI and decreased left ventricular functions, due to increased myocardial damage in the acute period, as well as atrial and ventricular fibrosis occurring in the late period.[22] In studies conducted in patients with acute myocarditis in previous years, QT, QTc, Tpe intervals, Tpe/QT ratio, and Tpe/QTc ratio were found to be increased in the acute period.[23,24] To the best of our knowledge, there is no study researching QT, QTc, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio in cases of myocarditis or cardiac involvement in patients with COVID-19. In our study, hs-cTnI levels were significantly higher in patients with COVID-19 with severe pneumonia. In our study, analysis and classification

Table 1 – Clinical, demographic, and laboratory findings according to study group

Variable	Group I n=30	Group II n=30	Group III n=30	Group IV n=30	p
Age (years)	63.5 ± 13.5	65.2 ± 14.2	64.8 ± 12.3	61.2 ± 10.1	0.627
Sex (male/female)	17/13	19/11	18/12	20/10	0.506
Hypertension, n (%)	0 (0%)	7 (23%)	15 (50%)	17 (57%)	<0.001
Diabetes mellitus, n (%)	0 (0%)	6 (20%)	7 (23%)	11(38%)	<0.001
Current smoker, n (%)	0 (0%)	14 (47%)	15 (50%)	12(40%)	0.425
SBP (mmHg)	125 ± 11$^{\alpha}$	130 ± 10.1$^{\beta}$	136 ± 14*	108 ± 30	<0.001
DBP (mmHg)	76.9 ± 4.8$^{\alpha}$	79.9 ± 7.6$^{\beta}$	80.2 ± 7.5*	62.3 ± 23.1	<0.001
Pulse (bpm)	67 ± 8.2$^{\alpha}$	68 ± 9.1$^{\beta}$	75.6 ± 12.1*	89.6 ± 19.5	<0.001
White blood cell (uL)	9039 ± 1188$^{\alpha,¥}$	1097 ± 1516$^{\beta,\Delta}$	1277 ± 1484*	1906 ± 2698	<0.001
Hemoglobin (gr/dL)	13.3 ± 1.05$^{\alpha,¥}$	13.4 ± 1.58$^{\beta,\Delta}$	12.7 ± 0.81*	10.6 ± 0.74	<0.001
Glucose (mg/dL)	105 ± 13	138 ± 13	141 ± 11	138 ± 12	0.172
Blood urea nitrogen (mg/dL)	25.3 ± 6.7$^{\alpha}$	28.1 ± 8.8$^{\beta}$	37.2 ± 25*	66.9 ± 80	0.001
Creatinine (mg/dL)	0.60 ± 0.07$^{\alpha}$	0.62 ± 0.07$^{\beta}$	0.67 ± 0.18*	1.08 ± 0.80	<0.001
Sodium (mEq/L)	140 ± 4.0	140 ± 3.7	140 ± 6.8	140 ± 2.5	0.986
Potassium (mEq/L)	4.31 ± 0.33$^{\alpha}$	4.34 ± 0.34$^{\beta}$	4.30 ± 0.68*	4.74 ± 0.58	0.002
Calcium (mg/dL)	9.45 ± 0.50$^{\alpha,¥}$	9.47 ± 0.56$^{\beta,\Delta}$	8.38 ± 0.82*	7.99 ± 1.20	<0.001
AST (u/L)	28 (26–29)$^{\alpha,¥}$	28 (28–29)$^{\beta,\Delta}$	47 (43–49)*	50 (44–56)	<0.001
ALT (u/L)	27 (23–27)$^{\alpha,¥}$	26 (23–27)$^{\beta,\Delta}$	34 (33–27)*	37 (36–40)	<0.001
LDL cholesterol (mg/dL)	117 ± 25	115 ± 25	117 ± 24	113 ± 25	0.911
hs-CRP (mg/dL)	1.2 (1.0–1.4)$^{\alpha}$	1.2 (1.0–1.4)$^{\beta}$	2.1 (1.5–3.1)*	17 (11–22)	<0.001
D-dimer (ng/mL)	4 (3–36)$^{\alpha,¥}$	4 (4–35)$^{\beta,\Delta}$	499 (34–725)*	750 (499–1550)	<0.001
NT-proBNP (pg/mL)	23 (10–33)$^{\alpha}$	21 (11–34)$^{\beta}$	100 (41–111)*	123 (110–567)	0.033
hs-cTnI (ng/L)	5 (3–13)$^{\alpha}$	5 (3–14)$^{\beta}$	16 (14–30)*	20 (14–156)	0.005

*Values are shown as mean ± standard deviation, median and interquartile range, or n (%). ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBP: diastolic blood pressure; hs-CRP: high sensitive C reactive protein; hs-cTnI: high sensitive cardiac troponin I; LDL: low density lipoprotein; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure. Group I: Healthy controls, group II: patients with COVID-19 without pneumonia, group III: patients with COVID-19 and mild pneumonia, group IV: patients with COVID-19 and severe pneumonia. α = significant difference between group I and group IV (p < 0.05). ¥ = significant difference between group I and group III (p < 0.05). ► = significant difference between group I and group II (p < 0.05). β = significant difference between group II and group IV (p < 0.05). Δ = significant difference between group II and group III (p < 0.05). * = significant difference between group III and group IV (p < 0.05).*

of arrhythmias were not performed. However, ventricular repolarization parameters of patients, which can predict arrhythmic events in advance, were evaluated at admission. It was determined that Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio, which are among ventricular repolarization parameters, increased with the activity and severity of the disease, and they were much higher in patients with severe pneumonia. In addition, it was determined that there was a positive and significant relationship between hs-cTnI and Tpe, Tpe/QT ratio, and Tpe/QTc ratio, which supports studies showing that the frequency of arrhythmias increased in patients with high hs-cTnT.

There are many parameters related to disease activity and prognosis in patients with COVID-19. The majority of parameters associated with disease activity and prognosis are also associated with cardiac involvement. In our study, disease activity was associated with the presence and severity of pneumonia. In addition, impaired ventricular repolarization parameters in our study were positively and significantly related to increased HR,[3] NT-proBNP,[8] D-dimer,[5] and hs-cTnI,[1-5] which are closely related to the disease activity of COVID-19 in the literature. Therefore, we hypothesized that increased myocardial repolarization prolongation in patients with COVID-19 might be affected by disease activity and that arrhythmic events in these patients could be predicted in advance.

Table 2 – Comparison of ventricular depolarization and repolarization findings according to study groups.

Variable	group I n=30	group II n=30	group III n=30	group IV n=30	p
QT interval, time (ms)	367 ± 49	380 ± 21	381 ± 24	382 ± 51	0.338
QTc interval, time (ms)	405 ± 23	406 ± 34 β,Δ	406 ± 15	407 ± 16	0.989
Tpe interval, time (ms)	70.3 ± 7.1α	72.7 ± 7.7β	74.1 ± 8.5¥*	90.1 ± 9.2	<0.001
Tpe/QT ratio	0.186 ± 0.021α	0.191 ± 0.023β	0.203 ± 0.051¥*	0.235 ± 0.034	<0.001
Tpe/QTc ratio	0.188 ± 0.022α	0.186 ± 0.024β	0.200 ± 0.018¥*	0.216 ± 0.029	<0.001

*Values are shown as mean ± standard deviation or n (%). Group I: Healthy controls, group II: patients with COVID-19 without pneumonia, group III: patients with COVID-19 and mild pneumonia, group IV: patients with COVID-19 and severe pneumonia. α = significant difference between group I and group IV (p < 0.05). ¥ = significant difference between group I and group III (p < 0.05). ► = significant difference between group I and group II p<0.05). β = significant difference between group II and group IV (p < 0.05). Δ = significant difference between group II and group III (p < 0.05).. * = significant difference between group III and group IV p<0.05)*

Table 3 – Correlation analyses for parameters associated with Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio

	Tpe interval		Tpe/QT		Tpe/QTc	
	r	p	r	p	r	p
Systolic blood pressure (mmHg)	−0.296	0.001	−0.175	0.056	−0.149	0.105
Diastolic blood pressure (mmHg)	−0.218	0.017	−0.187	0.040	−0.183	0.046
Pulse (bpm)	0.298	0.001	0.309	0.001	0.125	0.424
Creatinine (mg/dL)	0.279	0.002	0.223	0.014	0.247	0.007
Potassium (mEq/L)	0.274	0.002	0.299	0.001	0.120	0.405
Calcium (mg/dL)	−0.461	<0.001	−0.241	0.008	−0.287	0.002
hs-CRP (mg/dL)	0.245	0.007	0.208	0.023	0.219	0.012
D-dimer (ng/mL)	0.431	<0.001	0.298	0.001	0.569	<0.001
NT-proBNP (pg/mL)	0.192	0.035	0.190	0.045	0.351	<0.001
hs-cTnI (ng/L)	0.185	0.042	0.210	0.019	0.255	0.005

hs-CRP: High sensitive C reactive protei;, hs-cTnI: high sensitive cardiac troponin I; NT-proBNP: N-terminal probrain natriuretic peptide.

Limitations

There are some important limitations to our study, including the retrospective design of the study and the number of patients enrolled. In addition, arrhythmic events and clinical follow-up parameters were not evaluated, due to the small number of patients and lack of clinical follow-up. Prospective studies with more patients can provide more meaningful information. In our study, medications and medical treatments that prolong QT were taken as exclusion criteria, but no genetic evaluation was performed for long or short QT. This hereditary channelopathy may not be very meaningful due to its rarity. Magnetic resonance imaging was not performed for cardiac involvement or myocarditis due to COVID-19. Another important limitation to our study is the inability to evaluate the effects of drugs such as hydroxychloroquine and azithromycin, which are frequently used to treat COVID-19, on ventricular repolarization.

Conclusion

Although the main issue related to mortality and morbidity in patients with COVID-19 is acute lung disease, the available evidence indicates that one out of every five COVID-19 patients has myocardial damage. Our study showed that, in addition to previous COVID-19 studies in the literature, myocardial repolarization disorder occurred in addition to increased myocardial damage in patients with severe pneumonia. In patients with COVID-19, Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio, which are among the dispersion of transmural ventricular repolarization parameters, were found to be increased, without prolonged QT and QTc intervals. This was more pronounced in patients with severe COVID-19 and severe pneumonia, and it may be associated with increased inflammation and myocardial damage. For patients with COVID-19, especially those with severe pneumonia, it should be kept in mind that prolongation may occur in ventricular repolarization. In this study, we cannot definitively conclude that the ECG changes observed are directly

Table 4 – Linear regression analysis for parameters significantly associated with Tpe interval, Tpe/QT ratio, and Tpe/QTc ratio

	Tpe interval		Tpe/QT		Tpe/QTc	
	β	p	β	p	β	p
Systolic blood pressure (mmHg)	−0.092	0.236	−0.056	0.530	−0.013	0.865
Diastolic blood pressure (mmHg)	−0.017	0.827	−0.057	0.536	−0.698	0.487
Pulse (bpm)	0.271	0.001	0.286	0.001	0.205	0.007
Creatinine (mg/dL)	0.143	0.054	0.153	0.074	0.054	0.499
Potassium (mEq/L)	0.105	0.168	0.175	0.158	0.158	0.168
Calcium (mg/dL)	−0.298	<0.001	−0.103	0.263	−0.241	0.002
hs-CRP (mg/dL)	0.078	0.306	0.113	0.188	0.021	0.773
D-dimer (ng/mL)	0.342	<0.001	0.271	0.002	0.493	<0.001
NT-proBNP (pg/mL)	0.114	0.125	0.055	0.526	0.233	0.001
hs-cTnI (ng/L)	0.235	0.002	0.205	0.010	0.198	0.012

hs-CRP: High sensitive C reactive protein; hs-cTnI: high sensitive cardiac troponin I; NT-proBNP: N-terminal probrain natriuretic peptide. $R_{adjusted}^2$ for Tpe interval, Tpe/QT, and Tpe/QTc as 0.426, 0.446, and 0.487, respectively.

related to COVID-19 infection or inflammation, but rather associated with severe COVID-19 scenarios, which might involve other causes of inflammation and comorbidities.

Author Contributions

Conception and design of the research: Sumbul HE, Koca H; Acquisition of data: Gulumsek E, Koca H, Turunc T, Bayrak E, Ozturk HA, Demirtas AO; Analysis and interpretation of the data: Koc M, Bulut Y, Bayrak E, Aslan MZ; Statistical analysis: Koc M, Icen YK; Writing of the manuscript: Koc M, Sumbul HE, Turunc T; Critical revision of the manuscript for intellectual content: Koc M, Karakoc E, Ozturk HA.

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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Ventricular Repolarization as a Tool to Monitor Electrical Activity of the Heart

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Short Editorial related to the article: Disease Severity Affects Ventricular Repolarization Parameters in Patients With COVID-19

The centennial ECG is still an excellent tool to assess electrical activity of the heart. ECG has been renovated over the last decades to keep pace with evolution in other areas of knowledge, such as genetics, molecular biology and electrophysiology.

Our experience has demonstrated that, among the large diagnostic arsenal available to investigate heart diseases, the electrocardiogram, this simple, practical, remote and quick tool, is capable of accurately monitoring the extent and severity of cardiac involvement in various scenarios.

QT interval and its variations, many decades after being first reported, still holds relevant parameters to indicate whether a patient is at risk for severe and sometimes fatal cardiological events.

In 1856, the first patient with long QT syndrome was reported by Meissner. Although its genetic origin was established in 1901, it was only in 1991 that Keating first demonstrated the association of patients with long QT syndrome and short arm mutation of chromosome 11. Bazzet, in 1920, reported his formula for heart rate correction of the QT interval.[1]

The emergence of the COVID-19 pandemic in March 2020 showed a disease initially with respiratory symptoms, but with the possible involvement of several other organs due to its very aggressive inflammatory response.

Taking advantage of their experience with treating the COVID-19 cardiac repercussions, experts analyzed electrocardiographic findings during the period of infection.

In the study by Koc et al.[2] published in this edition of *Arquivos Brasileiros de Cardiologia*, the authors examined the alterations of QT, QTc and Tpe (Ppeak-Tend) intervals, and the Tpe/QT and Tpe/QTc ratios, all of which are parameters of ventricular repolarization.

The study group of 120 patients, 90 of whom infected with COVID-19, and 30 age-and-sex-matched healthy controls, was divided into four groups: I — healthy controls and COVID-19 patients: II — without pneumonia, III — with mild pneumonia, and IV — with severe pneumonia. Results showed that one out of five patients with COVID-19 had myocardial damage.

The study showed that in cases with severe pneumonia there are clear ventricular repolarization alterations. In spite of practically normal QT values, analysis of the parameters studied demonstrated increased dispersion of transmural repolarization, which is the usual etiology of severe arrhythmias.

The most frequent causes of cardiac mortality in patients with COVID-19 were arrhythmic events. The types of arrhythmia were diverse, with many relevant aspects. The mechanism of arrhythmias could not be characterized, but the literature reports the presence of arrhythmic phenomena in 27.8%, and of ventricular tachycardia /ventricular fibrillation (VT/VF) in 5.9% among the 187 patients studied by Guo et al.[3]

The most important mechanism of ventricular arrhythmias reported in patients with COVID-19 is similar to that of arrhythmias found in patients with acute myocarditis. The analysis of acute myocarditis repercussions in other studies showed increased QT, QTc and Tpe intervals, and Tpe/QT and Tpe/QTc ratios.

In the study discussed here, all these measures clearly increased with disease severity, as seen in the COVID-19 patients with severe pneumonia.

Confirming reports of higher frequency of arrhythmias in patients with increased troponin levels, increase in high-sensitivity troponin I levels showed a positive and effective relationship with the measures of QT parameters.

In a recent report,[4] the authors mention a study[5] that categorized the cardiac complications of COVID-19 into five types:

(1) Cardiac damage (ischemia or myocarditis)

(2) Arrhythmias

(3) New-onset or worsening of preexisting heart failure

(4) Thromboembolic disease

(5) Cardiac abnormalities induced by medical treatment

The authors state that "cardiac involvement in COVID-19 patients is reflected in ECG alterations as ST-T alterations, QT prolongation, conduction disorders and ventricular arrhythmias." Thus, "patients with cardiac symptoms and ECG abnormalities must be carefully assessed in order to diagnose COVID-19-related cardiac complications, such as myocarditis, myocardial ischemia or severe arrhythmias."[4]

In this pandemic, we must maintain these clinical suspicions even for patients who present with discrete symptoms or signs. There is no doubt that the presence of cardiovascular disease worsens the prognosis of the process. The virus cannot be

Keywords

Pandemics; Coronavirus; Betacoronavirus; COVID-19/complications; Cardiac Arrhythmias; Embolism and Thrombosis.

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considered as the cause of all cardiovascular complications, but it can worsen or reveal precarious underlying conditions.

In the article discussed here,[2] the alterations of repolarization observed, although not specific, call for further investigation to exclude disease-related complications.

The presence of general (16.7%) and malignant (11.5%) arrhythmias also raised greater concern in conditions with a more severe myocardial involvement than with mild involvement.

Comparison of the study by Haseeb et al.[4] and the one in this edition of *Arquivos Brasileiros de Cardiologia*[2] leads us to conclude that electrical alterations detected in the ECG can be relevant to make a decision about diagnosis and management.

The presence of ischemic alterations, QT prolongation, electrical conduction disorders and arrhythmias in the ECG can be a big warning sign to guide management in case of cardiological involvement.

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Hospitalization for Acute Myocardial Infarction: A Population-Based Registry

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Abstract

Background: **ST-segment elevation myocardial infarction (STEMI) is one of the main clinical manifestations of ischemic heart disease. Population-based data are relevant to better understand the current epidemiology of this condition.**

Objective: **To describe the incidence, therapeutic management, hospital clinical outcomes and cardiovascular events in the first year of follow-up of individuals hospitalized for STEMI.**

Methods: **Population-based prospective cohort study with consecutive registries of hospitalization for STEMI in a city in southern Brazil from 2011 to 2014. It included patients with STEMI who presented acute myocardial ischemia symptoms in the last 72 hours. A p-value < 0.05 was considered significant.**

Results: **The annual incidence of STEMI hospitalizations was 108 cases per 100,000 inhabitants. Adjusted incidence was higher among older individuals (relative risk 64.9; 95% CI 26.9–156.9; p for linear trend < 0.001) and among men (relative risk 2.8; 95% CI 2.3–3.3; p < 0.001). There were 530 hospitalizations in the period under evaluation and the reperfusion rate reached 80.9%. Hospital mortality and the one-year follow-up cardiovascular event rate were, respectively, 8.9% and 6.1%. The oldest patients had higher hospital mortality (relative risk 3.72; 95% CI 1.57–8.82; p for linear trend = 0.002) and more one-year follow-up cardiovascular events (hazard ratio 2.35; 95% CI 1.12–4.95; p = 0.03).**

Conclusion: **This study shows that both the therapeutic approach and hospital mortality are similar to the ones found in developed countries. However, the hospitalization rate was higher in these countries.(Arq Bras Cardiol. 2020; 115(5):916-924)**

Keywords: **Myocardial/mortality; Hospitalization; Epidemiology; Risk Factors; Prevention and Control; Percutaneous Coronary Intervention.**

Introduction

Cardiovascular diseases (CVD) are the main cause of mortality in adult males and females and the leading cause of premature death worldwide. Regarding the latter, about 75% occur in low- and middle-income countries.[1] In Brazil, even though there has been a declining trend, CVD are also the main cause of death in adults.[2]

Ischemic heart disease is responsible for most deaths caused by CVD. The World Health Organization (WHO) estimates that 7.4 million out of 17.7 million people who died of CVD in 2015 had ischemic heart disease. In Brazil, it is also the leading cause of mortality among cardiovascular diseases.[2]

ST-segment elevation myocardial infarction (STEMI) is one of the main clinical manifestations of ischemic heart disease. Its clinical recognition is fundamental so that immediate therapeutic strategies can be drawn up. Studies have shown that, despite decrease in its incidence, mortality related to STEMI has not undergone relevant variations.[3,4]

In Brazil, there are no population-based data on the hospitalization rate for STEMI. Besides, most information about STEMI hospitalization, such as mortality and reperfusion rate, is collected from registries that have limitations. In general, registries are either restricted to a specific hospital or, when they are multicentric, they do not represent the population, since they result from convenience sampling (invitation or voluntary participation), which may result in biased estimates. Other limitations are non-consecutive recruitment of patients and restrictive eligibility criteria, such as the selection of patients whose symptoms last up to 12 hours (after this period, they are associated with higher mortality).

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Therefore, this study aims at describing incidence, therapeutic management, hospital clinical outcomes and cardiovascular events in the first year of follow-up of individuals hospitalized with STEMI in a certain region in southern Brazil. Evaluating these data is relevant not only because this disease has a high incidence in Brazil, but also because there are few population-based studies[5] in the country. In addition, registries are an efficient way of addressing the implementation of clinical guidelines and databases for healthcare managers, professionals and researchers.[6,7]

Methods

Study design

A prospective cohort study of consecutive registries of hospitalization for STEMI in Rio Grande, RS, Brazil, was carried out from January 2011 to December 2014. The city, located in southern Brazil, has about 200,000 inhabitants, most of whom live in the urban area (Demographic Census, 2010). It has an open emergency service called Hospital de Cardiologia/Santa Casa do Rio Grande, a referral center to treat acute coronary syndromes. Thus, it is the hospital where people whose symptoms suggest that disorder are taken to. As a result, the level of patient referral loss is very low. The city does not have any care line in acute myocardial infarction, which means that patients look for health centers spontaneously.

Eligibility criteria

To be included in the study, individuals had to meet the following criteria when they were admitted to the hospital: (1) being 18 years old or older and living in Rio Grande, RS; (2) having symptoms of acute myocardial ischemia within 72 hours prior to admission; (3) showing ST-segment elevation (STE) on the electrocardiogram, with ≥ 1 mm in two or more peripheral contiguous leads (≥ 2 mm in precordial leads), or a new, or presumably new, left bundle branch block; and (4) increased markers of myocardial necrosis (troponin or CK-MB).

Patients who did not have their markers of myocardial necrosis measured were included in the study if they had typical symptoms of acute myocardial ischemia associated with unequivocal STE which justified immediate reperfusion therapy. Patients who had new STEMI events throughout the study period were included as new ones, provided that they had occurred at least 28 days after the first one.

Patients with transient STE (defined as spontaneous resolution associated with decreased pain before the beginning of the reperfusion therapy) were excluded from the study. Re-infarction events[8] (defined as new episodes up to 28 days after the incident one), were also excluded; thus, they only contributed to the clinical follow-up.

Sample size calculation

The following parameters were used for calculating the sample size of hospitalization rate: expected rate of 100 cases/100,000 inhabitants/year,[9] precision of 20 cases/100,000 inhabitants/year and 95% confidence level. This process resulted in 95,941 individuals; the target population of this study is about 160,000 inhabitants (Demographic Census, 2010). Parameters used for calculating the sample size of hospital mortality were an expected ratio of 10%,[9] precision of 2.5 percentage points and 95% confidence level. This process resulted in 554 patients. Based on the expected hospitalization rate of 100/100,000/year and on the target population of 160,000 individuals, four years would be needed to reach the calculated sample.

Data collection

The following data were collected:

a) Sociodemographic data — age, sex, medical care at the Brazilian public health system called *Sistema Único de Saúde (SUS)* and economic income class, in line with the Brazilian economic classification criteria, issued by Associação Brasileira de Empresas de Pesquisa (ABEP).[10] The classification, based on the number of household items and on the householder's education level, comprises five economic classes: A (the highest level), B, C, D and E (the lowest level).

b) Medical history — body mass index (based on self-reported height and weight); tobacco smoking (based on the patient's or a family member's report and on the fact that the patient must have smoked at least one cigarette in the month preceding the admission); systemic arterial hypertension, dyslipidemia and diabetes (evaluated by the patient's or a family member's report based on medical diagnosis); and history of prior infarction, percutaneous coronary intervention (PCI) and myocardial revascularization surgery.

c) Clinical status at hospital admission — main symptom (the one that made the patient look for the emergency service) and its time interval (period between the beginning of the symptom and admission); heart rate, systemic arterial pressure, Killip classification, complete atrioventricular block, topography of myocardial ischemia and serum creatinine.

d) Therapeutic management — reperfusion therapy (fibrinolysis or PCI), reasons for not trying reperfusion and adjunct medication in the first 48 hours.

e) Hospital clinical outcomes — death, re-infarction, cardiogenic shock, ventricular arrhythmia, mechanical complications, stroke and bleeding, in line with the criteria issued by the Bleeding Academic Research Consortium (BARC).[11]

f) Cardiovascular events in the first year after hospital discharge — cardiovascular death, acute myocardial infarction or stroke.

In order to identify eligible patients admitted to the referral hospital, a registered nurse — specialized in Cardiology and trained to carry out the tasks — kept daily lists of patients who arrived at the emergency service. Afterwards, a cardiologist reviewed potential cases and selected them according to the eligibility criteria. Sociodemographic characteristics and medical history were registered by the nurse when patients were admitted to the hospital. Clinical status, therapeutic management and clinical outcomes were evaluated by a cardiologist who followed patients and reviewed medical records on a daily basis.

To evaluate the occurrence of cardiovascular events in the first year of follow-up, patients were contacted by telephone one year after hospital discharge. When appropriate, medical records were checked. If any of the patients did not answer, household visits were made. When data could not be collected directly from the patients, either their relatives or close connections were contacted.

Hospitalization data were registered on printed forms, then scanned using Microsoft Access.[12] Quality control comprised form review and checking of data comprehensiveness and consistency.

Statistical analysis

In order to calculate hospitalization incidence of STEMI (cases per 100,000 inhabitants per year), the number of hospitalization events was the numerator while the city population (Demographic Census, 2010) was the denominator. The Poisson regression model was used for adjusted analyses of hospitalization incidence.

Hospitalization data were summarized into frequency and percentage for categorical variables, and were summarized into mean/standard deviation or median/percentile for continuous variables, depending on data normality (distribution check using the Shapiro-Wilk test). Adjusted analysis of hospital mortality was carried out using the generalized linear model (binomial family). The Kaplan-Meier method was used for the analysis of survival and the Cox regression was applied to adjusted analyses. All analyses were adjusted to repeated measures (a patient with more than one hospitalization event)[13] and conducted using the Stata program — version 14.0.[14] To show statistical significance, p was considered below 0.05.

Results

Throughout the study period, 575 patients were admitted with symptoms of acute myocardial ischemia within 72 hours prior to admission, associated with STE on the electrocardiogram. Forty-five of them were excluded because 41 had transient STE and four underwent re-infarction. There was no loss during recruitment.

Hospitalization incidence

Annual hospitalization incidence of STEMI in Rio Grande, RS, was 108 cases per 100,000 inhabitants aged 25 or older (Table 1). The highest rate was found among males whose ages ranged from 65 to 74. The analysis adjusted for sex showed that the older the individuals, the higher the hospitalization rate (p for linear trend < 0.001). By comparison with younger patients, hospitalization risk was 8.9-fold higher (95% CI 3.5–22.7) in the group aged 35–44, 28.8-fold higher (95% CI 11.8–70.6) in the group aged 45–54 and 64.9-fold higher (95% CI 26.9–156.9) in the group of individuals who were 55 or older.

Annual hospitalization incidences in males and females were 159 and 64 cases per 100,000 inhabitants, respectively. Incidence adjusted for age was 2.8-fold higher in males than in females (95% CI 2.3–3.3; $p < 0.001$).

Hospitalization data

Data showed that 522 patients underwent 530 hospitalization events due to STEMI — six patients were admitted twice and one patient was admitted three times. Patients going straight to the hospital accounted for 74% of admissions and healthcare conducted at the hospital accounted for 85% of admissions.

Sociodemographic characteristics and medical history are shown in Table 2. Most patients were males who were 55 years old or older and belonged to the economic class C. Almost 50% of patients were smokers, 59% had arterial hypertension and 25% had diabetes mellitus.

Characteristics of hospital admission are described in Table 3. About 65% of patients arrived within three hours after the onset of symptoms, while 94% of them got there within 12 hours. Most patients were admitted in Killip I and about 4%, in Killip IV. Inferior myocardial infarction (and inferior-posterior myocardial infarction) was responsible for 50% of cases, whereas extensive anterior myocardial infarction represented 16%.

Therapeutic management data are shown in Table 4. Reperfusion therapy was performed in 80.9% of patients. Forty-four patients (8.3%) were not considered eligible for reperfusion therapy because admission occurred 12 hours after the onset of symptoms, in most cases. Considering eligible patients, reperfusion therapy was performed in 88.3% and primary percutaneous coronary intervention (PCI) was the preferred method. Reperfusion therapy was not performed in 11.7% of eligible patients; most reasons are unknown. Almost all patients got dual platelet aggregation, but none got any glycoprotein IIb/IIIa inhibitors. Regarding primary PCI, radial access was used in 69.3% and angiographic success was used in 94.7%.

Hospital clinical outcomes are shown in Table 5. There was 3% of re-infarction during hospitalization; almost all cases resulted from stent thrombosis. Cardiogenic shock at admission and while in hospital was 9%. There was less than 1% of mechanical complications, bleedings and ischemic stroke. Concerning length of hospital stay, the median of seven days was found (interquartile range was 6–10 days).

Hospital mortality was 8.9%. Mortality rates according to age, sex and socioeconomic level, as well as crude and adjusted analyses, are shown in Table 6. Mortality adjusted for sex and economic level was higher among the oldest patients (p for linear trend = 0.002) and achieved a relative risk of 3.72 (95% CI: 1.57–8.82) in those who were 75 years old or older. Even though adjusted estimates showed higher mortality among females (relative risk 1.21; 95% CI: 0.69–2.14; $p = 0.50$) and individuals who belong to the lowest economic levels (relative risk 1.66; 95% CI: 0.72–3.85; $p = 0.24$), these differences were not statistically significant. Thirty-day mortality was 9.1%.

Clinical follow-up

Data on 13 out of 475 patients who were considered for clinical follow-up were not found, so follow-up loss was 2.7%.

Cumulative incidence of cardiovascular events at the end of the first year of follow-up, after hospital discharge

Table 1 – Annual hospitalization rate due to STEMI in adults in Rio Grande, RS, Brazil (2011–2014)

	Males			Females			Total	
Age (years)	Population	Number of cases	Rate (100,000 inh./ year)	Population	Number of cases	Rate (100,000 inh./ year)	Number of cases	Rate (100,000 inh./ year)
25 – 34	15,609	2	3	16,068	3	5	5	4
35 – 44	12,550	24	48	13,238	12	23	36	35
45 – 54	12,485	84	169	14,087	34	60	118	111
55 – 64	9,486	142	377	10,633	53	125	195	243
65 – 74	4,601	79	433	6,083	27	111	106	249
≥ 75	2,619	33	317	5,158	37	180	70	226
Total	57,350	364	159	65,267	166	64	530	108

Table 2 – Sociodemographic and clinical characteristics of individuals admitted due to STEMI (n=530)

Sociodemographic characteristics	
Age (years), mean (standard deviation)	60.4 (11.6)
Age (years), n (%)	
25–44	41 (7.7)
45–54	118 (22.3)
55–64	195 (36.8)
65–74	106 (20.0)
≥ 75	70 (13.2)
Males, n (%)	364 (68.7)
Economic level (ABEP), n (%)	
Classes A and B (highest levels)	179 (33.8)
Class C	268 (50.6)
Classes D and E (lowest levels)	83 (15.6)
Medical history	
Overweight, n (%) (n=474)	207 (43.7)
Obesity, n (%) (n=474)	112 (23.6)
Smoking, n (%)	235 (44.3)
Systemic arterial hypertension, n (%) (n=500)	295 (59.0)
Diabetes, n (%) (n=470)	121 (25.7)
Dyslipidemia, n (%) (n=456)	203 (44.5)
Prior myocardial infarction, n (%)	103 (19.9)
Prior coronary revascularization (surgical and/or percutaneous), n (%)	67 (12.6)

ABEP: Associação Brasileira de Empresas de Pesquisa.

Table 3 – Characteristics of hospital admission of individuals admitted due to STEMI (n=530)

Interval of symptoms (hours), n (%)	
0–3	342 (64.6)
> 3–6	79 (14.9)
> 6–12	76 (14.3)
> 12–24	17 (3.2)
> 24–72	16 (3.0)
Heart rate > 100 bpm, n (%) (n=524)	72 (13.7)
SAP ≥ 180 mmHg and/or DAP ≥ 110 mmHg, n (%) (n=516)	114 (26.2)
Killip classification at admission, n (%) (n=527)	
Killip I	463 (87.8)
Killip II	31 (5.9)
Killip III	10 (1.9)
Killip IV	23 (4.4)
Location of infarction (ECG), n (%)	
Septal, anteroapical and lateral	140 (26.4)
Extensive anterior	85 (16.0)
Inferior and inferoposterior	271 (51.2)
Posterior	32 (6.0)
New left bundle branch block	2 (0.4)
Complete AV block, n (%)	21 (4.0)
Creatinine (mg/dl) at admission, median (interquartile interval) (n=516)	0.97 (0.80–1.20)

due to STEMI, was 6.1% (cardiovascular death was 3.0%; acute myocardial infarction was 2.4% and stroke was 0.7%). Adjusted incidence of cardiovascular events was higher among patients who were 60 years old or older (hazard ratio 2.35; 95% CI: 1.12–4.95; p = 0.03) (Figure 1 — Panel A). It was also higher among females (hazard ratio 1.55; 95% CI: 0.77–3.13; p = 0.22) and among individuals that belonged to the lowest economical levels (hazard ratio 1.31; 95% CI: 0.61–2.82; p = 0.49). However, these differences did not have any statistical significance (Figure 1 — Panels B and C). All estimates were adjusted for age, sex, economic level and prior ischemic cardiomyopathy, which was defined as the history of myocardial infarction and/or myocardial revascularization (surgical and/or percutaneous). Cumulative incidence of

Table 4 – Therapeutic management of individuals admitted due to STEMI (n=530)

Non-eligible for reperfusion therapy, n (%)	44 (8.3)
Interval of symptoms > 12 hours, n (%)	42 (95.5)
Death before the therapy, n (%)	2 (0.5)
Eligible submitted to reperfusion therapy, n (%)	429 (88.3)
Primary PCI	356 (83.0)
Planned primary PCI but not performed*	28 (6.5)
Fibrinolysis	45 (10.5)
Eligible but not submitted to reperfusion therapy, n (%)	57 (11.7)
Unknown reason	50 (88.0)
Allergic reaction to fibrinolytics	6 (10.3)
Active bleeding	1 (1.7)
Radial access at primary PCI, n (%)	266 (69.3)
Angiographic success at primary PCI, n (%)	337 (94.7)
Medication in the first 48 hours, n (%)	
ASA	523 (98.7)
Clopidogrel	523 (98.7)
Unfractionated heparin or low-weight heparin	439 (82.8)
Statins	487 (91.9)
Beta blockers	411 (77.6)
ACEI or ARB	379 (71.5)

*PCI: percutaneous coronary intervention; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers. * All patients were with TIMI grade flow 3. Reasons for not performing: option for elective revascularization surgery, option for elective PCI, target lesion stenosis < 50%, small target vessel and death.*

Table 5 – Hospital clinical outcomes of individuals admitted due to STEMI (n=530)

Death, n (%)	47 (8.9)
Cardiac death	38 (7.2)
Non-cardiac death (sepsis)	9 (1.7)
Re-infarction, n (%)	16 (3.0)
Stent thrombosis, n (%)	15 (2.8)
Thrombosis after isolated use of thrombus extraction catheter, n (%)	1 (0.2)
Cardiogenic shock (at admission or during hospitalization)	48 (9.1)
Ventricular fibrillation or ventricular tachycardia (during hospitalization)	13 (2.5)
Mitral papillary muscle rupture, n (%)	1 (0.2)
Ventricular septal rupture, n (%)	1 (0.2)
Left ventricular free wall rupture, n (%)	1 (0.2)
Bleeding, n (%)	5 (0.9)
BARC Type 2	2 (0.4)
BARC Type 3a	3 (0.6)
Ischemic stroke, n (%)	5 (0.9)

non-planned revascularization (surgical or percutaneous) in the follow-up period was 4.7%.

Discussion

The annual hospitalization rate for STEMI, which was 108 cases per 100,000 inhabitants, was higher among males older than 65. Hospital mortality and one-year cumulative incidence of cardiovascular events were 8.9% and 6.1%, respectively. Both occurrences were higher among the oldest individuals.

The annual hospitalization rate for STEMI found by this study was higher than the ones found in developed countries. In the United States, where there has been a decrease in the incidence over time:[3] rates of 77 cases per 100,000 inhabitants and 50/100,000 were found in 2005[4] and in 2008,[3,15] respectively. In Europe, many countries also had lower hospitalization rates for STEMI than the one found in this study.[9] However, a study carried out in a city in Latin America found a rate of 90 cases per 100,000 inhabitants,[16] which was close to the one of this study. The highest incidence of hospitalization for STEMI in developing countries may result from the facts that they have poor control of risk factors[2] and their populations have less access and adherence to medication.[17] Concerning the highest hospitalization rate found among males and older individuals, similar results were also reported by other studies.[18,19]

The reperfusion therapy rate was close to the one observed in developed countries[9,20] and higher than the ones found in national registries. Registries found in hospitals that assist mostly SUS patients showed reperfusion rates ranging from 40% to 56%.[21,23] However, there is a considerable number of patients who were not submitted to reperfusion, a fact that resulted mainly from modifiable causes. Delay in seeking medical care and poor recognition of STEMI patients' clinical status are factors that may be improved with higher education levels.

Regarding hospital mortality resulting from STEMI, it depends on the registry and country, i.e., in Brazilian registries, it ranged from 8% to 14%,[21,22,24,25] while in Latin American registries, it ranged from 8% to 11%.[26-30] The same scenario may be observed in Europe, where registries carried out by several countries showed rates that ranged from 4% to 13%.[9,31] In the United States, two registries showed rates of 5.1%[15] and 9.7%.[4] By comparison with these registries, which were selected in a non-systematic way, mortality due to STEMI, in this study, was below the highest limits of these variations. Reperfusion rate and the use of radial access PCI as the preferred method may have contributed to this result.

However, some causes of variations in mortality rates found by these studies should be considered in this analysis. Variation in mortality rates provided by the registries may result from the methodological process: a) population-based sampling with consecutive registry has low risk of selection bias; b) only individuals that underwent the first infarction are selected; c) time interval of the short symptom (≤ 12 hours) excludes patients at high risk of death; and d) studies carried out either in hospitals that provide tertiary care or in intensive care units tend to register the most severe patients. Other important causes of variations may occur because of the percentage of patients submitted to reperfusion therapy and to its method (fibrinolysis or PCI).

Table 6 – Crude and adjusted analyses of hospital mortality according to age, sex and economic class

	Mortality	Crude analysis		Adjusted analysis	
		RR (95% CI)	P value	RR (95% CI)	P value
Age, years					
25–54	5.0%	1.0	< 0.001*	1.0	0.002*
55–64	6.7%	1.33 (0.56–3.12)		1.35 (0.58–3.16)	
65–74	10.4%	2.06 (0.86–4.97)		2.01 (0.83–4.90)	
≥ 75	21.4%	4.26 (1.89–9.60)		3.72 (1.57–8.82)	
Sex					
Male	7.7%	1.0	0.16†	1.0	0.50†
Female	11.5%	1.49 (0.85–2.59)		1.21 (0.69–2.14)	
Economic level					
Classes A and B	6.2%	1.0	0.03*	1.0	0.24*
Class C	9.0%	1.46 (0.73–2.90)		1.34 (0.68–2.64)	
Classes D and E	14.5%	2.35 (1.08–5.11)		1.66 (0.72–3.85)	

*RR: relative risk; CI: confidence interval. * Wald test for linear trend. † Wald test for heterogeneity.*

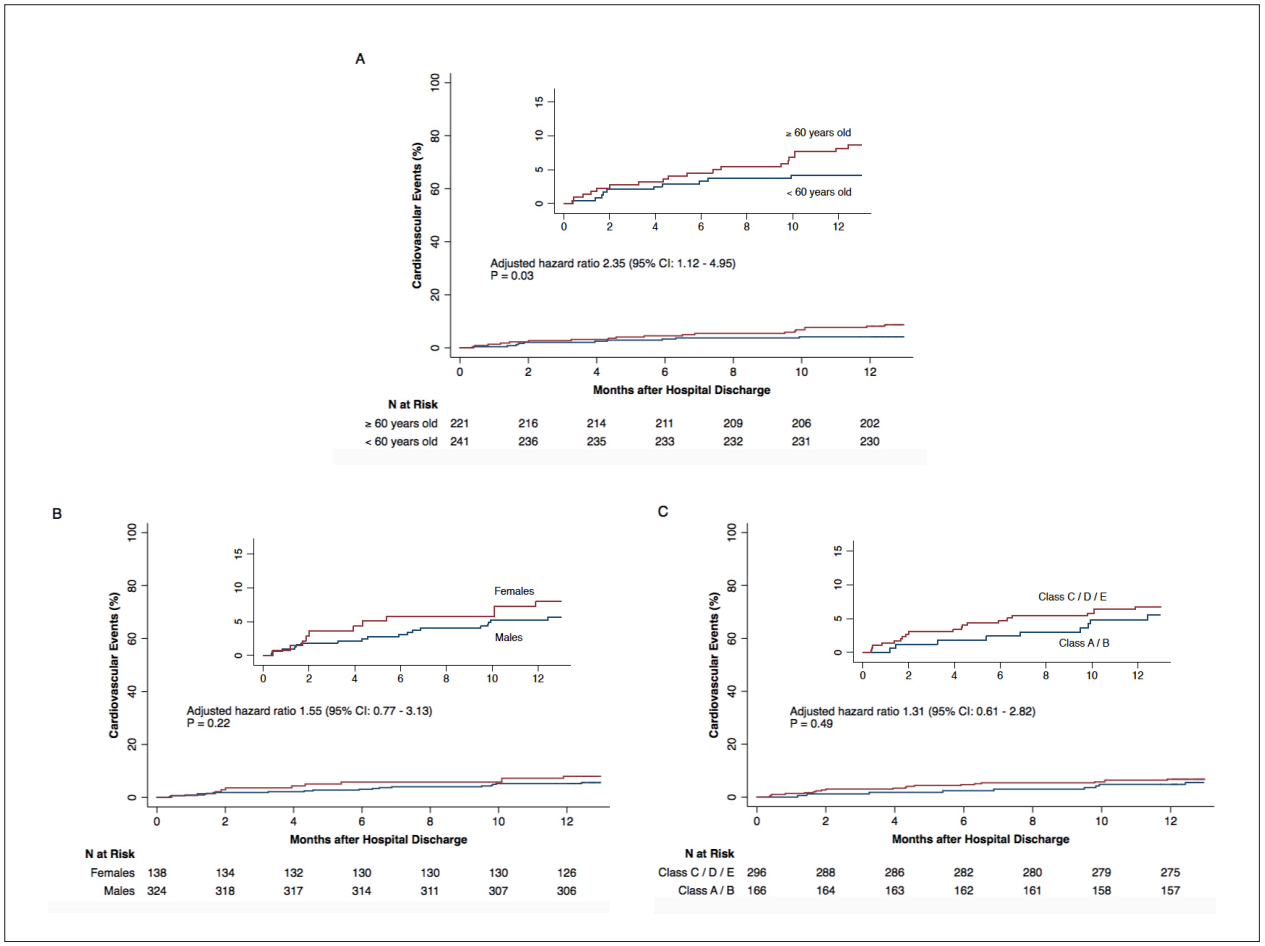

Figure 1 – *Cumulative incidence of cardiovascular outcomes (cardiovascular death, infarction, stroke) at the end of the first year of follow-up after hospital discharge due to STEMI based on age (Panel A), sex (Panel B) and economic class (Panel C).*

The highest hospital mortality rate and the highest occurrence of cardiovascular events in the 1-year follow-up found among the oldest individuals and females were known.[32,33] An association between these outcomes and the oldest individuals was also identified in this study. However, an association with females was not statistically significant; it may not have been detected because the study did not have power.

An association between socioeconomic levels and cardiovascular outcomes was also known.[34,35] Individuals with low socioeconomic status (low level of education and low income) tend to be affected by cardiovascular morbimortality, an association that is found in local studies.[36-39] Likewise, this study showed that there was high one-year hospital mortality and high one-year incidence of cardiovascular events among individuals who belonged to the lowest socioeconomic levels, but there was no statistical significance. In this case, the fact that the study did not have power may also have influenced its results.

The main strength of this study was its population-based registry, since it enabled an unbiased hospitalization rate and mortality due to STEMI to be estimated, as well as the occurrence of cardiovascular events in one year. Consecutive recruitment, with no loss, also contributed to decrease selection bias. Another relevant issue that favored direct estimates was the recruitment of patients whose time interval was 72 hours, since the ones whose period of pain was longer had higher risk of death. Finally, the low rate of loss in the evaluation of clinical follow-up at the end of the first year after hospital discharge should be highlighted.

Limitations of the study should be considered. The time interval between STEMI diagnosis and reperfusion therapy was not evaluated; this data is important to evaluate the quality of care provided to STEMI patients. However, data collected in the hospital from 2005 to 2007 showed median door-to-balloon time of 70 minutes (unpublished data). Another limitation was the clinical follow-up by phone, which prevented an objective evaluation of events. Since the hospital is a referral center, cardiovascular events that occurred there were investigated in medical records.

As highlighted before, registries are fundamental. Thus, in order to provide unbiased estimates and enable comparison with studies carried out in other countries, future registries should be representative of the population (either randomized selection or inclusion of all health centers) and consecutive recruitment.[5] Besides, this study recommends that selection should include patients with a longer time interval from the symptom (at least 48 hours).

Conclusion

This study shows that therapeutic management and hospital mortality in developing countries was similar to both found in developed countries. However, the hospitalization rate was higher in the former.

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Author contributions

Conception and design of the research and Acquisition of data: Alves L; Analysis and interpretation of the data; Statistical analysis; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Alves L, Polanczyk CA

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Associação de Caridade Santa Casa de Rio Grande under the protocol number 2.492.526. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Analysis of a Population-Based Registry of Hospitalizations for Acute Myocardial Infarction

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Short Editorial related to the article: Hospitalization for Acute Myocardial Infarction: A Population-Based Registry

Ischemic heart disease (IHD) is the leading cause of mortality in the world, being responsible for more than 9 million deaths in 2016. The trend profile of IHD mortality rates varied according to the economic level of countries. Developed nations have experienced a dramatic reduction in IHD mortality rates in recent years, perhaps attributed to a greater focus on primary prevention and better diagnosis and treatment. However, in the so-called developing countries, the reduction was not so accentuated, representing a major challenge for public health.[1,2]

Among the IHDs, the most severe form of presentation is acute myocardial infarction with ST-segment elevation (STEMI), which corresponds to approximately one-third of IHD presentations but has higher mortality when compared to non-ST-segment elevation myocardial infarction and unstable angina.[3,4]

Studying the behavior of IHD cases, especially of STEMI with wide geographical, population and temporal coverage, is essential to improve the approach to the biggest cause of death worldwide, justifying the performing and publication of the present study.[5] An initial criticism of the study is worthwhile, as it is actually a hospital record and not necessarily a population record, as it is restricted to data collected from the admission of patients with STEMI to a single and specific hospital unit. Despite the authors' justification for the fact that the data collection hospital is the regional reference for the vast majority of patients with infarction who initially seek or are subsequently referred to this institution due to AMI, it is not possible to estimate that all cases of STEMI in the target population of the study has been treated at the study referral center. Some possibilities must be raised; first, the fact that patients from other locations around the region were treated at the study hospital or even the fact that patients who lived in the region had STEMI and received treatment at another hospital in the city or elsewhere.

Most epidemiological studies involving STEMI in Brazil address mortality rates,[6-8] and few data on morbidity are analyzed and disclosed. An excellent indicator of morbidity, the rate of hospitalizations, is addressed in the present study and very well explored with divisions by age group, search for predictors and outcomes. Also, these hospitalization rates have shown to be high when compared to those in the USA or European countries, but there are no data available for comparison with the national average rates of hospitalizations for AMI and few reliable population data from other regions of Brazil can be found. The division of the Brazilian health system into the Unified Health System (SUS) and the supplementary health system makes it even more difficult to establish national hospitalization rates for any type of disease.[9] The hospital unit of the study, as reported, treats patients from both health systems, as it states that 85% of patients were hospitalized through SUS, which makes us assume that the other 15% were treated through the supplementary health system, so it was possible to group patients from both systems in a single study.

We can also characterize the city of Rio Grande, a medium-sized municipality with around 200,000 inhabitants, but with an elevated Municipal Human Development Index (MHDI) of 0.744, classified as high, between 0.700 and 0.799.[10]

The positive points arising from the epidemiological study should be highlighted. It involved more than 500 patients from a population of almost 200,000 inhabitants. It was a prospective study with a long duration, 4 years, with follow-up of patients for at least one year. There were few losses, less than 10% by the exclusion criteria, and no recruitment losses. The study was able to generate mortality data, but it was not restricted to that, since results with variables including data on morbidity and therapeutic approach were also analyzed and published. Epidemiological studies with analysis of variables capable of measuring illness are essential to understand and search for factors aimed at achieving the reduction in the incidence and mortality of the disease that caused the most deaths in Brazil and worldwide in recent years.

Keywords

Myocardial Ischemia; Myocardial Infarction/mortality; cardiovascular Diseases/mortality; Morbidity; Hospitalization; Unified Health System

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Hypertrophic Cardiomyopathy: A Review

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common heart disease with a genetic origin, and its main characteristic is left ventricular hypertrophy that occurs in the absence of other conditions that trigger this change. HCM may present from asymptomatic forms to manifestations of sudden cardiac death and severe heart failure. Contemporary high-resolution imaging methods and more accurate clinical scores have been used and developed to provide a prognostic assessment and adequate functional assessments, as well as to allow for the stratification of clinical severity. These aspects will be addressed in this review, along with other classic topics inherent to the study of this disease.

Introduction

Hypertrophic cardiomyopathy (HCM) is a disease with a genetically determined cause that leads to structural changes in the cardiac conformation (Figure 1). The main anatomical characteristic of this disease is left ventricular hypertrophy (LVH) with various morphologies in the absence of other conditions that justify this finding.[1]

The prevalence of HCM is relatively frequent, occurring in about 0.2% of the adult population.[2] Its clinical presentation is extremely variable, ranging from asymptomatic forms to advanced heart failure (HF), among other presentations that culminate with sudden death.[3]

On the other hand, advances in the treatment of HCM have resulted in a current mortality rate of less than 1% per year.[4,5]

Thus, it is a subject of great interest due to its significant prevalence and the importance of early identification of at-risk groups, such as competitive athletes.

Keywords

Cardiomyopathy, Hypertrophic/genetics; Sudden Cardiac Death; Heart failure; Echocardiography/methods; Hypertrophy, Left Ventricle.

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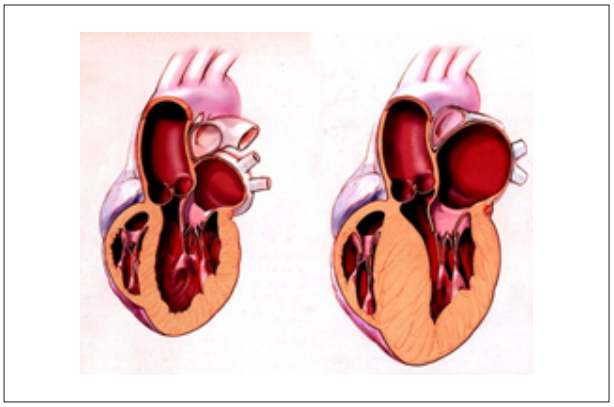

Figure 1 – *Schematic of a normal heart (left panel) and a heart with HCM (right panel).*

Genetic bases

Genetic analyses of HCM have identified a series of mutations in over 11 genes encoding sarcomeric proteins.[6] HCM can occur in a dominant autosomal inheritance pattern with variable expressivity and penetrance related to age or as a new mutation in non-family related cases.[7,8] The predominant mutation is the missense mutation, in which one nucleic acid is replaced by another, with a subsequent modification of the translated amino acid and the functional property of the resulting protein. Insertions and deletions are also common mutations identified as being involved in the pathogenesis of HCM that trigger the production of abnormal proteins.[8]

Patients with HCM are found to have some type of genetic alteration in approximately one-half cases.[9,10]

Most mutations affect the genes encoding the contractile proteins of the cardiac sarcomere: troponin T and I myosin light chain, myosin heavy chains alpha and beta, myosin-binding protein C, alpha-actin, alpha-tropomyosin and titin. However, mutations in nonsarcomeric protein-coding genes have already been identified in patients with HCM.[11] The genes most commonly related to the development of the disease are myosin heavy chain beta (MYH7), myosin-binding protein C (MYBPC3) and troponin T (TNNT2)[12] (Figure 2).

The pathogenicity of a mutation is evaluated probabilistically using a series of criteria that will determine the risk of developing HCM.[13]

The concept of phenocopies in the HCM context is also important to highlight. These patients have a CHM phenotype without the CMH genetic mutations, but instead

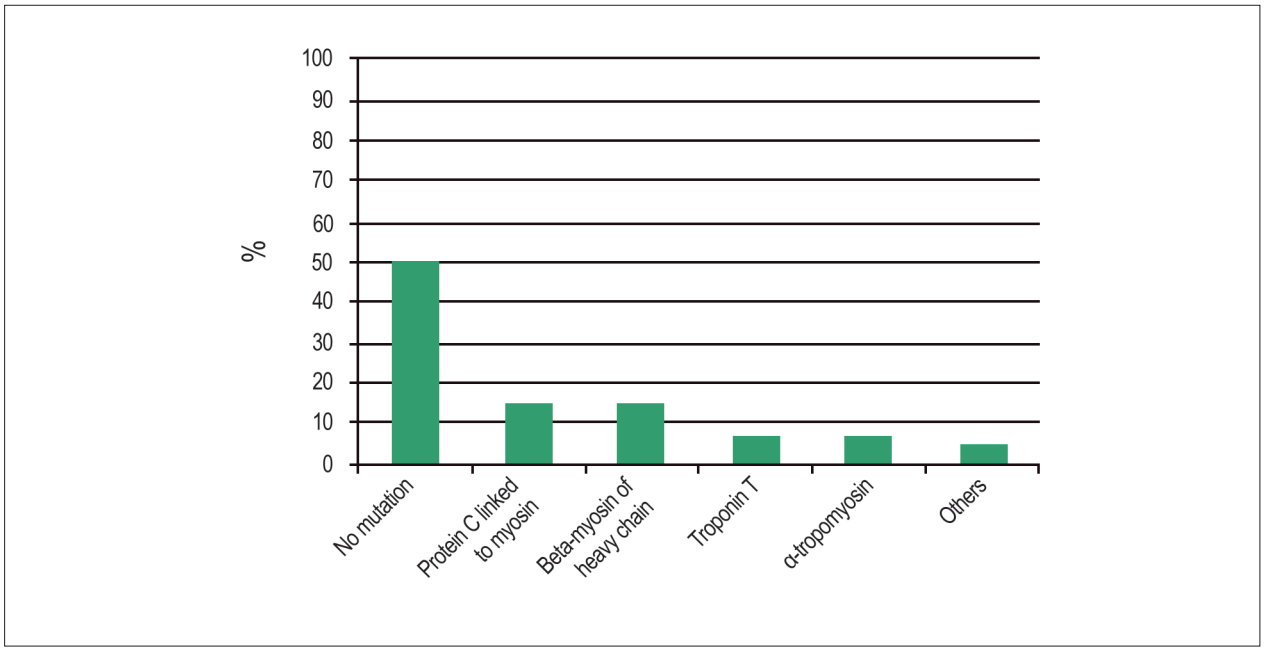

Figure 2 – *Distribution of gene mutations in HCM (Adapted from Maron BJ et al.[8])*

present with some other disease leading to a similar heart condition, such as Fabry disease, LAMP2 cardiomyopathy, PRKAG2 and/or amyloidosis.

Pathological findings

Histopathological analysis of HCM tissue shows hypertrophied myocardial fibers distributed in a disorganized pattern and interposed in a variable amount of interstitial fibrosis[14] (Figure 3).

In addition, intramural coronary arterioles are structurally abnormal and present a decreased intraluminal area with deteriorated vasodilatory capacity, which promotes inefficient blood flow during stress.[15] Over time, repeated episodes of ischemia lead to cell death, and repair is mediated by replacement with fibrotic tissue.[14]

Different types of anatomical presentations of HCM have been reported. The most common type is asymmetric septal hypertrophy (present in > 75% of cases), followed by apical, concentric, medioventricular and lateral presentations.[16]

Pathophysiology

HCM-related symptoms are related to the combination of diastolic dysfunction, obstruction of the left ventricular outflow tract (LVOT), mitral regurgitation, myocardial ischemia and arrhythmias. The most common factor contributing to the development of LVOT obstruction is systolic anterior motion (SAM) of the mitral valve against the IVS. SAM occurs due to the high speed of blood flow through the LVOT that drags the anterior mitral valve leaflet toward the interventricular septum, resulting in a direct impediment to blood flow through the outflow tract.[17]

In addition, the combination of myocyte disarray, autonomic disorder, LVH, ischemia and myocardial fibrosis generates a sufficient arrhythmogenic substrate for the development of the main arrhythmias observed in patients with HCM.[2]

These characteristics do not appear simultaneously, and a 4-stage classification has been proposed to assist with the diagnosis and management of patients: nonhypertrophic HCM, classic phenotype, adverse remodeling and overt dysfunction.[18] As the patient advances through the stages, he experiences a loss of ejection fraction, an increase in the left ventricular mass, a worsening of microvascular and diastolic dysfunction, an intensification of symptoms and a loss of a prior left ventricular outflow tract obstruction, which usually begins in stage 2.

Clinical presentations

HCM-related symptoms are related to the existing profiles of the disease, including an asymptomatic presentation, sudden cardiac death-ventricular arrhythmias, obstruction, heart failure with preserved ejection fraction, atrial fibrillation/stroke and heart failure with reduced ejection fraction. Although many patients with HCM have no symptoms or only experience minor symptoms, others may present dyspnea under stress, fatigue, chest pain, pre-syncope and syncope, during or shortly after stress, and heart palpitations.[19]

A well-established correlation has been observed between the presence or magnitude of the LVOT obstruction and the presence of symptoms.[20]

For most patients with HCM, LVH is not progressive and is compatible with a normal lifespan, with an annual mortality rate of approximately 1%.[21]

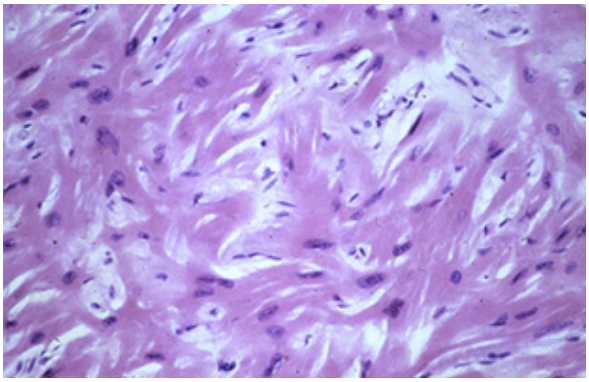

Figure 3 – *Myocyte disarray in the myocardial tissue of a patient with HCM.*

On the other hand, a small group of patients present a risk of developing symptoms related to the progression of systolic heart failure, sudden death, and atrial fibrillation related to thromboembolic phenomena.[22]

The presence of a pressure gradient in the LVOT at rest or provoked by exercise occurs in most patients with HCM.[23] Significant obstruction at rest is an independent factor for a worse prognosis and progression to heart failure.[24]

The physical examination of patients with HCM may reveal normal findings or the presence of various signs, such as the fourth heart sound (S4), regurgitation systolic heart murmur on the lower left sternal border, paradoxical splitting of second heart sound (S2), heaving apical impulse, and systolic thrill. Additionally, patients with obstruction of the LVOT may present an ejection systolic murmur at the left sternal edge that usually radiates to the right upper sternal edge and may increase upon standing from the squatting position and in the Valsalva maneuver.

The arterial pulse may be bifid and present a dome-shaped systolic peak, while a prominent "a" wave is detected in the venous pulse.

Complementary examinations

- Electrocardiogram (ECG): This test should be performed in all patients with suspected HCM. A normal ECG is unusual, as it was observed in less than 10% of patients with HCM, and this test is very sensitive for identifying the disease.[25] This group of patients tends to present a better prognosis than patients who present electrocardiographic alterations.[26] The most common abnormal pattern is the presence of localized or diffuse alterations in ventricular repolarization. Other findings may include signs of left ventricular hypertrophy, the inversion of T wave at the left leads, and an increase in the left atrium. Deep and narrow "Q" waves may occur in V5 and V6.

- Echocardiogram: An echocardiogram is an essential examination both for diagnostic confirmation and for evolutionary, functional and prognostic evaluations.[27] The transthoracic echocardiogram can show the heart morphology, estimate the systolic and diastolic function, assess the presence and severity of the gradient in the LVOT, and determine the degree of mitral regurgitation. The major echocardiographic findings associated with HCM are LVH (particularly if it is asymmetrical and involving the anterolateral wall or septum), an increased gradient in the LVOT, and the systolic anterior motion of the mitral leaflet (Figure 4).

Patients who remain symptomatic and do not present an obstruction at rest may undergo stress echocardiography to induce a gradient and subsequently adjust the therapeutic management and treatment according to the result.[23]

- Holter-ECG: This test is conducted as part of the stratification of the risk of developing ventricular arrhythmias and sudden death, as well as to investigate palpitations and in patients with suspected atrial fibrillation.

- Exercise stress test: This test is typically performed for risk stratification by measuring the blood pressure response to exercise and to investigate ischemia and arrhythmias.

- Cardiac Magnetic Resonance (CMR): CMR provides high-resolution images for evaluating cardiac structures. In addition to being able to identify hypertrophy in segments that are not displayed in echocardiography, it also shows myocardial fibrosis areas, which are usually detected through late gadolinium enhancement, and are one of the sudden death risk factors, enabling better characterization of structural abnormalities in the mitral valve apparatus[28-30] (Figure 5).

Treatment

The treatment is initiated with preventive measures, such as avoiding intravascular volume depletion and restricting the practice of intense physical exercise, with the recommended activity level being individualized for each patient.[31,32] Additional measures include the maintenance of negative inotropic drugs, avoiding the use of vasodilators and the use of an appropriate treatment for tachyarrhythmias.

Drug therapy

Pharmacological therapy is the first-line treatment for patients with symptoms of HF related to an LVOT obstruction.[26]

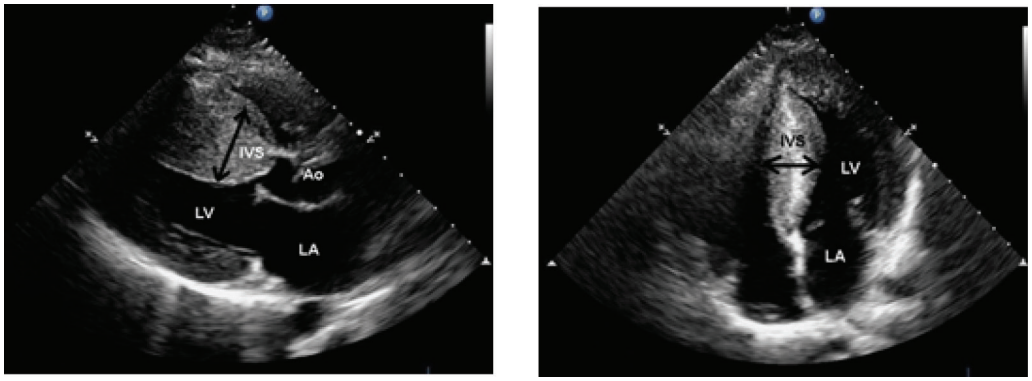

Figure 4 – *Transthoracic echocardiogram showing asymmetrical hypertrophy of the interventricular septum. IVS: interventricular septum; LV: left ventricle; LA: left atrium; AO: aortic root. (Serviço de Ecocardiografia do HC – Faculdade de Medicina de Botucatu – UNESP).*

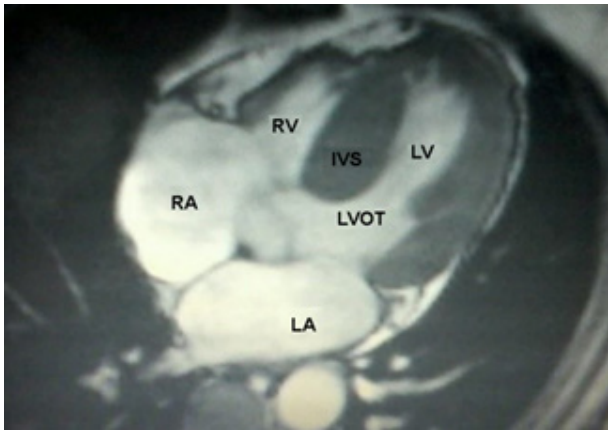

Figure 5 – *CMR of a patient with HCM and the nonobstructive asymmetric septal presentation. LA: left atrium; RA: right atrium; IVS: interventricular septum; LV: left ventricle; RV: right ventricle; LVOT: left ventricular outflow tract. (Courtesy of the Department of Radiology of the HC – Faculdade de Medicina de Botucatu – UNESP).*

The use of medications is not recommended before the development of symptoms, since evidence does not indicate that pharmacological therapy changes the natural history of asymptomatic patients.

The first-line treatment is beta-blockers. Currently, clinical trials have not indicated preference for a specific beta-blocker, as they have not been compared. However, studies have reported the benefits of propranolol and sotalol, although the latter is a class 3 anti-arrhythmic agent, in reducing the symptoms and decreasing arrhythmias.

Upon the failure of beta-blockers to alleviate the symptoms, the second option is disopyramide, which may increase effort tolerance, sometimes at the cost of anticholinergic side effects, such as urinary retention and dry mouth.

When beta-blockers are unable to be used, another option is verapamil, although this treatment must be carefully monitored in patients with severe obstruction due to the risk of pulmonary edema.

Diltiazem remains the last option when the previous therapies were unsuccessful.[1]

Patients who present an LVOT obstruction and persistent symptoms of HF despite monotherapy may benefit from the combination of disopyramide with the current treatment implemented[33] (Figure 6). Patients treated with disopyramide should undergo basal and periodic ECG during follow-up to monitor the QTc interval. The use of disopyramide should be avoided in patients with prostatic hyperplasia due to its anticholinergic effect.

Arrhythmias and prevention of sudden death

Atrial fibrillation (AF) is a relatively common arrhythmia in patients with HCM that potentially results in major adverse clinical outcomes, and its incidence is approximately five times greater in patients with HCM than in the general population.[34]

AF is usually poorly tolerated in patients with HCM due to the reduction in diastolic filling time and loss of atrial contraction, factors that are often associated with diastolic

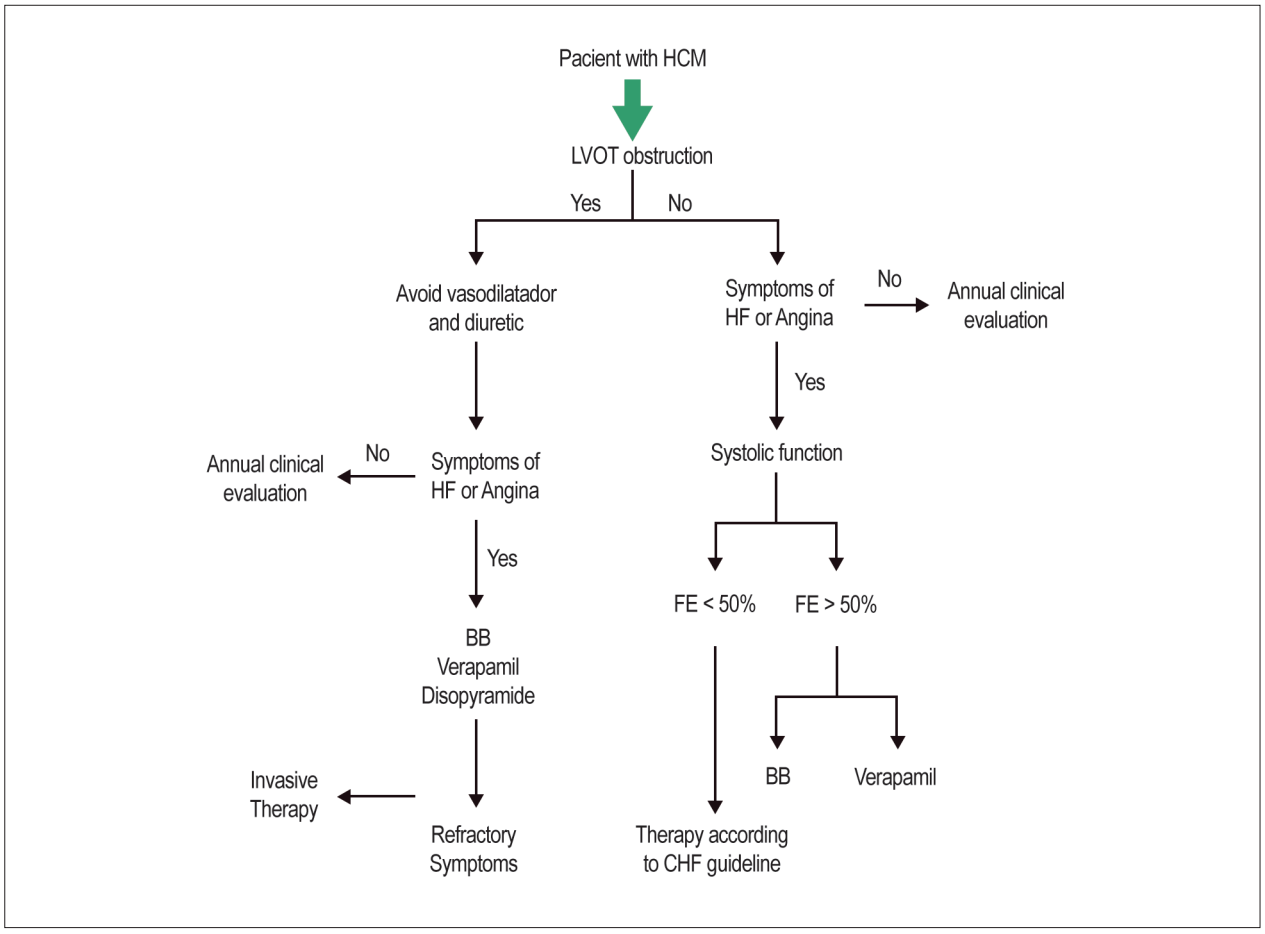

Figure 6 – *Flow chart to determine the appropriate medication for patients with HCM.*

dysfunction and are present in a large proportion of these patients. The development of AF is associated with a worsening of the functional class of these patients and with symptoms of HF.

In addition, AF is a marker of poor prognosis for patients with HCM[35] and signals a significantly increased risk of acute cerebrovascular events.[36]

The treatment of AF in patients with HCM is similar to the general recommendations for treating AF in patients without HCM, and both the control of rhythm and heart rate are available options,[37] with the choice of the best strategy being based on the clinical profile of each patient. Since the risk of thromboembolic events is increased in patients who develop AF, the recommendation of anticoagulant treatment in this group of patients is reasonable and indicated in most cases, regardless of the risk stratification based on the CHADS2 score.[27]

Ventricular arrhythmias are common in patients with HCM, including ventricular extrasystoles (VES), non-sustained ventricular tachycardia (NSVT), ventricular tachycardia (VT), ventricular fibrillation (VF), and sudden cardiac death (SCD). The first two types occur more frequently in patients with HCM.[38]

The treatment of VES is only necessary in patients who present symptoms, since the presence of this condition alone does not confer an increased risk of SCD.[39]

NSVT occurs more frequently in patients with higher degrees of LVH, in patients with more advanced functional classes (III/IV) and in older individuals. However, its presence in young individuals confers a greater risk of SCD. NSVT episodes are more frequent during sleep or during other periods of vagal hyperactivity. Patients with HCM who present NSVT during a Holter-ECG exhibit an increased risk of SCD,[39] and this risk is even higher if the episodes of NSVT are prolonged, repetitive, or associated with symptoms of low cardiac output.[40] When adjuvant pharmacological therapy is proposed to reduce symptoms or the incidence of ventricular arrhythmias, the medicine that is most commonly used as the initial therapy is the beta-blocker, and amiodarone has been used to treat refractory cases.[41] In patients at high risk of developing SCD, no drug is a suitable alternative to the implantation of an implantable cardioverter-defibrillator (ICD).

Clinically documented, sustained VT is usually rare and presents mostly as palpitations, pre-syncope or syncope. In the absence of the identification of a possible triggering factor, it is considered a major risk factor for SCD. Most patients

who develop this type of arrhythmia receive the ICD as a secondary prevention strategy.

Risk stratification for SCD should be performed in all patients with HCM. The first two major risk factors for this condition are prior aborted cardiac arrest and spontaneous sustained VT.[27] Patients who survive an episode of VF or VT are at very high risk of recurring events, which justifies the implant of an ICD for secondary prevention in these patients.[42]

Additional major risk factors for primary prevention have been identified, since the majority of patients do not survive the first episode of ventricular arrhythmia,[43] and because it may be the first manifestation of the disease in asymptomatic individuals.

Eight major factors are more commonly considered in the primary prevention of SCD:[44]

- A family history (FH) of HCM related to sudden cardiac death[45] (particularly if early SCD is present or multiple individuals within the same family are affected);

- Syncope that is not explained by another cause;[46]

- NSVT[38] (particularly if it is associated with symptoms or occurs in young individuals);

- Abnormal response of blood pressure in patients aged less than 40 years or patients with a family history of early SCD;[47]

- Severe LVH (≥30 mm),[48] particularly in patients aged less than 30 years;

- Contrast CMR showing late gadolinium enhancement - identified fibrosis, usually greater than 15% of the LV mass;

- Systolic dysfunction with an ejection fraction less than 50%; and

- Left ventricular apical aneurysm, regardless of size.[49]

Possible risk factors include the patient's age at the time of diagnosis, a pressure gradient greater than 30 mmHg in the LVOT, diastolic dysfunction, myocardial ischemia and the presence of high-risk genotypes, among others (Table 1).

Patients with two or three major risk factors have an aborted SCD rate of approximately 5% per year, which justifies the implantation of an ICD in this population.[50]

Thus, most professional societies and organizations recommend that patients with HCM presenting with two or more major risk factors receive an ICD for the primary prevention of SCD[27], although studies have shown that the presence of a major risk factor justifies the implantation of an ICD.[42,51]

Recently, a new model for risk stratification has been developed. This score uses an equation that introduces continuous variables such as age, left ventricular shortening fraction, left ventricular maximum thickness, maximum gradient in the LVOT, and left atrial diameter, and proved to be promising in the search for a more accurate method to determine the prognosis of patients with HCM.[52]

Table 1 – Predictors of SCD in patients with HCM

Classical Factors	Possible factors
Aborted SCD	Elevated gradient (above 30 mmHg) in LVOT
HF of SCD	Diastolic dysfunction
Unexplained syncope	Myocardial ischemia
NSVT to Holter	Late enhancement in MRI
BP abnormal to exercise	High-risk mutation
Severe LVH (>30 mm)	

Invasive therapy

A pressure gradient in the LVOT occurs in most patients with HCM,[23] and represents a poor prognostic factor and predictor of the emergence of HF symptoms when present at rest.[24] Patients with an LVOT obstruction and LV/aorta pressure gradient (either at rest or induced) > 50 mmHg and that persist with limiting symptoms despite the use of the maximum optimized drug therapy are candidates for invasive septal reduction.

Septal myectomy is a good option when the mitral valve or papillary muscle abnormalities must be repaired or myocardial revascularization is required, in addition to directly removing the septal muscle and expanding the LVOT.[53] Myectomy generally results in the resolution of the gradient in the LVOT and improves the symptoms of patients,[54] in addition to being associated with excellent long-term survival.[55]

Percutaneous alcohol septal ablation is also a good alternative, as no meta-analysis has favored one method to date. It is particularly indicated when myectomy should not be conducted due to a high surgical risk or the desire of the patient. This procedure reduces the LVOT obstruction, promotes improvement in the functional class, and increases exercise capacity.[56] Patients subjected to alcohol ablation present a five-year survival rate that is comparable to patients subjected to septal myectomy and to the general population.[57]

The main advantage of septal myectomy compared with alcohol ablation are: reduced need for implantation of a definitive pacemaker (PM) due an advanced atrial-ventricular block, reduced need for reintervention because of the recurrence of the LVOT obstruction, and reduced LV/aorta gradient after the procedure.[58] In addition, in contrast to septal ablation, septal myectomy has been shown to reduce the risks of SCD and inappropriate discharges of the ICD.[59]

The implantation of a DDD bicameral PM is a reasonable option during myectomy to reduce the gradient in the LVOT and improve symptoms related to this condition. However, this indication is restricted to patients who already have a bicameral device for other indications, since data on the long-term effects of right ventricle pacing on an HCM left ventricle are unavailable, and the benefit is restricted to only a small subset of patients.[1,60]

Family screening

Considering the genetic cause of HCM, close relatives of affected individuals should be evaluated periodically due to the possibility of inheriting the disease. The evaluation consists of anamnesis, physical examination, ECG and echocardiogram, as a strategy for early detection of HCM.[61]

Evaluations every 12-18 months are recommended, starting at the age of 12, and every 5 years beginning at the age of 18.[62] Echocardiogram with tissue Doppler has been shown to detect alterations in ventricular contraction and relaxation that may predict the emergence of myocardial dysfunction in these patients.[63] However, the presence of these abnormalities is not considered in the diagnosis of HCM.

Genetic tests are not routinely performed in family screening, except in situations where the mutation causing the HCM has been identified in the index case. In this situation, the genetic status of the family members should be determined. However, the mutation is generally only detected in approximately 35% of all patients. On the other hand, if the index case has the mutation and the family member does not, the likelihood of disease onset is very low.[4]

Endocarditis prophylaxis

Patients with HCM present a higher risk of developing infective endocarditis (IE) than patients without HCM, according to a study showing an increased incidence of mitral valve IE in patients with obstructive HCM and with increased size of the left atrium.[64] However, recent reviews of international guidelines do not recommend the routine administration of prophylaxis for patients with HCM.[1] On the other hand, specialists' opinions are still in favor of maintaining the prophylaxis for endocarditis in this group of patients before dental procedures, particularly in patients with obstructive HCM.

Author contributions

Conception and design of the research: Bazan SGZ, Oliveira GO; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Bazan SGZ, Oliveira GO, Silveira CFSMP, Reis FM, Malagutte KNDS, Tinasi LSN, Bazan R, Hueb JC, Okoshi K; Critical revision of the manuscript for intellectual content: Bazan SGZ.

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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COVID-19 Infection in a Cardiopatic Pregnant Woman

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Introduction

Regarding the obstetric aspects of COVID-19 infection, one should consider that it is a recent disease, with no specific knowledge on the theme to draft medical care protocols. For this reason, various guidelines are based on its comparison with infections caused by other viruses (SARS-CoV, MERS-CoV, and H1N1); therefore, all information concerning current evidence on the issue is subject to change due to new discoveries.

Infections caused by SARS-CoV and MERS-CoV have tended to be regionally bound, but the few obstetric cases published in the literature point to the need for advanced medical support for pregnant women with severe involvements identified in maternal prognoses. All of these highlight the importance of care against the dissemination of the virus.[1-4]

In a recently published literature review, 23 studies were selected, including 32 pregnant women and 30 newborns. The pregnant women were asymptomatic in 22% of the cases, but 6% required advanced life support medical care in an Intensive Care Unit (ICU). Births were performed through Caesarean section (C-section) in 27 women, and 47% of the births occurred before 36 weeks of gestation. The authors informed that no case of maternal death was observed in this review. Likewise, another extensive literature review pointed out that, to date, no case of the vertical transmission of this virus has been confirmed.[5]

Case series on the impact of Coronavirus during pregnancy are scarce in the literature. In women affected by severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), the mortality rate proved to be higher in those affected during pregnancy, as compared to those women who were not pregnant.[6]

Description

This study examines a 26-year-old, pregnant woman, G3P1A1, with a medical history of rheumatic mitral valve disease, who underwent a biological mitral valve replacement nine years ago. This patient presented a medical history of previous hospitalizations, in 2014, for a C-section, pre-term birth. At that moment, the patient was asymptomatic, from the cardiovascular point of view, and for this reason, there was no recommendation of a definitive contraception prescribed by the team that evaluated the patient.

After, the patient underwent an outpatient cardiologic follow-up, prescribed with Carvedilol, 3,125 mg 12/12h; AAS, 100 mg/day; and Benzathine Penicillin G, 1.200.000 UI, every 21 days.

On October 31, 2019, the woman required hospitalization, and received medical care at the cardiologic emergency clinic due to a new 16-week gestational condition, evolving to sustained ventricular tachycardia, with a heart rate of 140 beats per minute (BPM), blood pressure of 120 x 70 mmHg, with no clinical signs of hemodynamic instability.

The result of the laboratory exams on the day of hospitalization showed no signs of anemia, coagulation disorders, infection, hydro-electrolyte imbalance, or hepatic or renal dysfunction. In an obstetric ultrasound (US) of a single fetus, no signs of fetal distress were observed.

After compensating for both the arrhythmia and the clinical condition, the pregnant woman remained in the hospital, receiving medical care from the obstetrics team and evaluation from the cardiology team. She was submitted to an echocardiogram, which showed evidence of a swollen left atrium (50mm), an ejection fraction of 64%, a prosthesis valve area of 1.0 cm^2, a left ventricle-left atrium (LV-LA) gradient of 12 and a pulmonary artery systolic blood pressure of 40. The patient received hospital discharge on November 5, 2019, with the medical advice to continue in outpatient follow-up for high-risk pre-natal care.

Nonetheless, on November 9, 2020, the patient was once again admitted to the emergency clinic, with a medical condition of tachycardia, with a heart rate of 200 BPM and lower abdominal pain. The electrocardiogram revealed paroxysmal supraventricular tachycardia.

On that date, the patient's physical exam, of 33 weeks and 5 days, showed no change in pulmonary auscultation, with no signs of hemodynamic instability, with eupnea in ambient air, a uterine height of 33 cm, a fetal heartbeat of 129 BPM, a closed posterior and thick cervix, with no gynecological losses or signs of bleeding. After the clinical measures, she returned to the sinus rhythm and was referred to the obstetric infirmary, where she remained in follow-up with the obstetrics team and was evaluated by the cardiology team. The cardiology team recommended choosing the birth time according to

Keywords

Pregnancy, High-Risk; Heart Diseases/complications, Respiratory Insufficiency; COVID-19; Coronavirus; Severe Acute Respiratory Syndrome.

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the criteria established by the obstetrics team and through a C-section, with subsequent sterilization due to the patient´s cardiovascular risk. This team also recommended the use of cardiac glycosides should a new event of tachycardia occur. Thus, the patient received hospital discharge on March 23, 2020, with a prescription of carvedilol, 3.125 mg 12/12 h and AAS, 100 mg/day, as well as the continuance of Benzathine Penicillin G, every 21 days.

On March 30, 2020, the patient, now at 36 weeks and 5 days of gestation, was admitted to the cardiovascular emergency clinic at Fundação Hospital de Clínicas Gaspar Vianna (FHCGV), with a fever, a productive cough, and severe respiratory insufficiency. The physical exam showed evidence of tachypnea in ambient air, with a blood pressure of 100 x 70 mmHg, and pulmonary auscultation with an audible vesicular murmur with diffuse rumbles.

The admissions laboratory reported the following rates: hemoglobin, 12.3; hematocrit, 31.6%; leukocytes, 20,900, segmented, 87.9%; lymphocytes, 5%; with no left deviation; platelets, 137,000; normalized international ratio (INR), 1; prothrombin time, 11.7 seconds; partial thromboplastin time (PTT), 35 seconds; post-orotreacheal intubation arterial-blood gas, with a pH of 7.26; partial pressure of blood carbon dioxide (PCO_2), 50 mmHg; partial pressure of blood oxygen (PO_2), 136 mmHg; blood bicarbonate (HOC3), 22 mEq/L; base excess, –4; saturation of blood oxygen ($SatO_2$), 98%; lactate, 1.2 mmol/l; creatinine, 0.7 g/dl; sodium, 135 mmol/l; patassium, 3.5; magnesium, 1.8; ionized calcium, 1.13; total bilirubin, 1.36; direct bilirubin, 0.85; indirect bilirubin, 0.51; aspartate transaminase (AST), 27; glutamic-pyruvic transaminase (GPT), 20; polymerase chain reaction (PCR), 5 (VR < 5).

Tomography of the patient's chest, with apex portion with evidence of diffuse ground glass, peripheral predominance and bilateral pleural effusion (figure 1), in addition to 1/3 medium with evidence of diffuse ground glass, also peripheral and bilateral pleural effusion (figure 2).

An orotracheal intubation was performed, placed under controlled blood pressure, positive end expiratory pressure (PEEP) 9, respiratory rate of 20 irpm, tidal volume of 300, fraction of inspired oxygen (FiO) of 30%, with a PO_2/FiO_2 relation of 388. Nasopharyngeal and oral swabs were also collected, and a PCR was performed to detect COVID-19 and H1N1. Later, the patient was referred for a C-section and urgent sterilization. The surgery was performed under general anesthesia.

After the operation, the patient was sent to the ICU, remaining sedated, considering a –5 Rass scale. She evolved with hemodynamic instability and a capillary refill time of more than 2 seconds, requiring the introduction of vasoactive substances (norepinephrine and dobutamine). The following prescription was then begun: olsetamivir, 75 mg 12/12 h; azithromycin, 500 mg/day; hydroxychloroquine, 400 mg 12/12 h; piperacillin-tazobactam, 4.5 g 6/6 h; furosemide, 2 ampoules 8/8 h; carbegoline in a single dose to inhibit lactation; and prophylaxis for pulmonary thromboembolism (PTE) with enoxaparin, 40 mg/day.

After the birth, a chest X-ray was performed, which showed the presence of consolidation, standard air bronchogram in a ground-glass pattern in the bilateral superior lobes, with discrete bilateral pleural effusion.

On April 1, 2020, the patient showed clinical improvement, hemodynamic stability, with the possibility to suspend the vasoactive drugs, still under mechanical ventilation, but now on pressure support, presenting an increase in the PO_2/FiO_2 relation of 644. Sedation was paused in the morning.

On April 2, 2020, the patient was extubated, and a catheter for low-flow oxygen was implemented. The daytime laboratory showed: hemoglobin, 8.4; hematocrit, 255; leukocytes, 10.190, segmented, 68%; platelets, 137.000; arterial-blood gas, 7.43; PCO_2, 35; PO_2, 119; base excess, 1; bicarbonate, 24; $SatO_2$, 99%; lactate, 1.0.

On the same day, the PCR exam for COVID-19 was positive. On April 2, 2020, the patient was transferred to the Fundação Santa Casa de Misericórdia do Pará, a reference service for the handling of COVID-19 patients. There, the patient underwent treatment with olsetamivir, 150 mg/day, chloroquine diphosphate, 450 mg/day; azithromycin, 500 mg/day; and piperacillin-tazobactam, 18 g/day. On April 4, 2020, she evolved to a supraventricular tachyarrhythmia, and on April 7th, she presented acute respiratory failure, again requiring invasive mechanical ventilation, in addition to sedation and curarization.

The patient was placed in pronation on April 9, 2020, for 16 hours, but the ventilatory asynchrony and a low PO_2/FiO_2 relation were maintained, even after high PEEP and FiO_2 levels. On April 11, 2020, the patient was kept on ventilatory asynchrony, $SatO_2$ of 50%, and a low PO_2/FiO_2 relation. She then evolved to a cardiac arrest with asystole, with an unsuccessful attempt to revive the patient, who died at 10:10am.

The newborn was born in bradycardia and fetal distress, requiring resuscitation; Apgar 2/6/7, clear and smooth amniotic liquid, with a birth weight of 2.750 kg, birth length of 50 cm, cephalic, thoracic, and abdominal perimeter de 34,

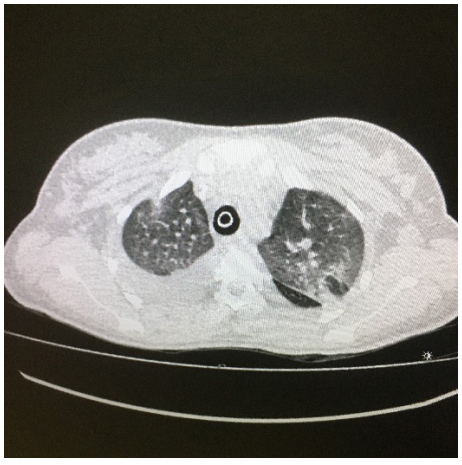

Figure 1 – *Patient's chest X-ray, portion of the apex with evidence of a diffuse ground-glass pattern, peripheral predominance, and bilateral pleural effusion.*

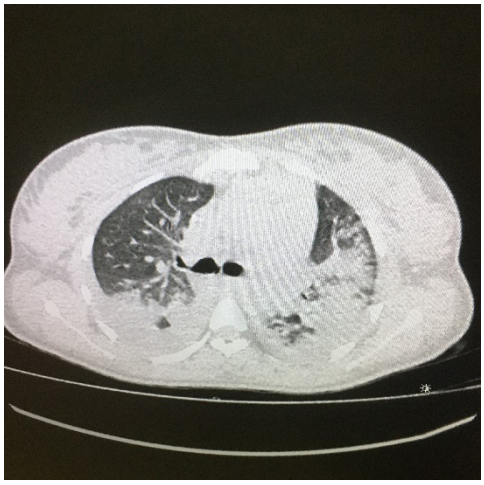

Figure 2 – *Patient's chest X-ray, 1/3 average with evidence of a diffuse ground-glass pattern, also with peripheral predominance and bilateral pleural effusion.*

32, and 31 cm, respectively. He was sent to the neonatal ICU upon birth and remained under mechanical ventilation from March 30th to April 8th, 2020. He continued to be hospitalized until April 21, 2020, when, fully recovered, he received hospital discharge. A COVID-19 exam was performed in the state of Rio Grande do Norte, Brazil, on April 21, 2020, after confirmation from the maternal diagnosis by PCR, but the result was negative.

Conclusions

Few studies exist in the literature about the impact of the new Coronavirus in pregnant women, given that the SARS and MERTS pandemics, which occurred before the COVID-19 pandemic, were geographically limited. This was the first case of a pregnant woman with SARS COVID-19 in the northern region of the state of Pará, a fact that was aggravated by gestational cardiopathy associated with an infectious clinical condition.

The lack of data on infections caused by COVID-19 in cardiopathic pregnant women makes it imperative to study and understand how this disease behaves in this patient group and what the possible consequences both for the mother and the newborn are.

Author Contributions

Conception and design of the research and Acquisition of data: Holanda LS and Vieira Junior FM; Acquisition of data: Holanda LS; Analysis and interpretation of the data: Vieira L, Campos MT; Writing of the manuscript: Holanda LS, Silva IAC; Critical revision of the manuscript for intellectual content: Holanda VBT, Serfaty D, Vieira Junior FM.

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Ethics Approval and Consent to Participate

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

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Actions Against Covid-19 in the Down Syndrome Population

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The World Health Organization (WHO) declared, on January 30, 2020, that the outbreak of the new coronavirus disease (COVID-19) constituted a Public Health Emergency of International Importance — the organization's highest alert level as per its International Health Regulations. On March 11, 2020, COVID-19 was declared a pandemic.[1] The fact that the lethality of COVID-19 is associated with common comorbidities has caused great concern among professionals who work with people with Down Syndrome (DS). The prevalence of cardiovascular diseases in people with DS is 40-50%,[2,3] and they are also more prone to overweight and obesity; moreover, patients with DS present changes in airways that facilitate infection by the virus,[4] which can worsen the effects of COVID-19. In addition, children with DS are more susceptible to infections due to changes in cytokines regulation, while adults frequently display increased proinflammatory biomarkers. These changes can impact the patients' anatomical disorders and increase the incidence of chronic inflammatory conditions and mortality by sepsis.[5]

Currently, the only recognized strategy to prevent infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is avoiding exposure to the virus.[4] Social isolation was advised by several Brazilian states with the aim of separating healthy people from those with suspected COVID-19, or who had contact with suspected or confirmed COVID-19 cases. It is worth noting that socialization is a very important aspect of the treatment of people with DS that contributes to a better quality of life and autonomy;[3] therefore, social isolation represents a major challenge for this population.

Keywords

Coronavirus; Pandemics; COVID-19; Public Health/organization and administration; Down Syndrome; Infections; Cardiovascular Diseases; Personal Autonomy;Quality of Life; Diet,Healthy; Cytokines.

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Considering these aspects of patients with DS, a quick response against COVID-19 regarding this population was considered crucial. Three Brazilian associations (Fundação Síndrome de Down [FSD]; Pontifícia Universidade Católica de Campinas [PUC-Campinas]; and the Brazilian Society of Cardiology [SBC]) came together to produce support material for young people with DS and their families. The care of people with DS must be interprofessional and requires different specialties;[3] the institutions thus brought together professionals and students of the areas of medicine, journalism, basic education, nutrition, psychology, occupational therapy, and pharmacy. Moreover, the initiative included the voluntary support of editors, producers, designers, and animators to build practical, fast, and communicative material addressing the main points of attention for preventing COVID-19 with an appropriate language for this population. The important support received by PUC-Campinas is worth mentioning; the university implemented the extension branch of its mission and generated knowledge to help the community develop solutions for its problems.

The material was produced in line with the "We decide" campaign, proposed by the Down Syndrome International global support on World Down Syndrome Day. Communication strategies employed in this project involved dialogue, as well as the reception and participation of the patient in the therapeutic process, which are considered efficient approaches for people with DS. First, an animated video was developed to explore visual awareness and visual learning skills. The message was reaffirmed in writing, exploring the ability to read. A clear and direct discourse considered the use of hearing aids, since this population may present some loss of auditory acuity.[6] This strategy prioritized providing the necessary information to empower the population with DS to perform primary health prevention and recognize the necessary actions to promote their safety.

As a second strategy, young people with DS were instructed to produce videos that provided information regarding COVID-19 prevention practices, exploring the desire to communicate and socialize as well as their willingness to model the behavior of their social environment.[7] This stage resulted in several short videos, shared with the media, in which the population with DS illustrated practices of hand washing, social distancing, healthy eating, physical activities, and described what were their favorite activities at home during the pandemic; these measures contributed to promote

mental and physical health during this period. We also broadcasted a video prepared by tutors, aiming to guarantee complete and concise information to assist those with less education. All videos were further adapted for Brazilian sign language (Libras) users, which expanded their public, and can be accessed at the link: https://www.facebook.com/watch/Previna-Covid-19-101822971493321/

It is a consensus among teams working in the care of people with DS that investments in health, education, and social inclusion result in a higher quality of life and higher levels of autonomy. Therefore, support strategies must be focused on providing information both directly to people with DS and indirectly to their family and caregivers; by focusing on their role and autonomy to share care, we are also promoting family health.3 A support letter for parents and caregivers was thus designed to complete the support materials and was made available on social networks; it can be accessed at the link: https://drive.google.com/drive/u/0/folders/1meN5KdHjeYzMkbsGRDM61ufJMjEg09Ml

It is important to emphasize that all materials prepared by the team were based on health care measures and healthy habits. Considering that DS is a risk factor for complications of COVID-19,[4] the aim was to offer concise and, especially, easy information that could be quickly adopted, highlighting the importance of social distancing and personal hygiene. We focused on explaining the importance of primary prevention: illustrating the correct way to disinfect hands, the importance of not sharing personal items, social distancing, and adequate attitudes in case they needed to leave their residence.[7] In addition, the main symptoms of COVID-19[4-7] were explained and patients were advised to ask for help from family members or caregivers in case they recognized any of them. The guidebook also instructed those in direct contact with people with DS to distinguish the severity of suspected COVID-19 cases, guiding and enabling them to request specialized help while avoiding unnecessary exposure. In addition, good health practices were reinforced, such as compliance to the vaccination schedule for people with DS, the importance of mental health, and the adoption of preventive health measures in pandemic periods, as well as the instruction to wear a face mask.

Regarding health habits, good eating habits are an important aspect of the healthy lifestyle of people with DS. Some people with DS may have a predisposition to obesity and an inappropriate diet could compromise their lifestyle and induce changes to their immune systems. Considering these aspects, our material was based on the Food Guide for the Brazilian Population, which encourages the consumption of fresh foods and warns against the consumption of ultra-processed foods. The presence of the family in the household also reinforces another important orientation of the guide, which is commensality. People are encouraged to eat and cook along with their families, promoting the consumption of fresh foods. In addition, there is evidence that SARS-CoV-2 may remain active on some types of surfaces for long periods of time: one study reported that viruses like SARS-CoV-2, SARS-CoV, and MERS-CoV could remain on surfaces for up to nine days. Thus, the disinfection of surfaces (such as food and packages when arriving from the supermarket and during meal preparation) must be performed frequently.[2,7]

Another important aspect to be considered during social isolation is the occurrence of sedentary behavior and low levels of physical activity, which are risk factors for people with DS. In fact, a sedentary lifestyle increases susceptibility to viral infections and the development of risk factors for cardiovascular and metabolic diseases[8] that are more frequent in people with DS, such as obesity, hypertension, and diabetes.[9] Thus, it is extremely important for people with DS to avoid sedentary behavior (sitting on the couch or lying in bed for long periods, or even fiddling with electronic devices) and to practice physical activities[8] during social isolation. Moderate-intensity aerobic physical activity (20 to 60 minutes) is recommended 3 to 7 times a week; this may include walking or running, jumping, playing soccer, or dancing. Strength exercises involving different muscle groups (making use of alternative accessories, such as elastic bands, pet bottles as dumbbells, and even the weight of the body itself), with at least 8-12 repetitions (moderate intensity), 2 times a week should also be included in this routine.[10,11]

The activities of daily living, such as cleaning the house or yard, climbing stairs, or playing with a pet are also important to keep people with DS physically active and integrated. Physical activities should preferably be performed in a safe and ventilated space. It is essential to look for pleasurable physical activities, such as playing with a ball or dancing, thus increasing the adherence and physiological and psychosocial benefits of this practice.

The current society is increasingly aware of the importance of valuing human diversity and offering equal opportunities for people with disabilities to exercise their right to live in the community. Therefore, the form of communication proposed in this action was exclusively aimed at the needs of people with DS, focusing on a social demand for understanding COVID-19. In the midst of the pandemic, faced with the need to bring accurate and safe information to this risk group, a multidisciplinary team with transdisciplinary actions developed strategies to reinforce the health care of adolescents and adults with DS. The ultimate aim was to maintain aspects of health care (including eating and sleeping habits, immunization, and physical activity), as well as the autonomy for basic and instrumental activities of daily living such as self-care, socialization, schooling, and vocational guidance.

The protagonism of people with DS in promoting COVID-19 prevention has contributed to their social inclusion and to breaking the stigma of limitations carried by the population with DS. Finally, education and family support are important aspects when teaching health care practices, relating the recommended habits and lifestyle as fundamental approaches for the prevention of COVID-19 in the population with DS.

Author Contributions

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Emerging Topics in Heart Failure: COVID-19 and Heart Failure

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Introduction

Acute COVID-19 cardiovascular syndrome has been the term proposed to describe changes in the cardiovascular system associated with SARS-CoV-2 infection.[1] The most common manifestations of cardiovascular involvement are myocardial injury, myocarditis, myocardial infarction with nonobstructive coronary arteries (MINOCA), arrhythmias, Takotsubo syndrome, pericardial effusion, heart failure (HF), and thromboembolic phenomena (Table 1).[2,3] Here, we emphasize myocardial injury, myocarditis, Takotsubo syndrome and the occurrence of COVID-19 in patients with preexisting HF.

Myocardial Injury

The impact of myocardial injury associated with SARS-CoV-2 infection was recognized early in the pandemic, when data from China and, subsequently, from multiple cohorts in different countries invariably showed an increase in mortality associated with elevated serum troponin levels.[2,4] The mechanisms of cardiac involvement in patients with COVID-19 are multiple and include factors directly related to viral infection and, mainly, indirectly related to myocardial damage. The presence of the angiotensin-2 converting enzyme receptor on the surface of cardiomyocyte and vascular endothelial cells suggested that SARS-CoV-2 could cause toxic damage and, consequently, myocarditis.[5] However, a German study based on autopsy cases detected copies of the virus in interstitial cells and macrophages invading the myocardium, but not in cardiomyocytes.[6] In addition, the presence of viral genome in the heart was not associated with inflammatory infiltrates typical of myocarditis, suggesting that SARS-CoV-2 may not cause a classic cell-mediated inflammatory condition. It is possible that other inflammatory injury pathways may play a role in myocardial damage by the virus, involving, in particular, vasculitis and systemic activation of cytokine release.

Keywords

COVID-19; Heart Failure; Myocarditis; Takotsubo Cardiomyopathy, Myocardial Infarction

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Myocarditis

Despite the uncertainty surrounding the pathophysiology of myocardial injury caused by SARS-CoV-2 infection, several cases of fulminant myocarditis have been reported.[5,7] Clinical manifestations appear to be similar to those of myocarditis caused by other viruses and include chest pain, dyspnea, arrhythmia, fever, and ventricular dysfunction. The electrocardiogram (ECG) shows diffuse ST-segment abnormalities and depression or elevation of the PR and ST segments; at times, it can mimic pathologic changes compatible with ST-segment elevation myocardial infarction.[2,3] Troponin is usually elevated, but at lower levels than those observed in acute coronary syndromes. Natriuretic peptides can contribute to the diagnostic confirmation of myocarditis, especially when troponin levels are only slightly increased. Diffuse changes in myocardial wall motion on echocardiography are more common in myocarditis than in acute ischemic syndromes, in which segmental changes are usually observed. Magnetic resonance imaging can be useful for diagnostic confirmation by revealing a typical pattern of inflammatory involvement. A high proportion of patients with elevated troponin and/or ECG changes appear to have persistent inflammatory abnormalities compatible with subclinical myocarditis on cardiac magnetic resonance, even after clinical recovery from COVID-19.[8]

The concomitant occurrence of elevated troponin, ECG changes, and left ventricular dysfunction is associated with a worse prognosis in SARS-CoV-2 myocarditis, although any evidence of myocardial injury should be considered a risk marker for patients with COVID-19, regardless of suspected myocarditis. Similar to the management of COVID-19 and its multiple systemic repercussions, specific therapeutic strategies for SARS-CoV-2 myocarditis are based mainly on systemic support. The use of immunomodulators, such as corticosteroids and interleukin-6 receptor antagonists (e.g. tocilizumab), has been described in case reports and in a recent systematic review.[9,10] Their effects on COVID-19 are still under investigation. Although arrhythmias require some degree of monitoring, no specific antiarrhythmic treatment is currently recommended in the setting of SARS-CoV-2 infection.[11]

Takotsubo Syndrome

The incidence of Takotsubo syndrome had a 5-fold increase during the COVID-19 pandemic, whereas acute coronary syndromes showed a decrease in the number of cases during the same period. A Cleveland Clinic cohort study showed that, during the pandemic, about 8% of the cases that presented as acute coronary syndrome were diagnosed as Takotsubo syndrome,

Table 1 – Spectrum of cardiovascular manifestations associated with COVID-19

Phenotype	Important characteristics
Myocardial injury	Elevated troponin (> 99th percentile)
Acute coronary syndrome	Elevated troponin (> 99th percentile) + symptoms + obstructive coronary artery disease
MINOCA	Elevated troponin (> 99th percentile) + symptoms + no obstructive coronary artery disease
Myocarditis or myopericarditis	Elevated troponin (> 99th percentile) + symptoms + EMB or CMR findings
Takotsubo syndrome	Elevated troponin (> 99th percentile) + symptoms + typical ventriculography
Arrhythmias	Atrial or ventricular tachyarrhythmias; bradyarrhythmias
Heart failure	Acutely decompensated chronic HF triggered by COVID-19 or de novo acute HF caused by one of the following: ACS, MINOCA, myocarditis, or Takotsubo syndrome
Pericardial effusion	Often associated with pericarditis or myopericarditis
Thromboembolism	DVT, PE, stroke, or peripheral emboli

MINOCA: myocardial infarction with nonobstructive coronary arteries; EMB: endomyocardial biopsy; CMR: cardiac magnetic resonance; HF: heart failure; ACS: acute coronary syndrome; DVT: deep vein thrombosis; PE: pulmonary embolism.

different from the 1% incidence reported before the pandemic.[12] Possible pathophysiologic mechanisms associated with this increase include a direct effect of the virus itself, causing myocarditis mimicking Takotsubo syndrome (Takotsubo-like cardiomyopathy), and, more likely, the effects of psychologic stress imposed by quarantine, risk of infection, reduced social interaction caused by social distancing, and socioeconomic consequences of the pandemic. Clinical presentation resembles that of other triggers, and mortality is similar to that reported in the prepandemic period.

COVID-19 in Patients with HF

HF identifies a subgroup of patients with complex management issues and greater morbidity and mortality in the setting of COVID-19. HF represents both a risk factor for worse infectious outcomes and a serious cardiovascular complication of SARS-CoV-2 infection.[13] Activation of the inflammatory cascade, hyperstimulation of the neurohumoral system, and direct viral toxicity are some of the possible pathophysiologic mechanisms for new-onset acute or decompensated HF in this scenario.

Patients hospitalized for HF should be tested for SARS-CoV-2 infection, due to overlapping signs and symptoms, and undergo a thorough assessment of volume status, in addition to laboratory, echocardiographic, and radiographic assessment. COVID-19 can manifest as a systemic inflammatory syndrome, and this feature should be considered when prescribing vasodilators for patients with acute HF. During hospitalization, the use of guideline-recommended medications should be maintained in patients with preserved hemodynamics and blood pressure. Other strategies, such as telemedicine, including telemonitoring and virtual consultations, have been important in the management of chronic HF and in infection prevention. In addition to reducing the risk of exposure to the virus, these strategies have helped to provide preventive counseling regarding COVID-19 and to identify patients at risk of decompensation.[14]

Final Considerations

The spectrum of cardiac involvement in COVID-19, in patients with or without previous HF, is currently an evolving knowledge. Likewise, medium- and long-term consequences of the effects of SARS-CoV-2 infection on the heart may carry important clinical and epidemiological ramifications, but poorly predictable as yet. It is provocative to consider that we may be facing a potential new etiology of cardiomyopathy, which may contribute to an increase in the incidence of HF in the coming years.

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Potential Conflict of Interest

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Emerging Topics in Heart Failure: New Paradigms in Cardiac Amyloidosis

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Abstract

Recent evidence suggests cardiac amyloidosis (CA) is a mostly underdiagnosed condition, particularly in the transthyretin-mediated form, and is a frequent cause of heart failure with preserved ejection fraction (HFpEF) in the elderly. New paradigms about CA also involve the development of disease-modifying specific therapies. This article summarizes these new concepts.

A paradigm shift in amyloidosis epidemiology

Amyloidosis is a multiorgan disease caused by tissue deposition of misfolded insoluble protein fibrils (i.e., that have lost their original conformation), leading to organ dysfunction, including the heart. Although more than 30 types of amyloidogenic proteins have been described,[1] two types account for to 95% of all cases involving the heart: immunoglobulin light chain (AL), which is related to production of monoclonal immunoglobulins due to a plasma-cell dyscrasia and causes light-chain amyloidosis, and transthyretin, a retinol and thyroxin carrier protein produced in the liver. Transthyretin-mediated amyloidosis (ATTR) can be secondary to an abnormal (mutant or variant) protein (ATTRm) or to the wild-type form (ATTRwt), caused by post-transcriptional modification or by chaperone-related mechanisms – both linked to senescence.

AL has an estimated incidence of 6 to 10 cases per million persons per year,[2] and was once considered the main cause of CA. However, with the advancement of non-invasive diagnostic methods and the development of effective treatment options, the diagnosis of ATTR – mainly the ATTRw form – is steadily growing.[3] ATTR is reported in up to 13%[4] of patients with HFpEF and left ventricular wall thickness >12 mm, and in up to 25%[5] of hearts in autopsies of the very elderly. ATTRm has an autosomal dominant inheritance pattern; more than 130 mutations have been reported, and the phenotype expression – cardiac or neurologic – varies according to the mutation.

Keywords

Heart Failure; Restrictive Cardiomyopathy; Amyloidosis; Cardiovascular Imaging; Cardiovascular Disease.

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When to suspect cardiac amyloidosis

Considering that ATTR is more prevalent than previously thought, particularly in the wild-type form, and may masquerade as other common clinical conditions, it is important to adopt a high level of clinical suspicion, including the search for clues that may lead to diagnostic investigation (Table 1).

CA is a restrictive infiltrative cardiomyopathy, and the typical presentation involves ventricular wall thickening, diastolic dysfunction, and conduction abnormalities. In given clinical sets, CA should be differentiated from hypertrophic cardiomyopathy, HFpEF,[6] advanced AV block, and atrial arrhythmias without apparent causes. The simultaneous finding of ATTRwt and calcific aortic stenosis may originate severe left ventricular hypertrophy and may present as paradoxical low-flow and low-gradient aortic stenosis.

Additionally, several systemic manifestations may rouse suspicion of ATTR: bilateral carpal tunnel syndrome, biceps tendon rupture, lumbar canal stenosis, orthostatic hypotension, digestive manifestations, and intolerance to antihypertensive medications.[7] The family history is very important in the hereditary forms of amyloidosis, which carry a worse prognosis as compared to ATTRwt.

Diagnostic methods

Electrocardiography

A low-amplitude QRS complex is a frequent sign in AL, but is quite less prevalent in ATTR (around 30%), which more commonly presents with a discrepancy between the magnitude of left ventricular hypertrophy on the echocardiogram and the QRS voltage. Atrial fibrillation and a "pseudoinfarction" pattern can also be found.

Echocardiogram

Echocardiography is the most important imaging modality to raise suspicion of CA. Suggestive findings include: left ventricular wall thickness > 12 mm, especially in the absence of arterial hypertension; bi-atrial enlargement disproportional to the dimensions of the ventricular cavities; atrioventricular valve leaflet and atrial septal thickening; and increased myocardial echogenicity with a granular aspect.[8] Longitudinal strain rate imaging may show the typical pattern of "apical sparing" as compared to reduced contractility in the remaining segments.[8]

Table 1 – Diagnostic clues to cardiac amyloidosis

Clinical history and physical examination
HFpEF, particularly in elderly men (age > 65 years)
Angiotensin-converting enzyme inhibitor or beta-blocker intolerance
Bilateral carpal tunnel syndrome
Lumbar canal stenosis
Biceps tendon rupture
Unexplained peripheral neuropathy, particularly when associated with autonomic dysfunction
Cardiac imaging
Scintigraphy showing anomalous grade 2-3 increased cardiac uptake of pyrophosphate-Tc99m
Infiltrative phenotype on echocardiogram, with biventricular hypertrophy, pericardial effusion, valve thickening, and interatrial septum thickening
Longitudinal strain rate reduction that spares the apical region ("*apical sparing*" pattern)
Restrictive abnormality of ventricular filling with right ventricular wall thickening
CMR showing late gadolinium enhancement with diffuse subendocardial or transmural pattern, increased ECV
Combined clues
Heart failure with unexplained left ventricular wall thickening and a non-dilated ventricular cavity
Concentric left ventricular hypertrophy with reduced or non-increased QRS amplitude
Reduced left ventricular systolic function despite normal global ejection fraction
Aortic stenosis with right ventricular wall thickening, particularly with a paradoxical low flow-low gradient pattern

Adapted from Maurer et al. Cic Heart Fail 2019;12:3006075.

Cardiac scintigraphy with bone-avid radiotracers

Cardiac scintigraphy with bone-avid radiotracers, such as technetium Tc99m pyrophosphate as used in Brazil, may be employed to distinguish AL from ATTR, with the latter showing anomalous myocardial uptake higher than the uptake observed in the ribs. However, cardiac uptake may occur, albeit with milder intensity, in up to 30% of AL cases. The combination of intense cardiac uptake (grades 2 or 3) and negative biochemical investigation for monoclonal light chains is 100% specific for ATTR, and can obviate endomyocardial biopsy for diagnosis.[3]

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) imaging has high sensitivity and specificity for CA diagnosis, while also allowing identification of other myocardial diseases. Amyloid deposits in the myocardium increase the distribution volume of the paramagnetic contrast agent in myocardial regions where the cardiomyocytes are displaced by the deposits, inflammation, or fibrosis, originating a diffuse subendocardial and circumferential late enhancement pattern; a diffuse transmural pattern can also be found.[8]

Rational diagnostic approach

Figure 1 illustrates a proposed diagnostic algorithm for CA. It highlights that, when CA is suspected (table 1), the first step should consist of a monoclonal light chain assay with a view to AL diagnosis, as specific chemotherapeutic management is available for this form of CA and the prognosis worsens dramatically if treatment onset is delayed. Confirmation of AL relies on detection of the amyloid protein in the involved organ tissue through biopsy, but the ATTR form can be diagnosed non-invasively by cardiac scintigraphy with technetium-Tc99m pyrophosphate as described above.

New therapies for ATTR

Several steps of amyloid fiber formation in ATTR constitute therapeutic targets. The tetramer stabilizer tafamidis was evaluated in a multicenter, randomized, placebo-controlled trial (ATTR-ACT study).[9] Tafamidis was associated with a 30% reduction in all-cause mortality (RR=0.70, 95%CI 0.51–0.96), a 32% reduction in cardiovascular hospitalization (RR=0.68, 95%CI 0.56–0.81) and reduction of the rate of deterioration of functional capacity and quality of life. Based on these results, tafamidis was approved by ANVISA for the treatment of ATTR-CA.

Therapies based on silencing the expression of genes that codify the hepatic production of TTR are very promising, including small interference RNA (patisiran) and antisense oligonucleotides (inotersen). Both strategies have proven effective in reducing the progression of neurologic manifestations in ATTR and are currently under evaluation in multicenter studies for the treatment of ATTR-CA.[10,11]

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Potential Conflict of Interest

Marcus Vinicius Simões – speaker and advisory board: Pfizer and Alnylan.

Fabio Fernandes – speaker: Pfizer, Alnylan and PTC.

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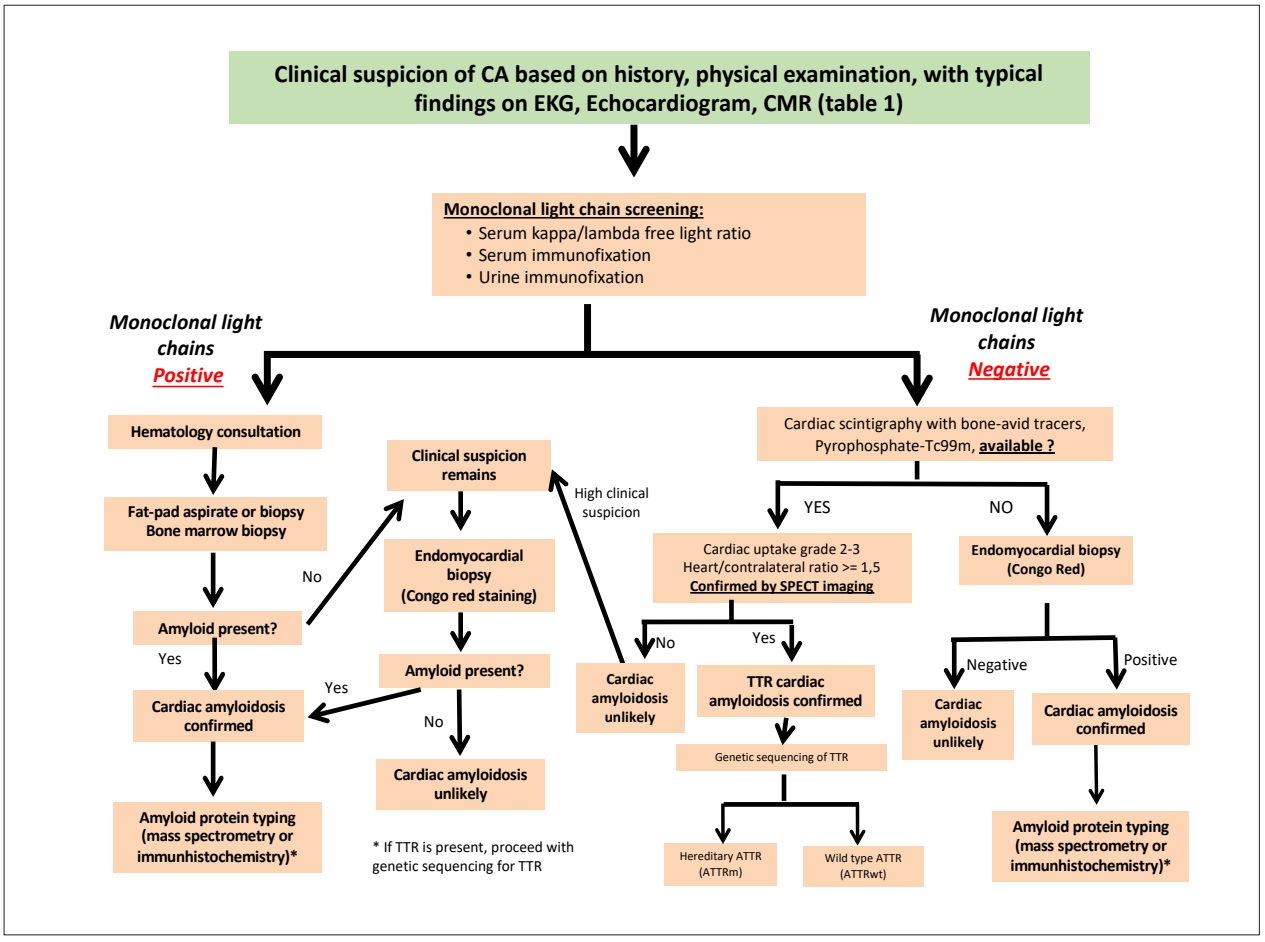

Figure 1 – *Algorithm for CA diagnosis.*

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Emerging Topics in Heart Failure: Heart Failure With Preserved and Mid-Range Ejection Fraction

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Heart Failure with Preserved Ejection Fraction (HFpEF) Diagnosis

Current diagnostic recommendations require evidence of congestion or low cardiac output, considering a combination of clinical information, electrocardiogram, imaging, biomarkers, and, in selected cases, hemodynamic exercise testing.[1]

A pretest clinical approach (step 1) followed by a confirmatory score (step 2) is recommended to confirm or rule out the diagnosis of HFpEF. Hemodynamic exercise testing (step 3) is indicated for patients with an intermediate score[2] (Figure 1).

Pretest Clinical Approach – step 1

Evaluation of dyspnea and fatigue requires a detailed history and physical examination. Electrocardiogram, chest radiography, echocardiogram, natriuretic peptides, and cardiopulmonary testing are suggested to define the clinical pretest probability of HFpEF or rule it out altogether.

Confirmatory Scores – step 2

Two scoring systems, the H2FPEF score and the HFA-PEFF score, have recently been developed to establish the probability of HFpEF diagnosis.

The H2FPEF score was derived from selected clinical and imaging variables independently associated with the invasive diagnosis of HFpEF in a population-based cohort (Table 1).

Keywords

Heart Failure; Preserved Ejection Fraction; Mid-Range Ejection Fraction.

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The HFA PEFF score is composed of morphological and functional echocardiographic measures and serum biomarker criteria. There are minor and major criteria, which add up to 1 or 2 points each, respectively (Table 2).

In this strategy, HFpEF can be ruled out in patients with low scores (0 or 1). Conversely, the diagnosis of HFpEF can be established in patients with high scores (H2FPEF ≥ 6 or HFA PEFF ≥ 5).[3] In patients with intermediate scores (H2FPEF 2 to 5 or HFA PEFF 2 to 4), a hemodynamic exercise test may be necessary[4] (Figure 1).

Hemodynamic Exercise Testing – Step 3

At this stage, the patient undergoes an initially non-invasive diastolic stress test. The selected indexes are E/e', which estimates the LV filling pressure, and the tricuspid valve regurgitation speed (VRT), which estimates the pulmonary artery systolic pressure. Upon reaching the cutoff point, an additional score is added to that obtained in step 2 (2 points if E/e' ≥15; 3 points if E/e' ≥15 and VRT >3.4 m/s). If the final sum is 5 or above, the patient meets diagnostic criteria for HFpEF. In selected cases, an invasive diastolic stress test can also be performed.[4]

Etiology of HFpEF

By labeling all patients with symptoms of HF and LVEF ≥50% as having HFpEF, we are assuming a common pathophysiological denominator among these patients, which is not true. Patients with HFpEF display a complex pathophysiology which includes increased systemic vascular resistance, increased arterial stiffness, abnormal ventricular-arterial coupling, reduced systolic function in the long axis of the LV, decreased ventricular relaxation, reduced LV compliance, abnormal RV contractile function, and chronotropic incompetence.[4]

HFpEF has wide phenotypic heterogeneity, with a combination of risk factors and comorbidities that may affect prognosis and treatment.[5]

The etiology of HFpEF can be divided into a primary form, which shares common metabolic and hemodynamic characteristics and similar therapeutic strategies, and another form that may be called secondary, which

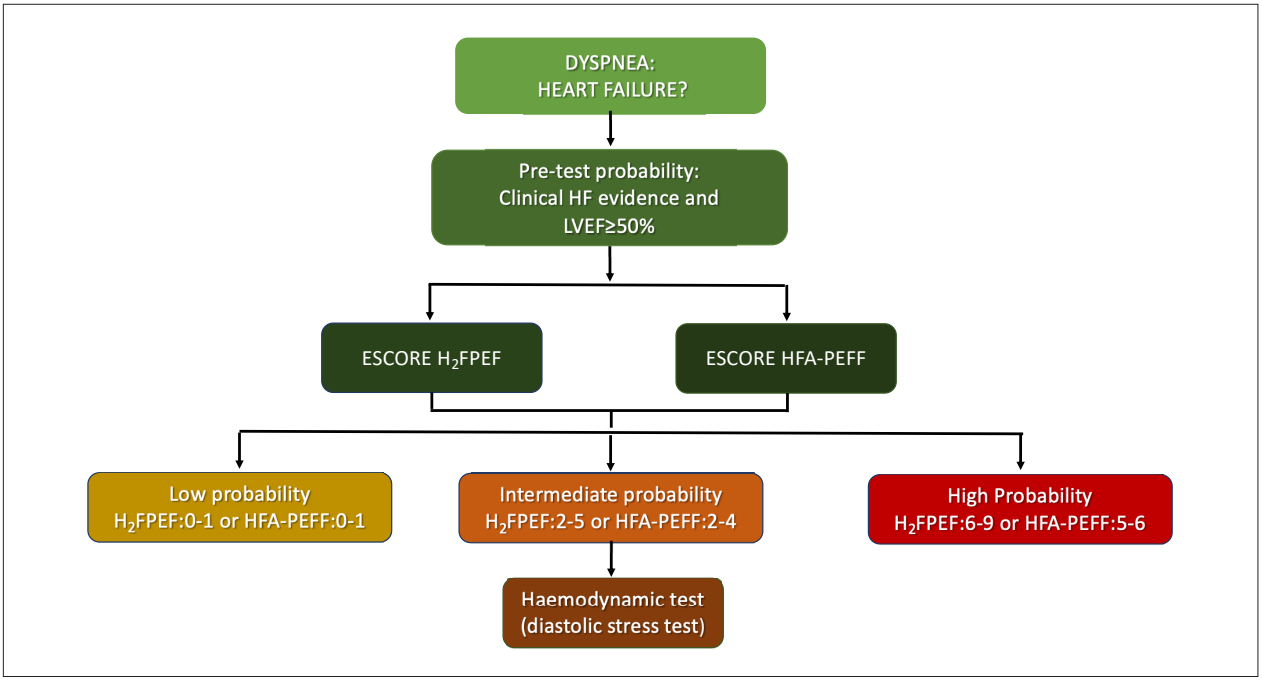

Figure 1 – *Diagnostic algorithm for HFpEF.*

Table 1 – H_2FPEF score.

Score Label	Clinical Variable	Characteristics	Points
H2	Heavy	BMI > 30 Kg/m²	2
	Hypertension	2 or more anti-hypertensive drugs	1
F	Atrial fibrillation	Paroxistic or Persistent	3
P	Pulmonary hypertension	PASP > 35 mmHg (measured on Doppler echo)	1
E	Elderly	Age > 60 years	1
F	Filling pressures	E/e´> 9 (measured on Doppler echo)	1

BMI: body mass index; PASP: pulmonary artery systolic pressure.

is less common and has specific etiologies, such as hereditary, infiltrative, restrictive, inflammatory or genetic cardiomyopathies.[4,6] (Table 3).

Recommendations for the Treatment of HFmrEF

Randomized clinical trials (RCT) in HFpEF evaluated the use of ACEI, ARB, and mineralocorticoid antagonists; none proved superior to placebo in reducing HF-related adverse outcomes.[1,7,8,11,12] Similarly, sacubitril-valsartan was not superior to valsartan alone in reducing the composite outcome of hospitalizations for HF or cardiovascular death.[13-15]

However, post-hoc analysis from these RCTs suggested that therapies currently indicated for the treatment of HF and reduced ejection fraction (LVEF <40%) can be extrapolated to patients with HF and mid-range ejection fraction (HFmrEF, LVEF 40-49%).

In this sense, a TOPCAT sub-analysis suggested a benefit of spironolactone in patients with LVEF from 44 to 50%,[7] and a CHARM sub-analysis revealed a benefit with candesartan in patients with LVEF from 40% to 49%.[8] In a meta-analysis of 11 RCTs, beta-blockers were associated with lower mortality in patients with HFmrEF and sinus rhythm.[9] Recently, a combined analysis of PARAGON-HF and PARADIGM-HF suggested that sacubitril-valsartan was associated with a reduction in the primary outcome at intermediate (mid-range) levels of LVEF, with this effect seen at higher levels of LVEF in women than in men. These data suggest that sacubitril-valsartan may be beneficial for patients with HFmrEF, especially in women.[10]

Perspectives in Treatment of HFpEF

The same sub-analysis of the RCTs above consistently indicated no benefit from these medications in patients with HF and higher LVEF (≥ 50%), which is the actual cutoff point for definition of HFpEF in the guidelines.[8-10,16] It is possible that the lack of benefit results from the heterogeneity of phenotypes, the presence of multiple comorbidities, and the diversity of mechanisms underlying disease progression. In this sense, the treatment of comorbidities such as myocardial ischemia, atrial fibrillation, and hypertension is essential to relieving symptoms and potentially reducing the progression of HFpEF.[16]

RCTs to evaluate the effect of two SGLT2 inhibitors (dapagliflozin and empagliflozin) and two mineralocorticoid antagonists (spironolactone and finerenone) on outcomes in patients with HFpEF are ongoing.[17]

Table 2 – HFA-PEFF score.

DOMAIN	MAJOR CRITERIA (2 points)	MINOR CRITERIA (1 point)
FUNCTIONAL	e´ septal < 7 or e´ lateral < 10 or E/e´≥ 15 or RT velocity > 2,8 m/s (PSAP > 35 mmHg)	E/e´ 9-14 or GLS < 16%
MORPHOLOGIC	LA Vol index > 34 mL/m² or LVMI ≥ 149/122 g/m² (H/M) and RWT > 0,42	LA Vol index 29 - 34 mL/m² ou LVMI > 115/95 g/m² (H/M) or RWT > 0,42 or left ventricle wall thinckness ≥ 12 mm
BIOMARKER (sinusal rythm)	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	NT-proBNP 125 - 220 pg/mL or BNP 35 - 80 pg/mL
BIOMARKER (atrial fibrillations)	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	NT-proBNP 365 - 660 pg/mL or BNP 105 - 240 pg/mL

BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro–B-type natriuretic peptide; LA vol: left atrial volume; LVMI: left ventricular mass index; RWT: relative wall thickness; M: men / W: women; GLS: global longitudinal strain; RT: velocity of tricuspid valve regurgitation flow.

Table 3 – Etiologies of heart failure with preserved ejection fraction

Etiologies	Characteristic	Causes
Primary HFpEF	Female sex, older age Common metabolic and hemodynamic factors	Hypertension, diabetes, obesity
Secondary HFpEF	Specific etiology	
Infiltrative cardiomyopathies	Related or not to malignancy	Metastasis, Fabry disease, Danon disease, Pompe disease
Restrictive cardiomyopathies		Amyloidosis, sarcoidosis, radiation, scleroderma
Inflammatory and autoimmune cardiomyopathies	Related or not to infection	Cardiotropic viruses, autoimmune diseases, lymphocytic myocarditis
Hereditary and Genetic Cardiomyopathies		Hypertrophic cardiomyopathy, Duchenne muscular dystrophy
Ischemic disease		Endothelial and microvascular dysfunction after myocardial infarction
Toxic	Substance abuse; heavy metals; medicines	Alcohol, cocaine, iron, chloroquine, anthracyclines
Others	High-output state; volume overload; heart rhythm disorders	Thyrotoxicosis, arteriovenous fistula, ventricular and atrial arrhythmias, severe anemia, Paget's disease

HFpEF: heart failure with preserved ejection fraction.

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Conception and design of the research: Fernandes-Silva MM, Danzmann LC; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Fernandes-Silva MM, Mourilhe-Rocha R, Brito FS, Jorge AJL, Issa VS, Danzmann LC.

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Emerging Topics in Heart Failure: Interventional Heart Failure Therapies

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Treatment of Secondary Mitral Regurgitation

Before considering percutaneous treatment of mitral regurgitation (MR) for patients with heart failure (HF) with reduced ejection fraction (HFrEF) and severe MR,[1] we recommend that guideline-directed medical therapy be optimized, including cardiac resynchronization therapy and revascularization, where appropriate.

The use of the edge-to-edge device could benefit patients with moderately severe or severe secondary MR (effective regurgitant orifice area [EROA] ≥ 30 mm^2 and/or regurgitant volume > 45 mL) with a left ventricular ejection fraction (LVEF) of 20 to 50%, left ventricular (LV) end-systolic diameter < 7.0 cm, and persistent symptoms despite maximized evidence-based medical therapy, with the participation of an experienced multidisciplinary team in the evaluation and treatment of HF and MR.[2]

The COAPT trial included patients with more severe MR and less advanced LV disease (dilatation/dysfunction) compared to patients of the MITRA-FR trial, creating the concept of disproportionate MR (Table 1).

When to Indicate an Implantable Cardioverter Defibrillator (ICD) in Face of New Medications in HFrEF?

Ischemic Cardiomyopathy

The randomized MADIT II and SCD-HeFT trials,[3,4] conducted more than 15 years ago, validated the indication of ICDs for the primary prevention of sudden cardiac death (SCD) in patients with ischemic cardiomyopathy with an ejection fraction $\leq 35\%$ in New York Heart Association (NYHA) class II or III after optimization of medical therapy, after at least 40 days of the acute phase of myocardial infarction and at least 90 days of any myocardial revascularization procedure, without severe comorbidities and with good 1-year life expectancy. These trials were conducted at a time when pharmacologic treatment was far less than desirable in terms of doses. Currently, medications can promote a substantial reduction in the annual rate of SCD.[5,6]

Nonischemic Cardiomyopathy

Small randomized trials (CAT, AMIOVIRT, and DEFINITE), conducted more than 10 years ago, were unable to demonstrate a reduction in mortality with the use of ICDs for primary prevention of SCD in nonischemic cardiomyopathy.[5] Recently, the DANISH trial,[7] with a robust sample of properly treated patients, also demonstrated that ICDs did not reduce total mortality or cardiovascular death in this population. We should consider greater risk stratification in these patients by incorporating magnetic resonance imaging quantification of fibrosis, which has shown to be associated with cardiovascular death and SCD in patients with nonischemic cardiomyopathy.[8]

Pulmonary-vein Isolation for the Treatment of Atrial Fibrillation (AF) in Patients with HFrEF

AF ablation in patients with HF provides greater benefit than the use of antiarrhythmic medications due to higher sinus rhythm maintenance rate, improved functional capacity and quality of life, improved NYHA class, longer 6-minute-walk distance, improved peak VO_2,[9] reduced biomarker (brain natriuretic peptide [BNP]) levels, increased ejection fraction,[9,10] and reduced HF hospitalization, HF death or hospitalization, and death from any cause.[9–11] However, the success rate ranges from 60 to 80% at 1 year, when structural heart disease is a risk factor for recurrence.[12] Pulmonary-vein isolation can be achieved by radiofrequency or cryoablation, and these techniques can be combined with ablation of other substrates. Benefits include symptom control in patients with paroxysmal/persistent AF and the promotion of reverse remodeling in patients with ventricular dysfunction due to AF-induced tachycardiomyopathy, regardless of symptoms.

New Forms of Cardiac Pacing in HF

Ventricular pacing through the native His-Purkinje conduction system may be an option for patients with pacemaker indication, given the deleterious effects of isolated right ventricular (RV) pacing in patients with HF.[13]

Keywords

Mitral valve insufficiency; Pacemaker, Artificial; Catheter ablation; Defibrillators, Implantable; Tricuspid valve insufficiency

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Table 1 – Comparison of the characteristics and results of the COAPT and MITRA-FR trials

	MITRA-FR	COAPT
Total number of patients	304	**614**
Medical therapy	Adjusted in the trial	**Optimized therapy**
≥ moderate to severe (3+) iMR	EROA > 20 mm2 and/or RV > 30 mL	**EROA > 30 mm2 and/or RV > 45 mL**
LVESD, mm (LV size)	Without limit	**< 70 upon inclusion**
NYHA class > II, %	**67.0**	60.4
Hospital in previous years, %	**100**	57.1
EROA, mm2	31 ± 10	**41 ± 15**
Severe (EROA ≥ 40 mm2), %	16	**41**
iLVEDV, mL/m2	135 ± 35	**101 ± 34**
1-year mortality (IvsC), %	24.2 ± 22.4	**19.1 vs 23.2 (p < 0.001)**
1-year HF hospitalization (IvsC), %	48.7 ± 47.4	**35.8 vs 67.9 (p < 0.001) Primary objective**
Annual mortality/ HF hospitalization (IvsC), %	54.6 vs 51.3 (p = 0.53) Primary objective	**33.9 vs 46.5 (p < 0.001)**

iMR: ischemic mitral regurgitation; EROA: effective regurgitant orifice area; RV: regurgitant volume; LVESD: left ventricular end-systolic diameter; NYHA: New York Heart Association; iLVEDV: indexed left ventricular end-diastolic volume; IvsC: Invasive vs Control; HF: heart failure.

Small trials suggest that His bundle pacing may result in a decrease in the incidence of cardiomyopathy, reduction in the combined endpoint of hospitalization or death, and improvement in LV dimensions and HF symptoms compared to isolated RV pacing.[13,14] The American guideline for the management of bradycardia recommends His bundle pacing or cardiac resynchronization therapy for patients with ventricular dysfunction who have atrioventricular block with an indication for permanent pacemaker instead of isolated RV pacing.[15] Compared to cardiac resynchronization therapy, His bundle pacing had an equivalent effect, with a significant reduction in QRS duration and improvement in LVEF, HF symptoms, and quality of life.[16,17] His bundle pacing was also tested in patients with HFrEF and right bundle branch block, leading to increased LVEF and narrowing of QRS duration.[18]

Percutaneous Treatment of Tricuspid Regurgitation in HF

The advent of percutaneous treatment of functional tricuspid regurgitation is attractive in selected patients at high surgical risk, for an expected improvement of symptoms. Patients who may benefit from this treatment include those with HF refractory to optimized medical therapy or with early signs of RV dysfunction, who are considered at high risk for conventional cardiac surgery or inoperable. Devices are divided into annuloplasty systems, tricuspid valve repair systems, and prosthetic valves for vena cava stenting. Although safety and efficacy clinical trials appear to be promising, the available evidence is based on single-center observational studies or registries. Therefore, more robust evidence is needed before we can confidently indicate any treatment.[19]

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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: Rossi Neto JM, Almeida DR, Atik FA, Avila MS, Bonatto MG.

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Emerging Topics in Heart Failure: New Era of Pharmacological Treatment

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Research letter related to Heart Failure Summit Brazil 2020 / Heart Failure Department - Brazilian Society of Cardiology

Introduction

In recent decades, advances in pharmacological treatment and implantable devices have impacted the prognosis of heart failure (HF) with reduced ejection fraction (HFrEF). However, there remains high residual risk to be addressed. New therapies with different pathophysiologic targets can enhance the action of medications on the neurohormonal system and remodeling, and these benefits occur in addition to those of standard medical therapy. Table 1 depicts the main results of randomized clinical trials on HF treatment.

Standard Medical Therapy

Renin-angiotensin-aldosterone System (ACEIs/ARBs/MRAs)

The fundamental importance of the renin-angiotensin-aldosterone system (RAAS) has been underscored in randomized controlled trials reporting attenuation of angiotensin II (AngII) action with the use of angiotensin-converting enzyme inhibitors (ACEIs) or AngII receptor blockers (ARBs), with the latter being indicated in patients who do not tolerate ACEIs. Mineralocorticoid receptor antagonists (MRAs) also play a key role in RAAS modulation in both more symptomatic (New York Heart Association [NYHA] class III-IV) and less symptomatic (NYHA class II) patients.

Neprilysin Inhibition Combined with AngII Receptor Blockade

More recently, a new drug class, the dual-acting AngII receptor-neprilysin inhibitor (ARNI), whose commercially available molecule is sacubitril/valsartan, combined the attenuation of AngII harmful action with the protective effect of natriuretic peptides and proved to be superior to ACEIs in reducing both mortality and hospitalization for HF (HHF). It was initially indicated to replace ACEIs/ARBs only in outpatients who remained symptomatic (NYHA class II-III). However, new data support the possibility of starting treatment with sacubitril/valsartan, instead of ACEIs/ARBs, in patients with new-onset HF as well as in hospitalized patients.

Sympathetic Nervous System Blockade

Despite recent therapeutic advances, beta-blockers (carvedilol, metoprolol CR/XL, and bisoprolol) remain essential in the treatment of HFrEF, as they are associated with a reduction in symptoms, death (all-cause mortality, sudden cardiac death, or death due to worsening HF), and hospitalization in symptomatic patients and in those with asymptomatic ventricular dysfunction.[8-10] Beta-blockers, combined with RAAS inhibitors, should be initiated in all patients at reduced doses and then uptitrated to the doses used in clinical trials.

Additional Medical Therapies

Hydralazine-isosorbide Dinitrate

Combined isosorbide dinitrate-hydralazine therapy showed a reduction in all-cause mortality and HHF in patients self-identified as black who had HF. This combination may also be used in patients with worsening renal failure or hyperkalemia with ACEI/ARB/ARNI use.

Ivabradine

A high resting heart rate (HR) is a risk factor for patients with HFrEF and a potential therapeutic target. Ivabradine is a selective sinus-node I*f*-channel inhibitor whose action results in HR lowering. In patients with HF, ivabradine reduced the combined endpoint of cardiovascular death or HHF in patients in sinus rhythm with HR > 70 bpm and left ventricular ejection fraction (LVEF) < 35%. The main benefit was reduced HHF.

Keywords

Heart Failure; Pharmacological Treatment; Heart Failure with Reduced Ejection Fraction.

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Table 1 – Summary of the main results of randomized clinical trials on heart failure treatment

Clinical trials		Population	Primary outcome	NNT‡
β-blockers				
CIBIS II[9]	Bisoprolol* 10 mg once daily	2647 patients NYHA III-IV LVEF ≤ 35% Follow-up: 16 mo	All-cause mortality RRR=34%	18
MERIT HF[8]	Metoprolol succinate* 200 mg once daily	3991 patients NYHA II-IV LVEF ≤ 40% Follow-up: 12 mo	All-cause mortality RRR=34%	27
COPERNICUS[10]	Carvedilol* 25 mg twice daily	2289 patients NYHA IV LVEF < 25% Follow-up: 11 mo	All-cause mortality RRR=35%	15
ACEIs/ARBs				
SOLVD[2]	Enalapril* 10 mg twice daily	2569 patients NYHA II-IV LVEF ≤ 35% Follow-up: 37 mo	All-cause mortality RRR=16%	22
CHARM[3]	Candesartan* 32 mg once daily	2028 patients NYHA II-IV LVEF < 40% Follow-up: 37 mo	Cardiovascular mortality or HHF RRR=27%	14
MRAs				
RALES[4]	Spironolactone* 25-50 mg once daily	1663 patients NYHA III-IV LVEF ≤ 35% Follow-up: 24 mo	All-cause mortality RRR=30%	10
EMPHASIS[5]	Eplerenone* 25-50 mg once daily	2737 patients NYHA CF II LVEF ≤ 35% Follow-up: 21 mo	Cardiovascular mortality or HHF RRR=37%	13
ARNIs				
PARADIGM-HF[6]	Sacubitril-valsartan† 200 mg twice daily	8442 patients NYHA II-IV LVEF < 40% / LVEF ≤ 35% Follow-up: 27 mo	Cardiovascular mortality or HHF RRR=20%	21
Vasodilators				
A-HEFT[11]	Hydralazine 225 mg once daily + Isosorbide dinitrate* 120 mg once daily	1050 black patients NYHA III-IV LVEF ≤ 35% or LVEF < 45% if LVDD > 6.5 cm Follow-up: 18 mo	All-cause mortality, first HHF, and quality of life All-cause mortality RRR=43%	25
If inhibitor				
SHIFT[12]	Ivabradine* 5-7.5 mg twice daily	6558 patients NYHA II-IV LVEF ≤ 35% Sinus rhythm / HR >70 Follow-up: 23 mo	Cardiovascular mortality or HHF RRR=18%	26
Digitalis				
DIG[13]	Digoxin* 0.25 mg once daily	6800 patients NYHA II-III LVEF < 45% Follow-up: 37 mo	All-cause mortality No reduction	NA
SGLT2 inhibitors				
DAPA-HF[14]	Dapagliflozin* 10 mg once daily	4744 patients NYHA II-IV LVEF < 40% Follow-up: 18 mo	Cardiovascular mortality or HHF RRR=26%	21
EMPEROR-Reduced[15]	Empagliflozin* 10 mg once daily	3730 patients NYHA II-IV LVEF < 40% Follow-up: 16 mo	Cardiovascular mortality or HHF RRR=25%	19
GC stimulators				
VICTORIA[16]	Vericiguat* 10 mg once daily	5050 patients NYHA II-IV LVEF < 45% Follow-up: 11 mo	Cardiovascular mortality or first HHF RRR=10%	24

**Versus Placebo. †Versus Enalapril. ‡NNT: defined for the primary endpoint/all-cause mortality during follow-up. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; HHF: hospitalization for heart failure; ARNI: angiotensin II receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; NNT: number needed to treat; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitor; HR: heart rate; GC: guanylate cyclase; RRR: relative risk reduction; LVDD: left ventricular end-diastolic diameter.*

Digoxin

In the 1990s, digoxin was evaluated in patients with HFrEF and showed no association with reduced mortality compared to placebo, but there was a significant reduction in HHF. The role of digoxin in contemporaneous HF treatment remains unknown. Its use at low doses appears to be safe and effective in improving symptoms if treatment is guided by plasma levels and glomerular filtration rate (GFR).

Innovations in Pharmacological Treatment

Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors

The benefits of SGLT2 inhibitors in reducing major adverse cardiovascular events and HHF in patients with type 2 diabetes (T2D) were initially observed with the use of empagliflozin. Subsequently, different SGLT2 inhibitors also showed a reduction in HHF in patients with diabetes. In view of these findings, SGLT2 inhibitors were evaluated in patients with HF.

In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, 4744 patients with HFrEF were randomized to receive dapagliflozin or placebo in addition to standard therapy; of these, 41.8% had T2D. The primary outcome (a composite of cardiovascular death or worsening HF) was significantly lower in the dapagliflozin group (26% reduction). There was a significant reduction in both cardiovascular death (18% reduction) and worsening HF (30% reduction) when analyzed separately, regardless of the presence or absence of T2D. These results reveal a new therapy for HF, already approved for this purpose.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) evaluated empagliflozin vs placebo, in addition to standard therapy, in 3730 patients with HFrEF; 50.2% with T2D. Patients appeared to have more severe disease than those in the DAPA-HF trial, with a median LVEF of 27% against 31%. Also, more than 70% of patients had LVEF < 30% in the EMPEROR-Reduced trial and a higher median level of N-terminal prohormome of brain natriuretic peptide (NT-proBNP) (1907 vs 1437 pg/mL). There was a 25% reduction in the primary outcome (a composite of cardiovascular death or HHF) in favor of empagliflozin. Like in the DAPA-HF trial, the benefit was seen regardless of the presence or absence of T2D. However, different from the DAPA-HF trial, no reduction was observed in cardiovascular death when analyzed separately.

Soluble Guanylate Cyclase (sGC) Stimulators

Veriguat, a novel sGC stimulator, enhances the cyclic guanosine monophosphate (cGMP) pathway by directly stimulating sGC through a binding site, independent of nitric oxide (NO), and sensitizes sGC to endogenous NO. It acts by enhancing the relative insufficient production of cGMP, common in HF.

The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) randomly assigned 5050 patients with HFrEF, LVEF < 45%, and NYHA class II-IV to receive vericiguat or matching placebo, in addition to standard therapy. The primary outcome (a composite of cardiovascular death or first HHF) was significantly less frequent in the vericiguat group (35.5%) than in the placebo group (38.5%), and the number needed to treat was 24 for 1 year. The main benefit within the composite endpoint was a reduction in HF hospitalization, with no statistically significant difference in cardiovascular or all-cause mortality.

This medication has the potential to be included in the group of HF medications with an effect on symptoms and rehospitalizations, especially in patients with frequent hospitalizations despite optimal medical therapy, patients with renal failure (the VICTORIA trial included patients with an estimated GFR >15%), and those intolerant to other medications. Concomitant use with nitrates is contraindicated.

Final Considerations

New therapeutic options have been developed, with a great impact on HF prognosis (Figure 1). In this new era of HF treatment, once standard medical therapy is initiated, new medications that reduce mortality and HHF may be started.

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Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Marcondes-Braga FG, Ramires FJA, Figueiredo EL, Figueiredo Neto JA, Beck-da-Silva L, Rassi S.

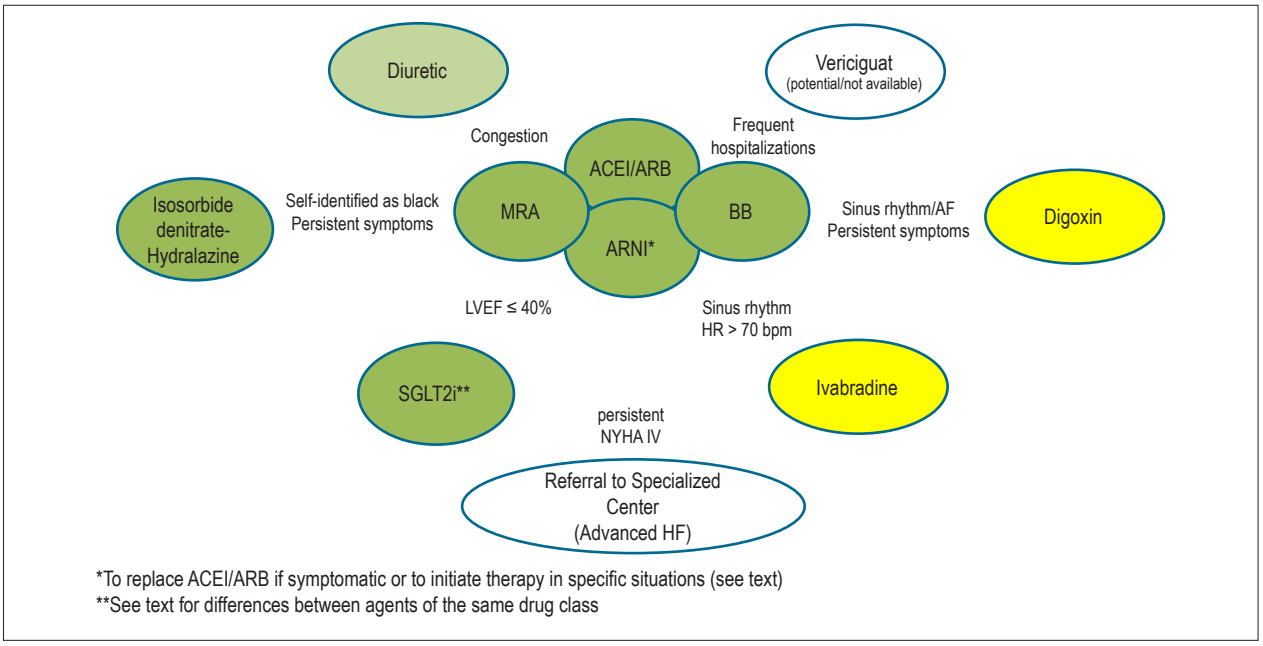

Figure 1 – *Pharmacological management of patients with heart failure with reduced ejection fraction (HFrEF). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin II receptor-neprilysin inhibitor; BB: beta-blocker; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitor; HR: heart rate.*

Potential Conflict of Interest

Fabiana G. Marcondes-Braga - Is the recipient of fees for lectures and / or consulting Jobs for Novartis, AstraZeneca laboratories. I participated as a sub-researcher in clinical research by Novartis and Amgen.

Felix J. A. Ramires - Is the recipient of fees for lectures, consulting jobs and / or clinical research for Novartis, AstraZeneca, Amgen, Pfizer laboratories.

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Salvador Rassi - Is the recipient of fees laboratories Novartis, AstraZeneca, Servier, Boehringer, Amgen for lectures, consulting jobs and clinical research.

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Oscillating Ductal Stent in Valvar Pulmonary Atresia

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A 2.7 kg term neonate was diagnosed on day 3 of life with Ebstein's anomaly of the tricuspid valve, severe tricuspid regurgitation, valvar pulmonary atresia and duct-dependent pulmonary circulation. The cardiothoracic ratio was 90%, and GOSE score was 1.48. Oxygen saturation was 65% and improved to 88% on 0.005 mcg/kg/min of prostaglandin. The right ventricular systolic pressure was 40mmHg against a systolic blood pressure of 65mmHg. The child was taken up for stenting of the arterial duct on day 7 of life after the confirmation of anatomic pulmonary atresia. The long arterial duct was stented with 3.5x16mm and 3.5x8mm stents, using a 4F right femoral artery access. Both the pulmonary and aortic ends were well covered and systemic saturation improved to 85% on room air and off prostaglandin.

The post-procedure echocardiography confirmed a well-positioned stent with good flow. However, the stent appeared to oscillate with every cardiac cycle (figure 1, video 1). This "oscillating stent sign" was confirmed on the post-stenting aortic angiogram (video 2). Valvar pulmonary atresia is associated with the well-described "seagull sign" on angiogram. Pooling of contrast in the main pulmonary artery that retains a fibrous attachment to pulmonary annular tissue leads to the seagull sign, with the branch pulmonary arteries assuming the shape of the wings of the 'seagull'. Valvar pulmonary atresia is generally associated with a straight arterial duct inserted into the main pulmonary artery in half of the cases.[1] Even when the duct is long and tortuous in the others, studies suggest that it is more readily negotiated during ductal stenting in valvar pulmonary atresia as opposed to long segment pulmonary atresia.[2,3] The oscillation of the ductal stent in valvar pulmonary atresia with every cardiac cycle suggests that the pulmonary end of the stent is within the main pulmonary artery, which is an intrapericardial structure and faithfully reflects the mechanical contractions of the heart.[4] We suggest that this echocardiographic finding may be utilized for the assessment of stent position with respect to the pulmonary end in valvar pulmonary atresia.

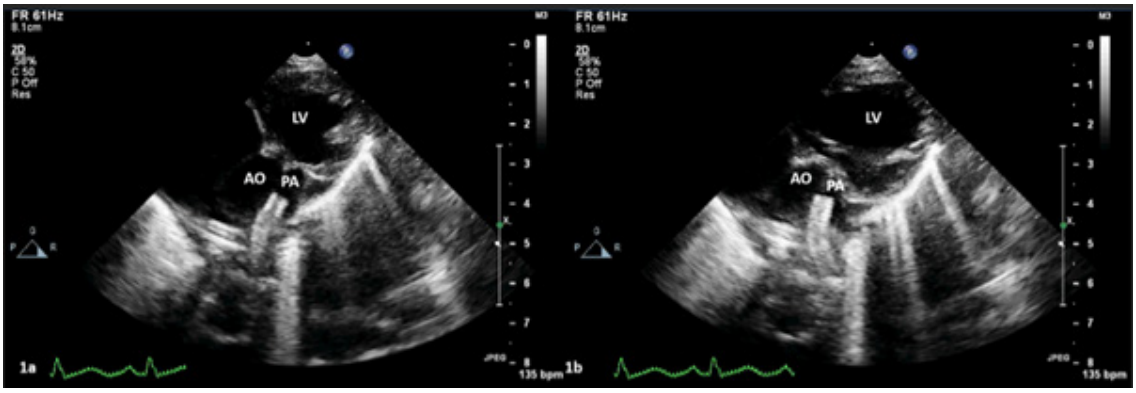

Figure 1 – *Transthoracic echocardiographic still images of the patient in modified parasternal short axis projection in systole (panel 1a) and diastole (panel 1b) shows marked difference in the long axis of the stent in the arterial duct.*

Keywords

Heart Defects, Congenital; Pulmonary Atresia; Ebstein Anomaly; Ductus Arteriosus, Patent; Echocardiography/methods.

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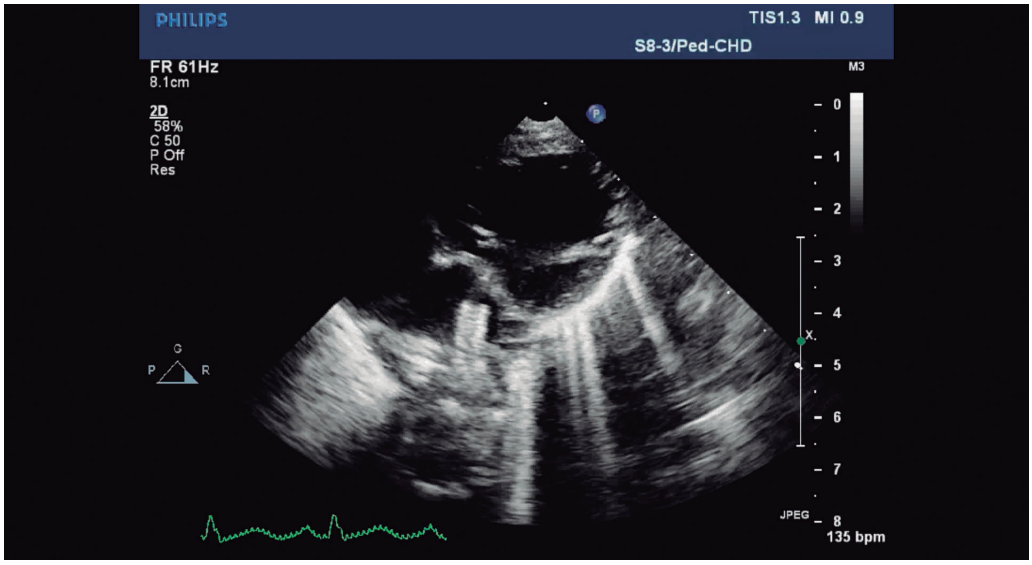
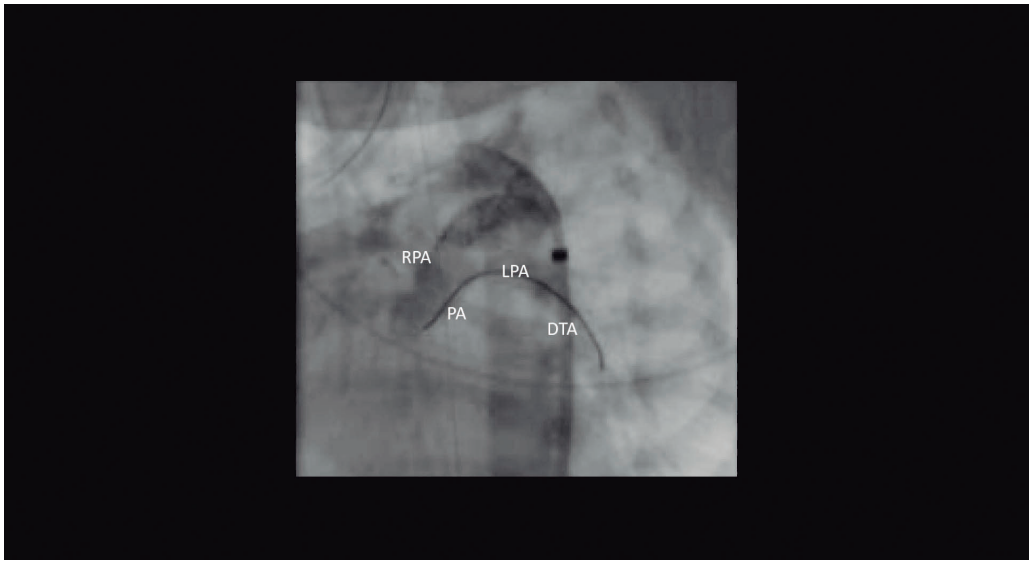
The potential risk of cyclic stent movement was assessed, and the baby was kept on close follow up. He is doing well at 5 months' follow up with good stent flow, good sized pulmonary arteries and the oscillatory movements of the stent persist.

Author contributions

Conception and design of the research: Gopalakrishnan A; Acquisition of data: Gopalakrishnan A, Kumar OS; Analysis and interpretation of the data: Gopalakrishnan A, Krishnamoorthy KM, Kumar PS, Sivasubramonian S; Writing of



Video 1 – *Transthoracic echocardiography in the modified parasternal short axis projection shows the oscillating stent in the arterial duct. The aortic end of the stent is fixed, while the vigorous movement of the main pulmonary artery segment in valvar pulmonary atresia is responsible for the oscillation.*
link: http://abccardiol.org/supplementary-material/2020/11505/2019-0829-video-1.mp4



Vídeo 2 – *Transthoracic echocardiography in the modified parasternal short axis projection shows the oscillating stent in the arterial duct. The aortic end of the stent is fixed, while the vigorous movement of the main pulmonary artery segment in valvar pulmonary atresia is responsible for the oscillation.*
link: http://abccardiol.org/supplementary-material/2020/11505/2019-0829-video-2.mp4

the manuscript: Gopalakrishnan A, Kumar PS, Sivasubramonian S; Critical revision of the manuscript for intellectual content: Gopalakrishnan A, Krishnamoorthy KM, Sivasubramonian S.

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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Non-Progressive Hepatic Form of Andersen Disease as a Mimic of Hypertrophic Cardiomyopathy

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An 18-year-old male patient presented to our ambulatory services due to a 3-month course of progressive dyspnea and non-productive cough. Symptoms were present even at rest, and he exhibited severe limitation at physical activity. He had a diagnosis of glycogen storage disease (GSD) type IV attained by liver biopsy since three years of age, when he developed hepatomegaly and mild hepatic dysfunction. At the time, histopathological examination showed grade 2 fibrosis along with numerous intracytoplasmic PAS-positive deposits that were resistant to diastase. Thenceforth, his liver function remained stable, and he persisted otherwise asymptomatic. His physical examination was unremarkable, and routine laboratory evaluation was within the normal ranges. However, his basal ECG (Figure 1) showed signs of left ventricular hypertrophy. He was submitted to a cardiovascular magnetic resonance (CMR), which showed asymmetrical hypertrophy with predominance in the interventricular septum (Figure 2). Late gadolinium enhancement (LGE) was present in a patchy, multifocal pattern (Figure 3). Medical therapy for heart failure was initiated; the patient is now asymptomatic and maintains regular follow-up in our ambulatory.

Patients with classic GSD type IV have unrelenting liver disease with fast progression to cirrhosis during childhood;[1] however, a small subset of affected individuals may present with milder hepatic dysfunction that does not advance to end-stage liver disease.[1,2] Accordingly, our patient had the diagnosis of GSD type IV by three years of age, but did not develop cirrhosis afterwards.

Although some glycogen storage diseases are known to mimic hypertrophic cardiomyopathy (e.g., Danon disease, PRKAG2 syndrome),[3] this pattern of heart involvement had been reported only twice[2,4] in cases of type IV GSD. Both patients coursed with asymptomatic myocardial hypertrophy revealed by echocardiogram. However, the CMR had not been performed to better characterize the cardiac involvement.

Our patient's findings are consistent with the classical description of hypertrophic cardiomyopathy.[3,4] Most phenotypes of the disease are characterized by asymmetrical heart involvement, and the interventricular septum is commonly affected. Nevertheless, some patients may present with hypertrophy predominance in other areas of the heart, or even with a symmetrical pattern. LGE is found in more than 50% of cases of hypertrophic cardiomyopathy and typically displays a mid-wall speckled pattern;[3,5] by contrast, other types of non-ischemic cardiomyopathies commonly lack LGE until the late stages of the disease.[3]

Storage diseases reported to mimic hypertrophic cardiomyopathy often present with massive left ventricular hypertrophy. Whereas concentric hypertrophy is the most common presentation of Fabry disease and Danon disease, our case coursed with predominant septal involvement. This pattern is usually caused by Pompe disease and PRKAG2 syndrome, sometimes with outflow tract obstruction.[3,5] In such cases, mid-ventricular LGE is an early finding, which may be restricted to the inferolateral walls; as the disease progresses, a diffuse pattern is more likely to be found.[3]

Author Contributions

Conception and design of the research: Oliveira WS; Acquisition of data: Oliveira WS, Porto AA, Mendonça RM, Oliveira Neto NR; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Oliveira WS, Mendonça RM, Oliveira Neto NR; Writing of the manuscript: Oliveira WS.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Study Association

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

Keywords

Glycogen Storage Disease Type IV; Fibrosis; Cardiomyopathy,Hypertrophic; Heart Failure; PRKAG2 Syndrome; Magnetic Resonance Spectroscopy/methods; Prognosis.

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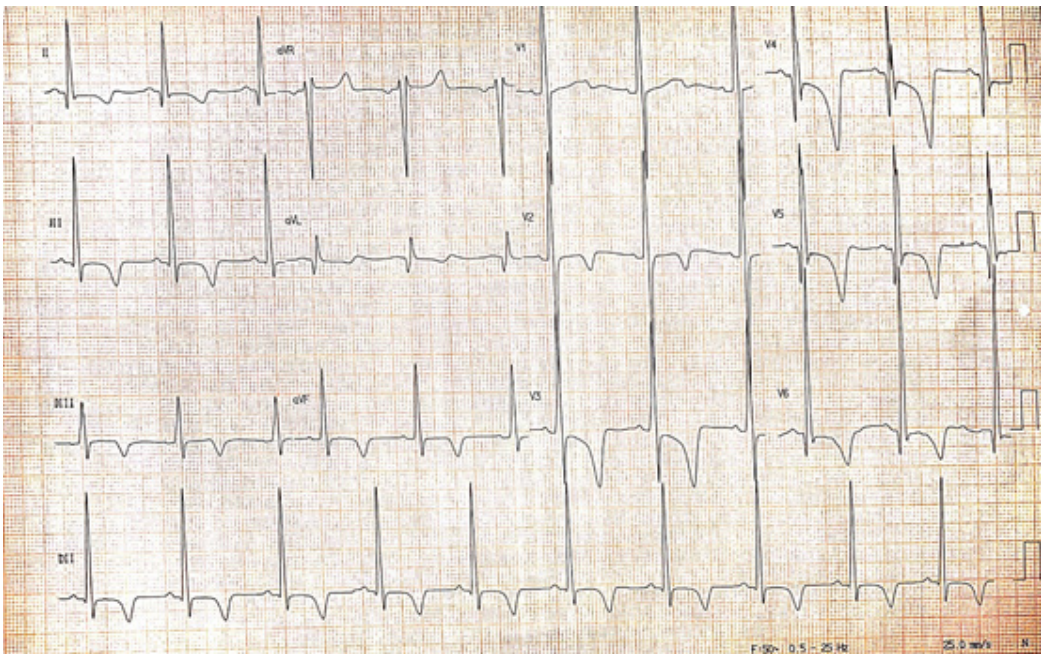

Figure 1 – *The baseline ECG shows sinus rhythm with a heart rate of 62 bpm. There are sings of left ventricular hypertrophy with deep asymmetrical T wave inversion. Also, there are narrow Q waves in leads V 4–V 6, I, and aVL, along with counterclockwise rotation; such findings are likely caused by a prominent septal depolarization vector.*

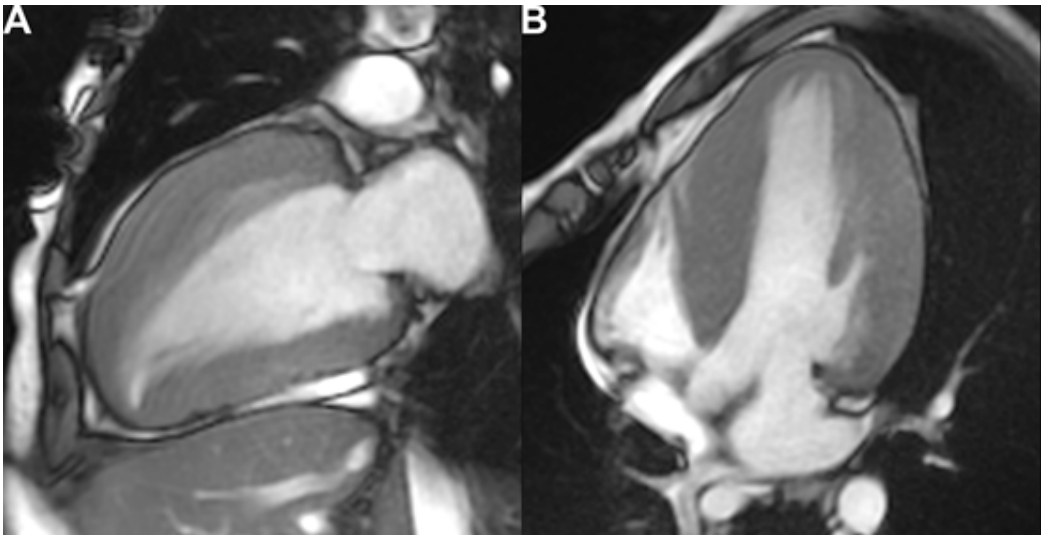

Figure 2 – *Cine-B-TFE sequences of cardiovascular magnetic resonance imaging. The basal septum is the area with most accentuated hypertrophy, yet there is diffuse involvement of the left ventricle. (A) Horizontal long axis view. (B) Vertical long axis view.*

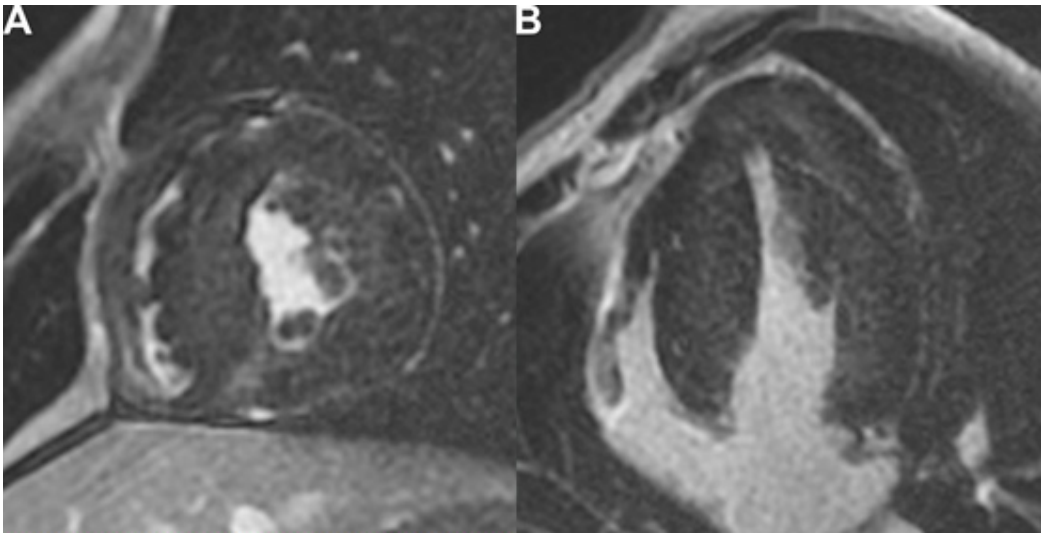

Figure 3 – *Cardiovascular magnetic resonance in late gadolinium enhancement (LGE) sequences. There is a patchy, mid-wall LGE in a noncoronary distribution, mainly in areas with more pronounced hypertrophy. (A) Short axis view. (B) Four-chamber view.*

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Cardiodepressive Effect of Eugenyl Acetate in Rodent Heart

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Introduction

Cardiovascular diseases are a public health problem being among the leading causes of death worldwide.[1] In this perspective, there is a growing interest in the search for new substances with pharmacological actions on the cardiovascular system, including drugs of natural origin.

The *Syzygium aromaticum* (L.) Merr. & L.M.Perry, popularly known as clove, produces several chemical compounds that have a wide range of biological effects. Eugenol (Figure 1A) is the most abundant bioactive compound found in clove essential oil, followed by eugenyl acetate (EA) (Figure 1B).[2]

Studies have shown that eugenol has cardiodepressor activity in rats[3] and guinea pigs[4] probably due to the inhibition of the L-type Ca^{2+} current ($I_{Ca,L}$). In addition, eugenol acts as cardioprotector.[5]

Although several studies have adressed the pharmacological properties of eugenol on mammalian heart, so far there is no information on the action of EA on the cardiomyocytes. Thus, this study describes the effects of EA on atrial contractility and its inhibitory action on $I_{Ca,L}$.

Methods

Animals

For contractility experiments guinea pigs (*Cavia porcellus*, both sexes, 400-600g) were used. For electrophysiological studies, adult male C57Bl/6J mice were used. All procedures were approved by the Ethics Committee for the Use of Animals (CEUA) of the University of the State of Bahia (license: 03/2017).

Experimental Protocols

Evaluation of EA Inotropic Effect

The left atrium from guinea pig was maintained in a modified Tyrode's solution (10 mL, 36.5±0.5°C) with the following composition (in mM): 140 NaCl; 5.4 KCl; 0.5 $MgCl_2$; 0.33 NaH_2PO_4; Glucose; 5 HEPES and 1.8 $CaCl_2$ (pH=7.4), aerated with oxygen (99.9%). The atrium was stretched to attain a resting tension of 1gF and it was electrically stimulated (2Hz, 100V, 15ms). The contractile force was captured by an isometric transducer. Signals were digitized (512Hz) and stored on a computer. The left atria were subjected to increasing concentrations of EA (1-5,000μM, 3 to 5 minutes for each tested concentration).

Dimethyl sulfoxide (DMSO) was used to make the stock solution of EA (obtained from Sigma-Aldrich).

Investigation of EA Effect on the L-type Calcium Current.

Ventricular cardiomyocytes from C57Bl/6J mice were isolated as previously described.[6] The composition of the internal solution (in mM) was: 120 CsCl, 10 HEPES, 5 EGTA, 20 TEA-Cl, and 5 NaCl (pH=7.2; CsOH). Modified Tyrode was used as external solution. To measure L-type Ca^{2+} current ($I_{Ca,L}$) patch-clamp technique in whole-cell voltage-clamp mode was used.[7,8] Cells were maintained at a resting membrane potential of -80mV, then the sarcolemma was subjected to a pre-pulse to -40mV (50ms) followed by a pulse to 0 mV (300ms, 0.1Hz). The $I_{Ca,L}$ amplitude was measured by the difference between the current at the end of the test pulse (0mV) and the peak current. The cells were exposed to EA (10-3,000 μM, 2-3 minutes for each concentration). The signals were digitized (5kHz) and stored on the computer.

Statistical Analysis

The results are expressed as mean ± standard error of the mean and were statistically analyzed using the two-tailed "t" test (significance level: $p<0.05$).

Results

EA Effect on the Left Atrial Contractility

Representative traces in Figure 1C show that EA (700 μM) reduced the amplitude of atrial contraction by approximately 60% when compared to the control. This effect was partially reversed (approximately 75%) after removing the drug (washout). In Figure 1D, it is possible to observe the EA concentration-effect curve on contractility (n = 4). EA presented an IC_{50} (concentration that induces half of the maximum effect) of 558±24.06μM and a maximum effect = 100%.

EA Action on $I_{Ca,L}$

Figure 2A depicts a representative trace of the $I_{Ca,L}$ measured in healthy isolated cardiomyocytes. Figure 2B shows the time

Keywords

Acectato Eugenil; Myocardial Contraction; Syzygium Aromaticum, Rats.

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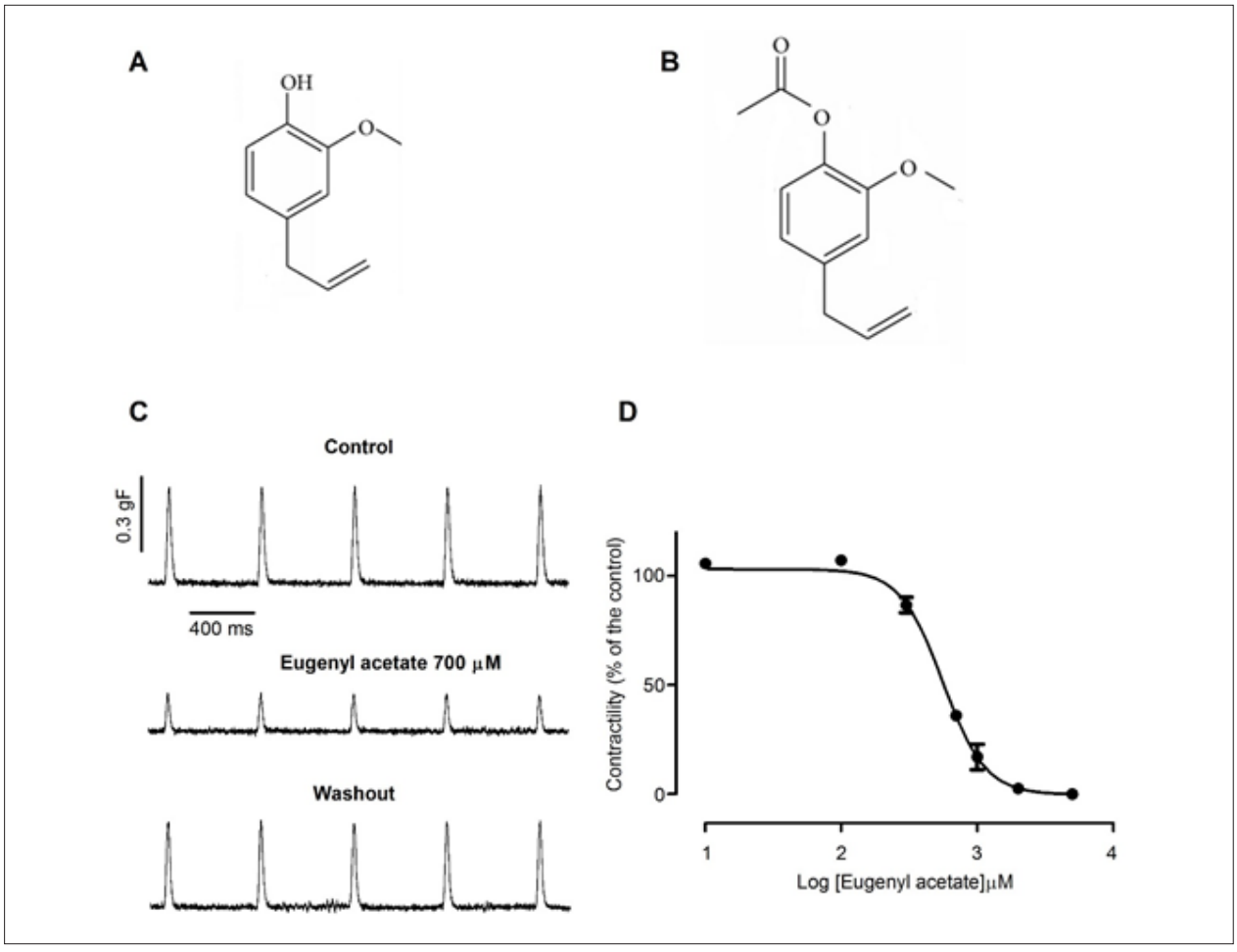

Figure 1 – *Effect of EA on left atrial contractility. A) Structure of eugenol. B) Structure of Eugenyl acetate (EA). C) Representative traces of left atrial contractility in the control situation (upper trace), in the presence of EA 700 μM (middle trace), and 10 minutes after the washout (lower trace). D) Concentration-negative inotropic effect curve of the EA (n = 4).*

course of the EA effect on the $I_{Ca,L}$. In Figure 2C, it is possible to see representative traces of $I_{Ca,L}$ in the control (absence of the drug), and in the presence of 10, 700, and 3,000 μM of EA. Figure 2D demonstrates that exposure to EA reduced the amplitude of $I_{Ca,L}$ in a concentration-dependent manner (IC_{50}=1,337±221μM).

Discussion

In our study we show that EA reduces the contraction force of guinea pig left atrial myocardium in a concentration-dependent manner. It was also observed that EA inhibits L-type Ca^{2+} channels ($Ca_V1.2$) in isolated cardiomyocytes from mice.

The EA showed a cardiodepressor effect on atrial inotropism. Although there are no data in the literature that demonstrate the negative inotropic effect of AE, information from its analogues, such as eugenol, is found. Similarly to the drug investigated here, Eugenol reduced the contraction force of ventricular cardiomyocyte from guinea pig[5] and rat,[4] corroborating the data in our present study.

The cardiomyocyte contraction correlates with the increase in cytosolic Ca^{2+} concentration which is determined by the Ca^{2+} influx through Ca^{2+} channels present in the sarcolemma, as well by the amount of Ca^{2+} released by the sarcoplasmic reticulum (SR) in the process called excitation-contraction coupling. The membrane depolarization leads to the opening of the L-type Ca^{2+} channels mainly during the plateau phase of action potential leading to an inward Ca^{2+} current. This Ca^{2+} entry stimulates the release of Ca^{2+} stored in SR, a process known as Ca^{2+}-induced Ca^{2+} release, which contributes to cardiac contractility.[7] Thus, the mechanisms that alter the intracellular Ca^{2+} handling are involved in the control of cardiac contractility.

In order to explain the negative inotropic effect of EA on the cardiac muscle, the drug effect on the $I_{Ca,L}$ amplitude was investigated in isolated cardiomyocytes. The findings described here show that EA reduces the peak of $I_{Ca,L}$. This effect may be associated with the activation of receptors that modulate $I_{Ca,L}$, and/or direct action of EA on $Ca_V1.2$. The reduction of $I_{Ca,L}$ is able to explain the decrease of contractility induced by EA, since it would lead to a reduction in the release of Ca^{2+} from SR. Although additional mechanism may also be involved.

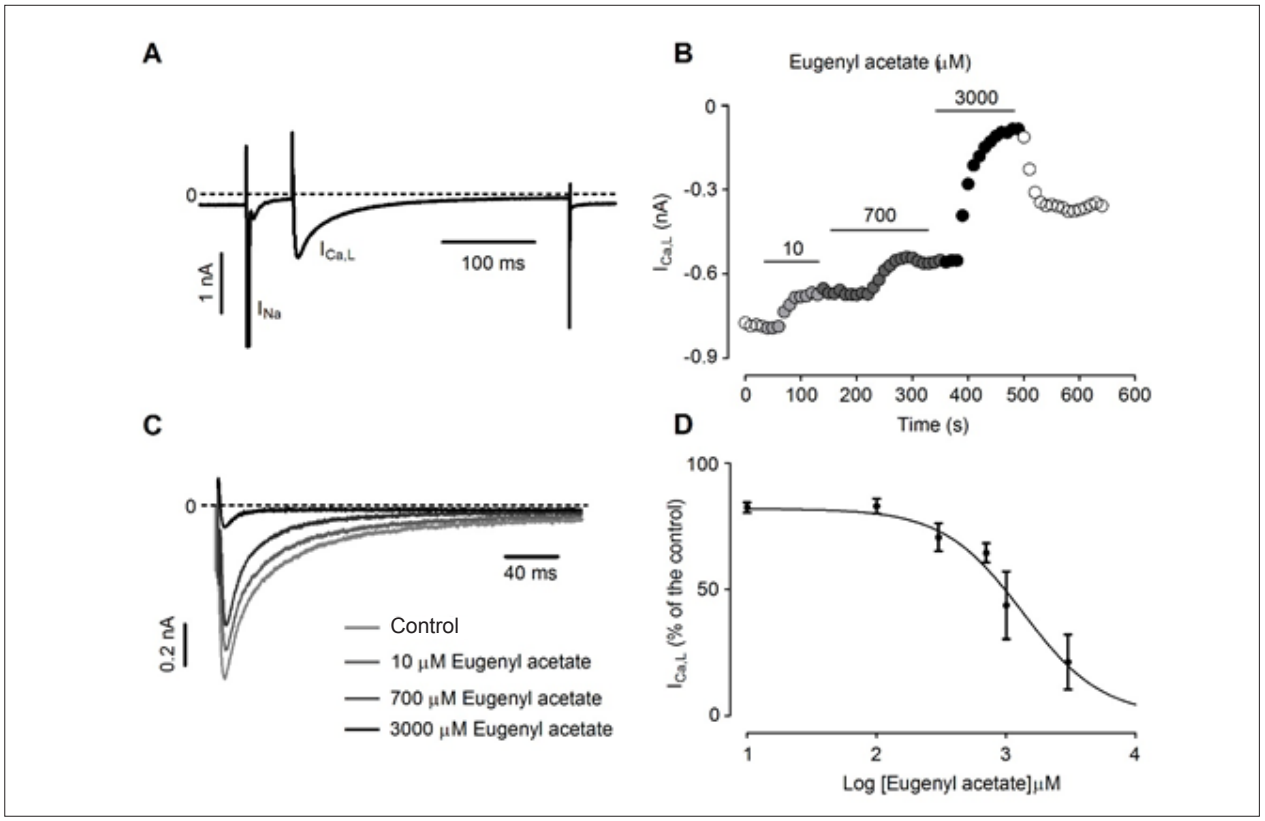

Figure 2 – *Effect of Eugenyl acetate (EA) on $I_{Ca,L}$. A) Representative Ca^{2+} current obtained in healthy isolated cardiomyocytes. B) Time course of the EA effect on peak $I_{Ca,L}$. C) Representative traces of $I_{Ca,L}$ in the control and in presence of EA (10, 700, 3,000 uM). Dashed line indicates zero current. D) EA concentration-effect curve on peak $I_{Ca,L}$ in cardiomyocytes (n = 4).*

Sensch et al.,[4] studying the pharmacological properties of EA analogue eugenol, demonstrated that this substance depresses the force of atrial contraction by reduction Ca^{2+} influx in cardiomyocytes. In these experiments, it was observed that eugenol has an IC_{50} of 127μM, a value lower than the IC_{50} observed for AE (1,337μM). These data suggest that blocking effect of eugenol on Ca^{2+} channels is more potent than EA.

Conclusion

Eugenyl acetate has a cardiodepressor effect that can be explained, at least in part, by the inhibition of $Ca_V1.2$.

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Conception and design of the research and Statistical analysis: Marques LP, Gondim ANS; Acquisition of data: Marques LP, Beserra SS, Gondim ANS; Analysis and interpretation of the data: Marques LP, Roman-Campos D, Gondim ANS; Obtaining financing and Critical revision of the manuscript for intellectual content: Roman-Campos D; Writing of the manuscript: Roman-Campos D, Gondim ANS.

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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Epicardial Adipose Tissue: A New Cardiovascular Imaging Parameter Deeply Connected with Cardiovascular Diseases

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Dear Editor,

We read with great interest the article entitled "The Relationship Between Epicardial Adipose Tissue and Insulin Resistance in Obese Children".[1] In that paper, the authors performed tissue doppler echocardiography to evaluate epicardial adipose tissue (EAT) thickness, electromechanical delay (EMD) and other standard measurements in 94 obese pediatric patients.[1] Patients with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) greater than the 90th percentile in an age and sex-specific percentile curve were labeled as having insulin resistance (IR).[1] This study found that the group with IR had significant higher thickness of EAT than patients included without IR (7.15 vs. 5.5 mm, $p<0.004$, respectively) and inter and intra-atrial EMD was prolonged in the IR group compared to the non-IR group ($p<0.010$; $p=0.032$, respectively).[1] Moreover, the authors found that a cut-off value for EAT of >3.85 mm could predict IR with 92.5% specificity and 68.5% sensitivity ($p=0.002$).[1] The study then concluded that EAT could be used to identify IR among children, as it is stated that EAT is a cheap and accessible parameter that could be easily measured with echocardiography.[1]

Regarding EMD, which is associated with atrial fibrillation (AF) development,[1] it would be interesting to perform a multivariate analysis to determine whether EAT thickness is independently associated with EMD. EAT is a visceral fat store located around the myocardium and pericardium that secretes several proinflammatory chemokines and cytokines, collectively called adipokines.[2] Due to the proximity of EAT with the myocardium, epicardial fat may promote local inflammatory and mechanical effects on the cardiac muscle and coronary vessels. EAT also has a cardioprotective role on the heart by preventing the toxic effects of high-circulating free fatty acids on the myocardium and coronary arteries, lowering vascular tension and preventing vascular remodeling.[2] Previous studies have also observed an independent association between EAT and several cardiovascular diseases such as coronary artery disease, heart failure and AF.[2] A meta-analysis by Gaeta et al.[3] showed an association between EAT and AF.[3] Therefore, EAT could have a role in arrhythmia genesis as it could be a modulator, substrate or trigger in AF development[3] and it would be interesting to investigate its association with EMD.

However, although the findings of this study[1] were interesting, we should take into account the considerably low sensitivity of measuring EAT to identify IR in obese pediatric patients (68.5%). Screening tests should have high sensitivity to minimize the risks of false negatives. Moreover, although echocardiography might be less expensive than certain laboratory tests in some countries, such as Brazil, echocardiography is more costly in the majority of countries as it has a high human labor cost associated. In addition to that, EAT is not usually measured in echocardiography laboratories, neither echocardiography is the gold standard method to measure EAT, as mentioned by the authors.

Keywords

Pericardium; Adipose Tissue; Obesity; Child; Insulin Resistance; Echocardiography/methods.

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Cardiovascular Imaging in Patients with COVID-19

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Dear Editor,

In the latest issue of the *Arquivos Brasileiros de Cardiologia*, Costa et al. reviewed the role of cardiovascular imaging and interventional procedures in patients with novel coronavirus infection.[1]

Although nuclear medicine procedures are unlikely to play a role in the primary diagnosis of COVID-19, which is probably the reason that they were not mentioned in this review, the disease may be detected incidentally in asymptomatic infected patients who are undergoing scans for other indications, and it has potentially relevant implications for further management. COVID-19-associated pneumonia is 18F-FDG-avid, and it may be detected as an incidental finding in asymptomatic patients who are undergoing positron emission tomography/computed tomography (PET/CT) for oncologic indications in regions with a high COVID-19 prevalence.[2] Similarly, incidental findings may be detected in CT used for attenuation correction in myocardial perfusion studies. CT images acquired for attenuation correction should be interpreted in the context of possible COVID-19 pulmonary findings.

Also, the diffuse extra-cardiac Tc-99m sestamibi signal observed in the lungs of COVID-19 patients who are submitted to myocardial perfusion imaging (MPI) scan might be explained by increased vascular permeability in relation to lung inflammation, as well as by the cellular uptake in activated macrophages and fibroblasts rich in mitochondria.[3]

Distinguishing high-risk and low-risk patients in terms of suspicion of COVID-19 serves to reduce the chance of intra-institutional spread of the disease, as well as to facilitate or simplify contact tracing. It is also imperative to consider the indications and urgency of MPI during this pandemic. Referring physicians should discuss and justify the urgency of the procedure with a nuclear cardiologist or physician if an MPI is ordered for patients with confirmed or suspected COVID-19, in order to reduce unnecessary exposure of healthcare workers to risks of infection.[4] In this scenario, it is important to select the protocol with the shortest duration and to consider a stress first imaging protocol.[5]

Exercise stress testing for MPI has been identified as a high-risk procedure in terms of droplet production. Consequently, pharmacological stress has been recommended over treadmill exercise stress, and medical and nursing staff who attend patients with suspected infection are required to wear N95 masks with appropriate personal protective equipment.[5]

Pulmonary embolism (PE) is an important complication associated with COVID-19 disease, as well as a potential differential diagnosis in sudden respiratory distress. In patients with contraindications for iodinated contrast media, perfusion single-photon emission tomography (SPECT) using [99mTc]-labeled macroaggregated albumin is a potential alternative. Due to the high risk of aerosol production associated with ventilation ([99mTc]-labeled aerosol) scans, the North American Society of Nuclear Medicine and Molecular Imaging, in a recent communication by Zuckier et al., has discouraged use of the classic imaging combination of ventilation-perfusion in patients with COVID-19,[6] this contraindication being recently relaxed by the same Society. Ventilation scans should be omitted in any patient with known or suspected COVID-19 infection; a chest X-ray based algorithm has consequently been proposed, with perfusion only SPECT scans in patients without pulmonary opacities. This excludes all patients with pulmonary infiltrates and, therefore, the majority of patients with critical illness associated with COVID-19.

In summary, nuclear medicine is pivotal for managing cardiovascular disease[7-11] in routine clinical cardiology, but it is not the first line approach for patients with COVID-19. Nevertheless, these procedures may eventually help in the management of these patients. Moreover, lung perfusion scans can be an alternative when PE is suspected. Importantly, nuclear cardiologists and nuclear medicine physicians must be aware of incidental findings in asymptomatic patients with COVID-19, and they should optimize MPI protocols, when the procedure is necessary.

Keywords

Coronavirus, Betacoronavirus; Pneumonia; Computed Tomography; Image Cardiovascular; Nuclear Medicine.

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Position Statement on COVID-19 and Pregnancy in Women with Heart Disease Department of Women Cardiology of the Brazilian Society of Cardiology – 2020

Development: Department of Women Cardiology of the Brazilian Society of Cardiology

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Note: These statements are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Position Statement on COVID-19 and Pregnancy in Women with Heart Disease Department of Women Cardiology of the Brazilian Society of Cardiology – 2020	
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Statement

Content

1. Background

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[1]

COVID-19 has a high transmissibility and a variable symptom presentation, ranging from asymptomatic or mild symptoms to critical conditions.[2] Its mild symptoms include dry cough, sore throat, dyspnea, gastrointestinal symptoms, fatigue, anosmia, ageusia, and headache, while serious events include thromboembolism and cardiovascular complications.[3] Approximately 10% of the patients may present pneumonia and progress to acute respiratory distress syndrome (ARDS), multiple organ failure, and death.[4]

Epidemiological evidence strongly suggested that pregnant women had a higher risk of serious illness and death from viral infections during the previous epidemics of H1N1 influenza[5] and two other diseases caused by coronaviruses: SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome).[6] The WHO thus considered that pregnant women should be considered at risk for COVID-19.

Thereafter, the Brazilian Ministry of Health included pregnant and postpartum women, along with those that had miscarriages, in the high-risk COVID-19 group.[7] The high mortality of COVID-19 when associated with chronic diseases such as heart disease, diabetes mellitus, and arterial hypertension is also worth noting.[8,9]

Undoubtedly, a pregnant patient with heart disease who is suspected or confirmed for COVID-19 presents a clinical challenge, since the overlapping of complications could greatly increase maternal mortality.

Therefore, a statement on COVID-19, pregnancy, and heart disease is required at the current moment of this pandemic. The aims of this document are to exhibit aspects of COVID-19 during pregnancy when accompanied by heart diseases and propose recommendations that can contribute to protocols on the care of pregnant women with heart disease during this pandemic.

2. COVID-19 and Pregnancy

2.1. Maternal Outcome

Current evidence indicates that pregnancy is a risk factor for COVID-19.[10] Defining an outcome of this infection in pregnant women is difficult due to limitations in case experiences so far. In addition, global differences in public health policies, as well as cultural and socioeconomic conditions, hamper conclusions about the prognosis of pregnant women with SARS-CoV-2.[11]

The Brazilian Ministry of Health, as of May 2020, had registered a high mortality in a cohort of 288 pregnant women with ARDS caused by COVID-19, most of whom were in their second or third trimesters. Data included 36 (12.5%) maternal deaths, with a high prevalence of heart disease among their co-morbidities (Table 1).[12] The most frequent signs and symptoms presented by pregnant women with COVID-19 were similar to those found in the general population, and oxygen desaturation was more frequent in patients who died (Figure 1).[12]

Considering the current COVID-19 pandemic, questions arise in the care of these patients concerning the continuation of pregnancy, choice of ideal delivery route, possibility of vertical viral transmission, isolation of the neonates, and breastfeeding advisement.

2.2. Obstetrical and Fetal Outcomes

No conclusive data currently indicate fetal damage in pregnant woman with SARS-CoV-2 infection.[14] In a systematic review including 43 pregnant women with COVID-19, the only reported complications were a higher rate of preeclampsia and perinatal complications such as preterm birth.[15]

The route of birth depends on obstetric reasons and clinical urgency. Vaginal delivery is not contraindicated, considering that there is no convincing evidence of vertical transmission. A reasonable labor duration and the safest delivery route should be individualized irrespective of SARS-CoV-2 infection. [16] In critically ill parturients (with hypoxia, cardiovascular or neurological complications, or signs of progressive multiple organ failure), a cesarean section is the most appropriate route of birth.[17]

2.3. Perinatal Transmission

Expression of the ACE2 receptor has been reported in the placenta, particularly in the villous cytotrophoblast and syncytiotrophoblast cells. This means that the mother could be in higher risk of contracting SARS-CoV-2 and that transmission from mother to child could occur.[10] However, the perinatal transmission of SARS-CoV-2 is still controversial.[18]

Table 1 – Outcome of pregnant women with COVID-19 respiratory distress syndrome according to gestational age and comorbidities[13]

	Outcome of pregnant women (N = 288)			
	Cure (n = 252)		Death (n = 36)	
	n	%	n	%
Gestational age				
First trimester	20	7.9	1	2.8
Second trimester	51	20.2	11	30.6
Third trimester	168	66.7	22	61.1
Unknown	13	5.2	2	5.6
Comorbidities				
Heart disease	11	4.4	9	25
Asthma	11	4.4	3	8.3
Diabetes mellitus	31	12.3	6	16.7
Arterial hypertension	10	3.9	5	13.9
Obesity	11	4.4	4	11.1
Hypothyroidism	2	0.8	1	2.8
Chronic neurological disease	3	1.2	0	-
Chronic pulmonary disease	3	1.2	1	2.8
Chronic hematologic disease	9	3.6	0	-
Chronic kidney disease	2	0.8	0	-
Immunodeficiency/immunosuppression	3	1.2	0	-

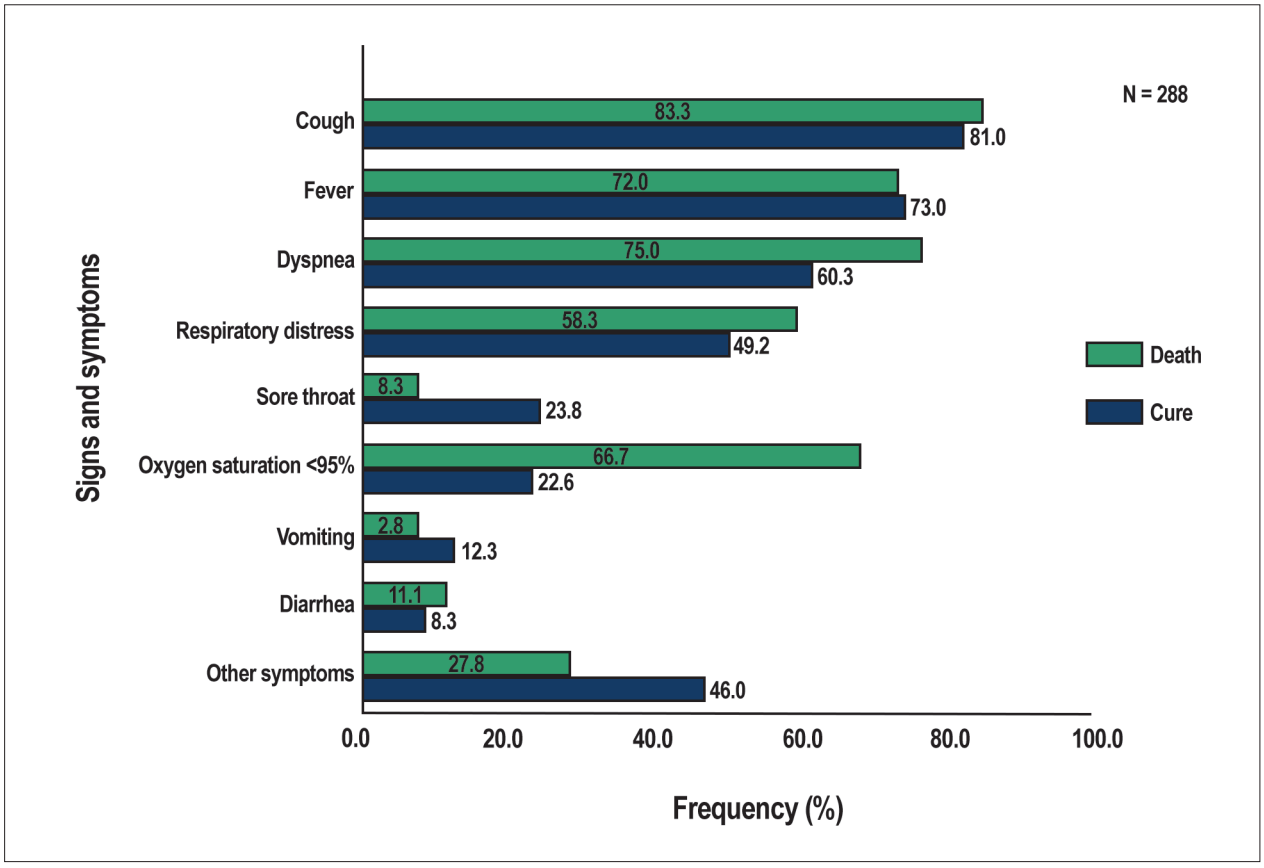


Figure 1 – *Symptoms and outcome (cure or death) of pregnant women with COVID-19 respiratory distress syndrome.[13]*

Out of 75 neonates of mothers with COVID-19, only 1 tested positive for the disease; clinical evolution was satisfactory, with slight changes in liver enzymes. Among babies with COVID-19, studies reported lymphocytopenia, radiological findings of pneumonia, and one case of disseminated intravascular coagulation; all children reached full recovery. From these findings, we cannot exclude neither a sub-clinical response to the mother's infection displayed by the fetus and newborn, nor transplacental vertical transmission.[19] Therefore, close monitoring of newborns whose mothers are infected with COVID-19 is recommended.

Breast milk is the best nutrition source for newborns and infants, including those whose mothers have a confirmed or suspected coronavirus infection.[20] To date, SARS-CoV-19 has not been detected in breast milk. An analysis of 114 infected mothers and their newborns detected antibodies against SARS-CoV-2 (considered a protective factor against infection) in breast milk and concluded that breastfeeding should not be interrupted. Thus, breastfeeding is recommended, provided that mothers follow appropriate measures of respiratory hygiene and according to WHO recommendations.[21] On the other hand, if the mother's health does not allow direct breastfeeding, breast milk must be previously collected and kept unpasteurized. Milk banks could be used in order to ensure feeding of the newborn.

Considering that our experience with SARS-CoV-2 infection during pregnancy is still limited, further studies are necessary to better evaluate maternal and fetal risks and the effects of COVID-19 on pregnant patients.

3. Pregnancy, Heart Disease, and COVID-19

3.1. Physiological Changes of Pregnancy that Induce Cardiovascular Complications by COVID-19

During pregnancy, changes in coagulation and immune, respiratory, and cardiovascular systems are determinant factors that induce complications leading to maternal death from all causes (Table 2). Throughout this period, the immunological system[22] triggers an attenuation of the immunity mediated by Th1 cells due to a physiological change into a predominantly Th2 environment, which contributes to an increasing maternal susceptibility to intracellular pathogens and virus infections and general maternal morbidity.[23] The Th1-type cytokines include proinflammatory interleukins (IL-1a, IL-1b, IL-6, IL-12) and interferon-g (IFN-g), while Th2-type cytokines are anti-inflammatory interleukins (IL-4, IL-10, IL-13) and transforming growth factor β (TGF-β). Patients with SARS displayed preferential activation of Th1 immunity, resulting in a marked elevation of proinflammatory cytokines for at least two weeks after disease onset and severe lung damage.[24] Even though patients with COVID-19 demonstrated activation of both Th1 and Th2 immunities, culminating with the presence of IFN-g and IL-1b, in addition to IL-4 and IL-10, high levels of IL-6 (a predominantly Th1-type response) are associated with an increased risk of mortality.

The respiratory system undergoes an adjustment during pregnancy due to hormonal influences and the mechanical effects of increasing uterine volume, resulting in a progressive decrease in total lung capacity and chest wall compliance.[25] For these reasons, COVID-19 pneumonia may have a rapid and progressive evolution, from focal consolidation to diffuse and bilateral destruction of the pulmonary parenchyma and severe respiratory failure. Cases of maternal hypoxia resulting from impaired ventilation and gas exchange could reduce placental perfusion, ultimately resulting in fetal distress and even death.

The activation of the coagulation system is characteristic of a healthy pregnancy and involves the synthesis of coagulation factors II, VII, VIII, IX, and X, as well as fibrinogen, in addition to a reduction in endogenous anticoagulants (especially antithrombin and protein S); these determine the state of hypercoagulability.[26] These changes happen progressively after the first trimester with a shortening of prothrombin,

Table 2 – Impact of physiological changes in the cardiovascular and respiratory systems of pregnant women with cardiac disease and SARS-CoV-2 infection.

➢ Downregulation of the maternal immune system – attenuation of Th1 cell-mediated immunity to a predominantly Th2 environment - risk of viral infections
➢ Oxygen consumption – hypoventilation, apnea, or impaired gas exchange – hypoxemia
➢ Decreased functional residual capacity (10% to 25%) – hypoxemia
➢ Hyperemia and edema of the upper airways – challenges to endotracheal intubation
➢ ncreased breast volume, delayed gastric emptying, need for rapid sequence induction – risk of aspiration
➢ Decreased systemic vascular resistance – hypotension, hypoxemia
➢ Increased heart rate and stroke volume – heart failure
➢ Caution in mechanical ventilation
Hyperventilation and alkalosis – uterine vasoconstriction.
Hypoventilation and hypercapnia – fetal respiratory acidosis
Maternal PaO_2 should be kept ≥ 70 mmHg – fetal oxygenation
➢ Increased thromboembolic risks
Increase in coagulation factors (V, VIII, X, and von Willebrand factor); decreased protein S levels
Compression of the inferior vena cava and left iliac vein by the uterus
Local trauma to pelvic veins during delivery; postpartum period of cesarean section

partial thromboplastin, and thrombin times that weakens anticoagulant function . When adding to these mechanisms the mechanical compression of the venous plexus on the lower limbs by the gravid uterus, a predisposition to thromboembolism during pregnancy is justified.

The cardiovascular system suffers a hemodynamic overload during pregnancy that may aggravate the functional state of underlying heart diseases. Cardiac output progressively increases in the first trimester, reaching its highest at the beginning of the third trimester. Simultaneously, peripheral vascular resistance (not limited to the uterine plexus) decreases in a greater magnitude than the elevation in cardiac output.[27]

3.2. Pregnancy and Heart Disease Bring a High Risk for COVID-19

Since pregnant women with heart disease are at risk for serious cardiac complications, it is mandatory that health care professionals obtain the required knowledge to reduce mortality in this high-risk cohort of patients.[28]

In Brazil, rheumatic heart disease is the main etiology of heart diseases encountered during pregnancy, followed by congenital heart diseases and cardiomyopathies. Reports of maternal outcomes show that around 25% of pregnant women had cardiovascular complications (including heart failure, thromboembolism, and arrhythmias) as the main causes of hospitalization and maternal mortality.[29,30]

It is worth mentioning that pregnant women with congenital heart disease belong to a special group of patients because of their great diversity in anatomical and functional changes. The anatomical cardiac defects range from mild defects, which do not present additional risk when compared to healthy pregnant women, to complex heart abnormalities that result in very high and even prohibitive risks, especially cyanosis and pulmonary hypertension.

Therefore, a risk stratification of pregnancy in women with heart disease is essential to estimate the prognosis and to plan prevention and treatment strategies for possible complications.[31] The most accepted risk estimation method proposed for pregnancy is the modified WHO classification, which is divided into four risk categories (Table 3).[32]

4. Overlapping Complications of Covid-19, Pregnancy, and Heart Disease

4.1. Differential Diagnosis

Confirmation of COVID-19 diagnosis is essential. The similarity between its clinical characteristics and those of the pregnant woman with heart disease can delay diagnosis and postpone protective measures against its spread (Table 4).[2,3,12,33] Therefore, considering the current pandemic, tests for SARS-CoV-2 should be included as good practice in the universal screening of pregnant women with heart disease.

4.2. Impact of COVID-19 on the Cardiovascular System of Pregnant Women

The current COVID-19 pandemic has resulted in thousands of deaths due to severe systemic inflammation and multiple organ failure. The cardiovascular system is also affected by this disease, resulting in complications such as myocardial injury, myocarditis, acute myocardial infarction, heart failure, arrhythmias, and thromboembolic events.[34,35]

Within this topic, an important subject to be considered is the pivotal role of the angiotensin-converting enzyme 2 (ACE2) in COVID-19 cardiovascular complications.[36] ACE2 is found on the surface of lung alveolar epithelial cells (considered the entry site for SARS-CoV-2) and catalyzes the cleavage of angiotensin II, a proinflammatory factor. This imbalance in immune regulation, in addition to an increased metabolic demand and procoagulant activity, are responsible for the increased risk of adverse outcomes in patients with COVID-19-related cardiovascular disease.[37]

However, recent research has suggested that the virus may also cause direct damage to the heart utilizing ACE2 receptors in the cardiac tissue.[38] The prevalence of cardiovascular disease in COVID-19 patients is still unclear, but preexisting heart disease may be associated with more severe COVID-19 outcomes.

4.2.1. Myocardial Injury, Myocarditis, and Heart Failure

Among the mechanisms of acute myocardial injury caused by the SARS-CoV-2 infection, the following stand out: the expression of ACE2 in the cardiovascular system, a cytokine storm triggered by

Table 3 – Classification of maternal cardiovascular risk: World Health Organization (mWHO)

mWHO I (2.4% - 5%)	mWHO II (5.7% - 10.5%)	mWHO II-III (10% - 19%)	mWHO III (19% - 27%)	mWHO IV (40% - 100%)
Small or mild lesions Pulmonary stenosis ASD VSD PDA APVD Mitral valve prolapse Simple lesions, successfully operated Isolated atrial or ventricular extrasystoles	Non-operated ASD, VSD Operated tetralogy of Fallot Non-complex arrhythmias Turner syndrome without aortic dilation	Mild ventricular dysfunction (EF > 45%) Hypertrophic cardiomyopathy Mild to moderate mitral or aortic valve disease Marfan syndrome or other inherited diseases without aortic dilation Bicuspid aortic valve with AoD < 45 mm Operated coarctation of the aorta AVSD	Moderate ventricular dysfunction (EF 30%–45%) Peripartum cardiomyopathy without ventricular dysfunction Mechanical prostheses Systemic RV with or without mild ventricular dysfunction Uncomplicated Fontan circulation Non-operated cyanotic heart disease Other complex heart diseases Severe mitral stenosis	Pulmonary arterial hypertension Systemic ventricular dysfunction (EF < 30% or NYHA class III–IV) Peripartum cardiomyopathy with ventricular dysfunction Serious left heart obstructive lesions Severe systemic right ventricular dysfunction Aortic dilation > 45 mm in Marfan syndrome, > 50 mm in bicuspid aortic valve or other inherited diseases / Turner syndrome

Modified from Balci et al.[32] AoD: aortic diameter; APVD: anomalous pulmonary venous drainage; ASD: atrial septal defects; AVSD: atrioventricular septal defect; EF: ejection fraction; NYHA: New York Heart Association; PDA: patent ductus arteriosus; RV: right ventricle; VSD: ventricular septal defects.

Table 4 – The COVID-19/heart disease/pregnancy triad: features and differential diagnosis

	COVID-19	Cardiopathy	Normal pregnancy
Symptoms	Fever (> 37.8 °C), myalgia, fatigue, anorexia, sore throat, nasal and conjunctival congestions, cough, dyspnea, anosmia, , odynophagia, nausea, vomiting, diarrhea, abdominal pain	Dyspnea/palpitations, chest pain, syncope, hemoptysis, fatigue, lower limb edema, orthopnea, dry cough	Nausea, vomiting, edema/dyspnea/ fatigue, palpitations, dizziness, epistaxis, gestational rhinitis, headache, abdominal pain
Occurrence of symptoms according to gestational age	Any gestational age or puerperium	Usually during second and third trimesters of pregnancy or in the puerperium	Any gestational age
History	No previous heart disease	Previous heart disease	No previous heart disease
Laboratory aspects	Positive nasopharyngeal COVID-19 RT-PCR swab test lymphocytopenia Increased ALT/AST Increased urea/creatinine Increased D-dimer	High levels of BNP	Normal or slightly increased D-dimer
Imaging exams	Normal echocardiogram Chest X-ray with or without alterations Chest computed tomography imaging - ground-glass opacity	Echocardiogram - structural cardiac lesion Chest X-ray/computed tomography imaging alterations: cardiomegaly and/or pulmonary congestion	Normal echocardiogram Normal chest-X-ray

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; RT-PCR: reverse transcriptase-polymerase chain reaction.

an unbalanced autoimmune response, and hypoxemia resulting from ARDS.[34-37]

An extreme inflammatory response to COVID-19 can result in endothelial injury, myocarditis, and ventricular dysfunction, with symptoms of chest pain, dyspnea, and palpitation.[38] These symptoms overlap with the usual complaints of pregnant women with heart disease, making the diagnosis of heart failure during pregnancy even more difficult.

Peripartum cardiomyopathy should always be considered when cardiac decompensation occurs in the last months of pregnancy or following delivery in previously healthy women.[39] When symptoms such as exhaustion, chest pain, or fatigue (which usually occur in late pregnancy and postpartum periods) are not given appropriate attention, a delay in the diagnosis of peripartum cardiomyopathy may occur and the patient could have a worse prognosis and less chance of myocardial systolic function recovery. Therefore, prompt diagnosis of this disease is crucial for patient survival[40] and physicians should be aware of the differential diagnosis of pregnancy-related dyspnea, COVID-19, and heart failure from peripartum cardiomyopathy for efficient decision-making.[31,41] A specific algorithm for managing patients and the establishment of a multidisciplinary team is crucial in these cases.

Pulmonary edema is also seen in healthy women as a consequence of major changes in intravascular volume during labor and after delivery. Similarly, hemodynamic changes during pregnancy increase the gradient through the stenotic mitral valve and cause pulmonary congestion. Patients with congenital cyanotic heart disease, left heart obstructive lesions, or severe systolic ventricular dysfunction are at increased risk. A reduction in systemic vascular resistance worsens hypoxemia in patients with pulmonary hypertension and complex congenital heart disease.[28-30]

4.2.2. Hypercoagulable State and Thrombotic Events

Disorders of the coagulation system are a critical aspect of morbidity and mortality in COVID-19. The disease has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer.[42] In this context, it is assumed that the combination of COVID-19, pregnancy,[43] and heart conditions such as the use of mechanical valve prostheses or atrial fibrillation in rheumatic mitral valve disease greatly increases the risk of arterial thromboembolism, demanding a rigorous anticoagulation protocol.[44,45]

Notably, D-dimer is a prothrombotic biomarker used as an exclusion criterion of pulmonary thromboembolism, but its usefulness during pregnancy has limitations. Its levels increase progressively and significantly through pregnancy and peak in the third trimester, making it important to consider that D-dimer levels are above the conventional cut-off (500 μg/L) in 99% of healthy pregnant women.[46]

Recently, the pregnancy-adapted YEARS algorithm proposed that the diagnosis of pulmonary embolism during pregnancy could be safely ruled out in the absence of these three parameters: (1) clinical signs of deep vein thrombosis; (2) hemoptysis; and (3) pulmonary embolism as the most likely diagnosis and D-dimer level < 1000 ng/mL. However, the D-dimer cut-off for pregnant women with COVID-19 is still unknown. Hence, the use of noninvasive tools such as venous duplex scans and echocardiographies is encouraged in the search for the correct diagnosis of thromboembolism or cardiac events. These bedside examinations are highly available, present low costs, and can be repeated if needed.[47]

4.2.3. Proinflammatory Condition and Vascular Damage

The systemic inflammation and coagulopathy exhibited by COVID-19 increase the risk of atherosclerotic plaque rupture and acute myocardial infarction.[34,35] The release of inflammatory cytokines can cause a reduction in coronary blood flow and oxygen supply, plaque destabilization, and microthrombogenesis. The significant implication of the SARS-CoV-2 infection becomes evident with acute myocardial injury with high results of highly sensitive troponin

assays[48] and/or new electrocardiogram and echocardiogram abnormalities, complex cardiac arrhythmias, and cardiac arrest. On the other hand, the occurrence of acute coronary syndrome during pregnancy is not common,[49] even though infections (especially in the postpartum period) are among the risk factors for myocardial infarction. It is important to emphasize that the most frequent causes of myocardial infarction during pregnancy are spontaneous coronary artery dissection,[50] followed by atherosclerosis, coronary thrombosis, and angiographically normal arteries with impaired coronary microcirculation. So far, no data has been published on myocardial infarctions in pregnant patients with COVID-19.

4.2.4. Proinflammatory Condition, Hypoxemia, and Myocardial Injury Induce Arrhythmias

Finally, arrhythmias may be present in patients with COVID-19, with multiple simultaneous causes such as inflammation, hypoperfusion, fever, or hypoxia. Still, normal pregnancies present electrical cardiac disturbances that increase the incidence of maternal cardiac arrhythmias, ranging from clinically irrelevant isolated premature beats to debilitating supraventricular and ventricular tachycardias.[51] The occurrence of arrhythmias during pregnancy requires investigation with special attention to identifying or excluding structural cardiac lesions, electric cardiac injury, and general infections. This is a fundamental step when determining the treatment and prognosis of arrhythmias, particularly those with iatrogenic causes amid the COVID-19 pandemic. Under these conditions, the impact of COVID-19 therapy on QT prolongation can be verified on the Tisdale Risk Score (https://www.mdcalc.com/tisdale-risk-score-qt-prolongation).52

5. Summary and Conclusions

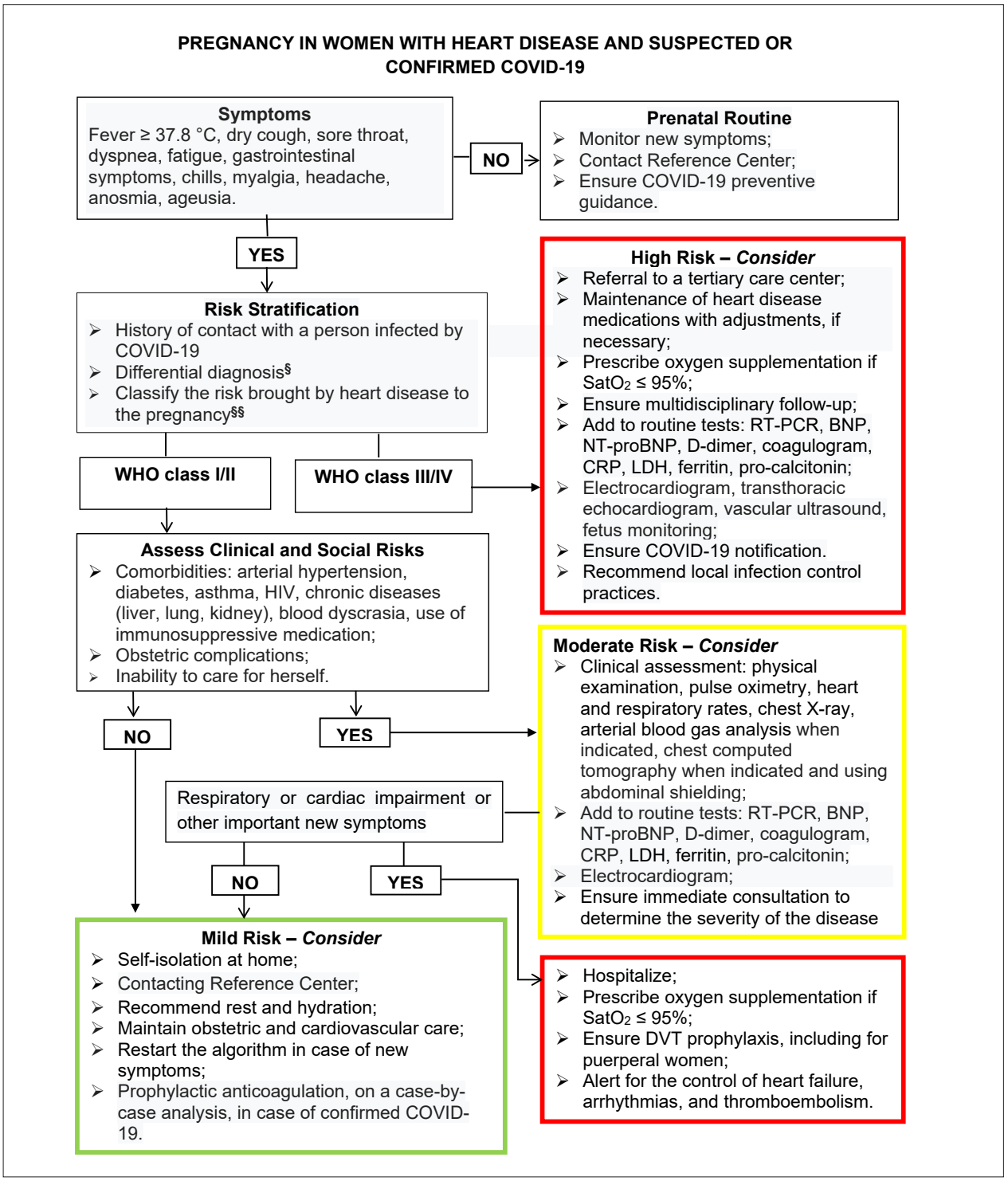
Pregnant women with heart disease are a high-risk group for COVID-19 mortality. The knowledge of overlapping complications between pregnancy and COVID-19 allows the establishment of preventive measures according to cardiac risk stratification. Therefore, early diagnosis of SARS-CoV-2 infection is of crucial importance and the routine use of SARS-CoV-2 testing is fundamental for pregnant women with heart disease . Potential benefits of these good practices include early diagnosis and determination of isolation practices, including guidance on the use of personal protective equipment and neonatal care.

The establishment of a specialized routine provides an important opportunity to protect mothers, babies, and health care professionals during these difficult times. Data on the COVID-19 pandemic are constantly being published and the following recommendations will certainly be reviewed and updated as new scientific information becomes available.

6. Recommendations for Pregnant Women with Heart Disease During the COVID-19 Pandemic (See Algorithm)

- Maintain a strict multidisciplinary follow-up at short intervals, according to the WHO risk stratification and maternal and fetal conditions;
- Maintain the administration of drugs prescribed for the treatment of heart disease, with necessary dose adjustments throughout the pregnancy;
- Reinforce information on forms of transmission, signs and symptoms, and prevention strategies for COVID-19 during prenatal visits;
- Avoid contact of all pregnant women over 24 weeks with patients in the COVID-19 area;
- Contact the patient in case of absence at a scheduled prenatal appointment;
- Advise seeking medical care at a referral service if the patient has any suspected COVID-19 symptoms or worsening of heart disease conditions;
- Conduct a standard investigation for COVID-19 in suspected cases, with an immediate indication for hospitalization if there is evidence of hemodynamic impairment and/or severity of the viral infection;
- Recommend self-isolation and monitoring for 14 days to patients with mild COVID-19 symptoms and stable cardiac and obstetric conditions;
- Hospitalization at initial assessment for suspected COVID-19 if O_2 saturation ≤ 95%, regardless of symptom severity;
- Carefully judge the clinical deterioration due to COVID-19 and that resulting from cardiac disease;
- Perform imaging tests, when indicated, using abdominal protection to reduce exposure to radiation;
- Employ specific treatment for COVID-19 according to established protocols for different stages of the disease;
- Routinely perform RT-PCR tests for COVID-19 suspected cases and for all patients on admission for miscarriage or 48 hours before scheduled delivery;
- Consider B-type brain natriuretic peptide (BNP) and NT-proBNP as validated markers for the diagnosis of heart failure;
- Consider the influence of pregnancy on the D-dimer level as a biomarker for the diagnosis of pulmonary thromboembolism;
- Consider the Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease in the management of cardiovascular complications;
- Evaluate possible interactions between COVID-19 therapy and pregnancy using drug databases (www.drugs.com or www.crediblemeds.org);
- Advise close monitoring of newborns of mothers with COVID-19, since vertical transmission is still a possibility;
- Reinforce breastfeeding for postpartum women with COVID-19, if the health conditions of the mother and newborn allow it, with the following precautions: (1) The mother should practice respiratory hygiene during breastfeeding, which includes wearing a mask that covers the mouth and nose; and (2) Wash hands with soap and water for 20 seconds before and after breastfeeding;
- Evaluate possible interactions between COVID-19 therapy and breastfeeding using drug databases (www.*drugs.e-lactancia.org*);
- Suggest future pregnancy planning considering the control of the COVID-19 pandemic.

7. Algorithm



BNP: B-type natriuretic peptide; CRP: C-reactive protein; DVT: deep venous thrombosis; LDH: lactic dehydrogenase; NT-proBNP: N-terminal fragment of proBNP; RT-PCR: reverse transcriptase-polymerase chain reaction; § Table 4; §§ Table 3.

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Statement

Content

1. Introduction

In accordance with the "Standards for Production of Guidelines, Position Statements, and Standardizations" sanctioned by the Brazilian Society of Cardiology, this document was written to update indications for echocardiography in fetal and pediatric cardiology and congenital heart disease of the adult, and to supplement the recently-published position paper on indications for echocardiography in adults.[1] The position statement is not intended to be an in-depth review of echocardiography in congenital heart disease, but an indispensable basic guide to support rational clinical decision-making by physicians when ordering examinations. While it takes into consideration the significant technological advances achieved recently in echocardiography, its purpose is not to describe echocardiography methods in detail, but to clearly and concisely summarize the most important situations in which echocardiography is of benefit for diagnosis and/or treatment planning in these groups of patients. In this document, recommendation classes will be presented in accordance with the following definitions:

- Class I: conditions for which there is conclusive evidence or, in the absence thereof, general agreement that the examination procedure is useful and safe.
- Class II: conditions for which there is conflicting evidence and/or divergence of opinion on the utility and/or safety of the examination.
- Class IIa: evidence or opinions favorable to the examination. Most experts approve.
- Class IIb: utility and/or safety less well established, with divergent opinions.
- Class III: conditions for which there is evidence or consensus that the examination is not useful and, in some cases, may even be harmful.

Evidence levels are also presented, defined as follows:

- A: agreement between multiple randomized clinical trials or robust meta-analyses;
- B: less robust meta-analysis data or single randomized clinical study or observational studies;
- C: expert opinion.

All of the tables summarizing recommendations for use of echocardiography in different clinical scenarios will therefore include columns showing recommendation classes and evidence levels

2. Fetal Echocardiography

The incidence of congenital heart disease is estimated at 6-12/1,000 live births;[2,3] however, it is estimated that fetal prevalence is higher. There are several factors associated with increased risk of congenital heart disease in the fetus, including familial factors and maternal and fetal conditions. Fetal echocardiography is the most important tool for diagnosis of these cardiac pathologies, from the end of the first trimester up to term. The best timing for conducting fetal echocardiography is determined by multiple factors, including the reason for using it and the gestational age at which a cardiac and/or extracardiac abnormality is detected. Echocardiography for screening high-risk pregnancies can be conducted at 18 to 22 weeks' gestation. Considering that initial screening may not detect developing lesions[4] or arrhythmia,[5,6] abnormal findings at routine obstetric consultations should be promptly referred for additional fetal echocardiography examinations.

Fetal echocardiography can be performed at younger gestational ages, including at the end of the first and start of the second trimesters, generally in pregnancies at high risk of congenital heart disease, particularly when elevated nuchal translucency is present on morphological ultrasound in the first trimester.[7,8] In the majority of gestations, transabdominal fetal echocardiography provides images of adequate resolution to detect anomalies at between 13 and 14 weeks. However, if the examination is conducted before 13 weeks, transvaginal echocardiography is needed, because of the small size of the cardiac structures and the distance between the fetus and the maternal abdominal wall.[7,8] When fetal echocardiography is conducted before 18 weeks, it should be repeated between 18 and 22 weeks' gestation, because the limited image resolution may not be sufficient for diagnosis of certain cardiac abnormalities and also because of potential progression of lesions not detected at earlier gestational ages.[7-9]

The timing and frequency of echocardiography should be guided by: severity of lesions, signs of heart failure, mechanisms of progression, and perinatal management assessment.

Fetal echocardiography recommendations are listed in Tables 1 and 2.

Table 1 – Recommendations for fetal echocardiography in high-risk pregnancies[5-9]

Recommendations	Recommendation class	Evidence level
Pre-gestational DM	I	A
GDM diagnosed in first trimester	II	B
Maternal phenylketonuria	I	A
Maternal SSA/SSB antibodies	IIa	B
Maternal medications: ACE inhibitors Retinoic acid NSAID in third trimester	 IIa I I	 B B A
Maternal rubella infection in first trimester	I	C
Maternal infection with suspicion of myocarditis/pericarditis	I	C
Assisted reproduction	IIa	A
Congenital heart disease in first-degree relative	I	B
Heart disease with Mendelian inheritance in first or second-degree relative	I	C
Suspicion of heart disease on obstetric ultrasound	I	B
Extracardiac fetal anomaly	I	B
Fetus with chromosome abnormality	I	C
Fetus with tachycardia or bradycardia or frequent irregular heartbeats	I	C
NT > 95%	I	A
Monochorionic twinning	I	A
Fetus with hydrops or effusions	I	B

ACE: angiotensin-converting enzyme; DM: diabetes mellitus; GDM: gestational diabetes mellitus; NSAID: nonsteroidal anti-inflammatory drugs; NT: nuchal translucency. Adapted from Donafrio et al.[7]

Table 2 – Recommendations for fetal echocardiography in low-risk pregnancies[5-9]

Recommendations	Recommendation class	Evidence level
Maternal medication: Anticonvulsant Lithium Vitamin A Selective serotonin reuptake inhibitors NSAID during first and second trimesters	IIb	B
Heart diseases in second-degree relatives	IIb	B
Abnormalities of the umbilical cord and placenta	IIb	C
Fetal intra-abdominal venous abnormality	IIb	C

NSAID: nonsteroidal anti-inflammatories. Adapted from Donafrio et al.[7]

3. Echocardiography in the Newborn

Newborn infants transition from a state in which circulation is in parallel, with low systemic vascular resistance and high pulmonary vascular resistance, during fetal life, to a state in which circulation is in series and the cardiac output of both ventricles must be equal in the presence of high systemic vascular resistance. These circulatory changes that take place with birth may take days or weeks to be completed, particularly in preterms, because the communications present during fetal life cannot close promptly. Thus, persistent ductus arteriosus (PDA), persistent high pulmonary pressures, and the incapacity of the immature myocardium to pump blood against systemic vascular resistance that has suddenly increased can cause a transitory reduction in systemic blood flow, changing these patients' hemodynamics.[9] Moreover, structural cardiac anomalies or extracardiac conditions such as sepsis or diaphragmatic hernia are tolerated differently in this age group.[10]

The transitional physiology of the cardiovascular circulation during the neonatal period means that these patients must be evaluated as a distinct group.

The most common reasons for conducting an echocardiogram during the neonatal period are to detect or rule out congenital structural cardiac diseases in patients who have heart murmur, abnormal neonatal oximetry screening results,[11] are in shock, are hypoxemic, develop respiratory failure, or have multiple malformations. The next most common group of indications are to screen for functional anomalies, such as persistent ductus arteriosus, and to test pulmonary hemodynamics and cardiac function (see Table 2).

Echocardiographic assessment of patients in neonatal intensive care units is justified, including in an evolving manner, as a factor in specific changes to clinical management of the neonate.

The recommendations for echocardiography in newborn infants are listed in Table 3.

4. Echocardiography in Infants, Children and Adolescents

Since echocardiography is a noninvasive method for obtaining anatomic, hemodynamic, and physiological information on the pediatric heart, it is the first-choice diagnostic method for initial assessment of congenital or acquired heart disease in infants, children, and adolescents.

Children with cardiac diseases are a varied group of patients who often have complex anatomic malformations and require lifelong follow-up. Repeated studies may therefore be indicated to monitor heart valve function, growth of cardiovascular structures, and ventricular function and for follow-up of drug-based or surgical interventions.[9,16-18]

Signs and symptoms such as cyanosis, growth deficits, exercise-induced anginas, syncope, respiratory distress, murmurs, heart failure, pulse abnormalities, and cardiomegaly may suggest structural heart disease.

Echocardiography may also be indicated even in the absence of specific clinical status in patients with family history of hereditary heart disease, genetic syndromes associated with structural heart disease, or abnormal examination findings (fetal echocardiography, chest X-ray, and electrocardiogram).

Table 3 – Recommendations for echocardiography in newborn infants[9,11-15]

Recommendations	Recommendation class	Evidence level
Pathological heart murmur or other abnormal cardiac auscultation findings	I	C
Central cyanosis, heart failure, cardiogenic shock, respiratory distress	I	A
Asymmetry of pulses and/or arterial blood pressure gradient between upper and lower extremities	I	A
Cardiomegaly on radiological chest examination or abnormal findings suggestive of heart disease	I	A
Syndromes associated with cardiovascular disease	I	B
Extracardiac anomalies	I	B
Anomaly of heart position or site	I	B
Fetal and/or obstetric echocardiography findings showing or suggesting heart malformation	I	C
Corrective or palliative heart surgery	I	B
History of hydrops fetalis	I	B
Clinical suspicion of patent ductus arteriosus	I	A
Evaluation of the hemodynamic significance of PDA, monitoring effects of treatment	I	A
Assessment of progress of neonate after surgery for closure of ductus arteriosus with hemodynamic instability	I	A
Perinatal asphyxia with abnormal hemodynamics and/or biomarkers	I	A
Suspected pulmonary hypertension	I	A
Assessment of progress of neonate with pulmonary hypertension on drug treatment	I	A
Hypotension	I	A
Assessment of extracorporeal life support cannulae, maintenance and weaning from ECMO	I	A
Systemic maternal disease associated with known neonatal anomaly	IIa	B
Maternal infection during gestation or delivery with potential for fetal or neonatal cardiac sequelae	IIa	B
Maternal diabetes without fetal echocardiography or with normal fetal echocardiography	IIb	B
Maternal phenylketonuria	I	A
Maternal autoimmune dysfunction	IIa	B
Maternal exposure to teratogens	IIa	B
Failure to thrive in the absence of definite clinical abnormalities	IIa	C
History of nonsustained fetal ectopic heart rhythm, in the absence of postpartum arrhythmia	III	C
Acrocyanosis with normal pulse oximeter saturation in upper and lower extremities	III	C
Morphological and functional assessment during the postoperative period after heart surgery	I	B
To assess pericardial hemorrhage and evaluate hemodynamic impact and guide interventional procedures	I	A
To determine central venous catheter position and identify related complications (thrombosis and infection)	I	A

ECMO: extracorporeal membrane oxygenation; PDA: persistent ductus arteriosus.

Patients with arrhythmia may have structural heart disease, such as corrected transposition of the great arteries and Ebstein's anomaly, cardiac tumors, or cardiomyopathies. Sustained arrhythmia and use of antiarrhythmic medications can cause changes to myocardial function and echocardiography plays an important role in clinical management of these patients.

The recommendations for echocardiography in infants, children and adolescents are listed in Table 4.

5. Pediatric Echocardiography in Acquired Heart Diseases

Acquired heart diseases primarily occur in the context of systemic diseases linked to inflammatory processes, renal diseases, use of cardiotoxic chemotherapy, or parenchymatous pulmonary disease, and after heart transplantation.

Myocardial involvement can occur in several conditions, such as systemic inflammatory diseases (particularly those with a more aggressive course, such as juvenile systemic lupus erythematosus, juvenile idiopathic arthritis, and rheumatic fever).[19-22] During treatment with cardiotoxic chemotherapy (particularly with anthracyclines) and radiotherapy in the mediastinal region, echocardiography is indicated before, during, and after treatment, with the objective of indicating the need for cardioprotective measures and even for changing the treatment in some cases.[23]

In patients with chronic liver disease or hypertension and/or on dialysis, echocardiography provides clinicians with valuable information on ventricular geometry, systolic/diastolic function, and blood volume. This can very often guide changes in the dialysis regimen and introduction of (or changes to) antihypertensive and vasoactive drugs.[24]

In patients with pulmonary disease, echocardiography can be used to estimate pulmonary pressures and also to evaluate right ventricle performance, which has an important correlation with clinical prognosis.[25-27]

In children and adolescents with AIDS, echocardiography is used to investigate right cardiac involvement caused by the virus, which can result in dilated cardiomyopathy, pulmonary hypertension, and even ventricular hypertrophy, in addition to effects caused by opportunistic diseases and/or drug side effects.[28]

The growing number of children with end-stage heart failure must be evaluated before and after heart and/or cardiopulmonary transplantation[29] and echocardiography is also an aid to decision-making on introduction/withdrawal of cardiovascular support.[30]

The recommendations for echocardiography in newborn infants, infants, children, and adolescents with acquired heart disease are listed in Table 5.

6. Echocardiography in Adults with Congenital Heart Disease

Over the last 30 years, considerable advances were made in pediatric cardiology, both in the sphere of diagnosis with the advent of echocardiography and in the realm of treatment to correct heart diseases, initially surgically and more recently using percutaneous techniques in the catheterization laboratory. Recent data show that the estimated size of the population of adults with congenital heart disease in United States in 2010 was 1.4 million patients.[30] This population has problems related to residual defects, new acquired defects (such as pulmonary reflux after definitive correction of tetralogy of Fallot or obstructions after a Jatene procedure), arrhythmia, heart failure, acquired disease of the adult, infectious endocarditis, or indications for heart transplantation. Many survive with palliative surgery that may or may not require definitive correction (such as the Senning, Mustard, Rastelli, Glenn, or Fontan procedures, which induce new complications that are implicit in the surgical method employed) and many patients present with heart conditions for the first time, with no prior diagnosis of heart disease.[32-35]

There is no doubt that two-dimensional transthoracic echocardiography has an important role to play in diagnosis and follow-up of these malformations.[36] Recent advances such as 3D echocardiography have proved superior for determination of volumes and even ventricular function, particularly in complex malformations such as those with univentricular physiology, or for evaluation of the right ventricle, and these systems should be used whenever they are available and there are trained professionals to operated them.[37] Additionally, using 3D images to guide surgery gives surgeons better understanding of the case, enabling better surgical planning. Along the same lines, new techniques for assessment of diastolic function and segmental function, such as tissue Doppler, strain, and strain rate can be very useful, particularly in conditions with univentricular physiology or cardiac chamber deformities, primarily when involving the right ventricle[38] (see sections 9 and 10 below).

The primary limitation of echocardiography for assessment of adults with congenital heart disease is a poor transthoracic acoustic window in patients with previous heart surgery or deformities of the chest wall, and echocardiography is also inappropriate for assessing the aortic arch, the coronary arteries, the pulmonary arteries, and the collateral vessels. In these situations, transesophageal echocardiography, angiotomography, and magnetic resonance (MR) are extremely useful.

The recommendations for echocardiography in adults with congenital heart disease are listed in Table 6.

7. Transesophageal Echocardiography in Pediatric Cardiology

Transesophageal echocardiography (TEE) uses special transducers and a different access route, offering better definition of cardiac structures, increasing the method's diagnostic applications.

It is particularly important for definition of complex anatomic structures and functional abnormalities, which cannot always be evaluated using transthoracic echocardiography alone.

Technological advances and miniaturization of probes has led to increasing adoption of TEE in the field of pediatric cardiology and it can provide important information about patients from the neonatal age group up to adolescents and adults, for diagnosis, intraoperative assessment, in the immediate and late postoperative periods, and in the intensive care unit, and also in the catheterization laboratory, aiding in interventional procedures.

Table 4 – Recommendations for echocardiography in infants, children and adolescents[9,12,16-18]

Recommendations	Recommendation class	Evidence level
Pathological heart murmur or other evidence of cardiac abnormality	I	C
Anomaly of heart position or site	I	B
Cardiomegaly on radiological chest examination or abnormal findings suggestive of heart disease	I	B
Abnormal electrocardiogram	I	B
Immediate preoperative assessment for heart surgery	I	C
Change in clinical status of patient with known heart disease	I	B
Morphological and functional assessment during the postoperative period after heart surgery	I	C
Family history of heart disease transmitted genetically	I	B
Neuromuscular disease with myocardial involvement	I	B
Signs and symptoms of infectious endocarditis	I	A
Signs and symptoms of heart failure	I	A
Palpitations without other symptoms, benign family history, and normal electrocardiogram	IIb	C
Palpitations with family history of arrhythmia, sudden death, or cardiomyopathy.	I	B
Palpitations in patient with known cardiomyopathy	I	B
Palpitations with abnormal electrocardiogram or known ion channel defects	IIa	C
Asymmetry of peripheral pulses	I	A
Syndrome associated with cardiovascular disease; genotype positive for cardiomyopathy; chromosome anomaly associated with cardiovascular disease	I	B
To determine the appropriate timing of clinical or surgical treatment in patients with known heart disease	I	B
Selection, placement, patency, and monitoring of endovascular devices	I	A
Identification of intracardiac and intravascular shunts before, during, and after interventional percutaneous cardiac catheterization	I	A
Prolonged fever, without apparent cause, in a patient with congenital heart disease	I	A
Functional murmur in an asymptomatic patient	IIb	C
Retarded growth in the absence of specific clinical abnormality	IIb	C
Atypical angina, identified as of musculoskeletal origin in an asymptomatic patient	III	
Syncope with abnormal electrocardiogram, exercise-related syncope	I	A
Syncope with family history of cardiomyopathy or sudden death	I	A
Neurocardiogenic (vasovagal) syncope	IIa	C
Effort angina or angina at rest with abnormal electrocardiogram	I	B
Angina associated with fever or use of illicit drugs	IIa	B
Presumably innocent murmur with signs and symptoms of heart disease	I	C
Central cyanosis	I	A
Chest wall deformity and preoperative scoliosis	IIb	C
Extracorporeal life support: initiation, maintenance, and weaning	I	B
Previous normal echocardiography with change in cardiovascular status and/or new family history suggestive of hereditary heart disease	IIa	C
Abnormal cardiac biomarkers	I	B
Hemoglobinopathies	I	B
Connective tissue diseases (Marfan, Loeys, Dietz, and others)	I	B
Muscular dystrophy	I	B
Autoimmune diseases	I	B
Arterial hypertension	I	A
Stroke	I	B
Metabolic, mitochondrial, or storage disease	I	B
Family history of cardiovascular disease: sudden death before 50 years of age, connective tissue diseases (Marfan or Loeys Dietz syndromes), idiopathic arterial hypertension	IIa	C
Family history of cardiovascular disease: hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy, hereditary pulmonary arterial hypertension	IIa	B

Table 5 – Recommendations for echocardiography in newborn infants, infants, children, and adolescents with acquired heart disease[9,16-31]

Recommendations	Recommendation class	Evidence level
Initial assessment and reassessments in patients with suspected or confirmed diagnosis of Kawasaki syndrome, Takayasu's Arteritis, myopericarditis, AIDS, and rheumatic fever	I	B
After heart or cardiopulmonary transplantation	I	B
Initial assessment and reassessments in patients treated with cardiotoxic chemotherapy and mediastinal radiotherapy	I	B
Initial assessment and reassessments in patients with myocardial disease	I	C
Assessment of cardiac involvement in severe kidney disease and/or systemic arterial hypertension	I	B
Assessment of donors for heart transplantation	I	C
Pulmonary arterial hypertension	I	A
Assessment of progression of pulmonary arterial hypertension treated with drugs or surgery	I	B
Initiation or withdrawal of extracorporeal cardiopulmonary support	I	C
Thromboembolic event	I	C
Sepsis, right heart failure, or cyanosis in a patient with venous catheter	I	B
Systemic or pulmonary embolization in a patient with right-left flow and venous catheter	I	C
Superior vena cava syndrome in a patient with venous catheter	I	C
Liver disease	IIa	C
Obesity with other cardiovascular risk factors or obstructive sleep apnea	IIa	C
Sepsis	IIa	B
Cystic fibrosis without evidence of cor pulmonale	IIa	C
Follow-up of patients after rheumatic fever without evidence of cardiac involvement	IIb	C
Cardiac assessment after pericarditis without evidence of recurrent pericarditis or chronic pericarditis	IIb	C
Fever in a patient with venous catheter without evidence of systemic or pulmonary embolization	IIb	C
Routine assessment for participation in competitive sports in patients with normal cardiovascular examination	IIb	C
Late follow-up of Kawasaki syndrome without evidence of coronary abnormalities in the acute phase	III	C
Routine assessment in an asymptomatic patient with venous catheter	III	C

7.1. Transesophageal Echocardiography as a Diagnostic Tool

Transesophageal echocardiography should be adopted to improve diagnostic definition of heart disease in situations in which better anatomic evaluation is needed in certain specific congenital heart diseases, in the majority of cases in adults, since in children the image quality of transthoracic echocardiography is generally good (Table 7).

7.2. Intraoperative Transesophageal Echocardiography

The most important impact of transesophageal echocardiography in the operating room is detection of significant residual defects that are very often unsuspected. Several authors have reported putting patients back on extracorporeal circulation to review surgery after intraoperative TEE, with rates that vary from 6 to 11.4% of cases, in the different series analyzed.[46]

The indications for intraoperative TEE for congenital heart disease are listed in Table 8.

7.3. Transesophageal Echocardiography in the Intensive Care Unit (ICU)

In the immediate postoperative period, the definition of TEE images may be compromised by drains, dressings, meshes, and mechanical ventilation, making it necessary to use TEE, which can provide anatomic (residual lesions) and hemodynamic information that is important for clinical and therapeutic management of patients (Table 9).

7.4. Transesophageal Echocardiography in the Catheterization Laboratory

Transesophageal echocardiography is helpful during hemodynamic interventions, providing diagnostic details in a range of heart diseases and for monitoring procedures, in addition to providing anatomic information on the results and on possible residual lesions[47] (Table 10).

Table 6 – Recommendations for echocardiography in adults with congenital heart disease[9,29,36,38-44]

Recommendations	Recommendation class	Evidence level
Initial structural and functional assessment in suspected congenital heart disease because of murmur, cyanosis, poor arterial saturation, or abnormal electrocardiogram or chest X-ray findings	I	C
Changes in the clinical status of a patient with known congenital heart disease, whether operated or not	I	C
Doubts with regard to original diagnosis or unexplained structural or hemodynamic abnormalities in a patient with known congenital heart disease	I	C
Follow-up of patients with intraventricular communication for assessment of evolving morphological changes	I	C
Periodic follow-up of patients with congenital heart disease, operated or not, in whom assessment of contraction, valve, and conduction function is needed	I	C
Postoperative annual follow-up after total, partial, or palliative repair in patients with residual defects and sequelae that could compromise clinical progress	I	C
Identification of the origin and initial course of the coronary arteries	I	C
Assessment of unexplained post-exercise syncope for initial diagnostic definition	I	C
Evaluation of aortic injury in patients with suspected or confirmed Marfan Syndrome for serial assessment of the aorta and/or mitral valve	I	C
Periodic examinations in patients operated for PDA, ASD, VSD aortic coarction or bicuspid aortic valve, without residual defect and without changes in clinical condition	III	C
Follow-up of patients with heart diseases without hemodynamic significance and without changes in clinical condition	III	C
Assessment of lesions in the aortic arch, pulmonary arteries and collateral arteries, the anatomy of which is better defined using other diagnostic methods	III	C
Periodic assessment of cardiac malformations without changes in physical examination findings, in the clinical condition of the patient, or in other examinations such as electrocardiogram and chest X-ray	III	C

ASD: atrial septal defect; PDA: patent ductus arteriosus; VSD: ventricular septal defect.

Table 7 – Recommendations for transesophageal echocardiography as a diagnostic tool[9,45]

Recommendations	Recommendation class	Evidence level
Confirmation or exclusion of a relevant clinical diagnostic suspicion not observable using TTE	I	A
Insufficient anatomic and hemodynamic information using TEE, primarily in children with chest deformities or obesity and in adults with congenital heart disease	I	A
Assessment of PFO as a possible etiology of central or peripheral embolic events in young patients (< 60 years), with agitated saline contrast to determine the possibility of right-left flow. To assess PFO risk factors for stroke/TIA: interatrial septum aneurysm, passage of > 30 microbubbles from right atrium to left atrium, PFO tunnel > 10 mm, and prominent Eustachian valve	I	A
Assessment of PFO before placement of a transvenous pacemaker	I	A
Classification, dimensions, and location of atrial septal defect, primarily in adult patients and those with poor transthoracic definition for selection of possible candidates for percutaneous occlusion and choice of occlusion device.	I	A
Assessment of aortic dissection in Marfan, Ehlers-Danlos, and Turner syndromes and in aortic coarctation	I	A
Assessment of the aorta in the Takayasu's Arteritis	I	A
Assessment of the intra or extra-cardiac tubes during the postoperative period after Senning, Mustard, or Fontan procedures	I	A
Assessment of thrombi, masses, vegetations, abscesses, and prostheses	I	A
For determination of the degree and mechanisms of mitral valve reflux to aid in surgical or percutaneous repair (Mitraclip)	I	B

PFO: patent foramen ovale; TEE: transesophageal echocardiogram; TIA: transient ischemic attack; TTE: transthoracic echocardiogram.

Table 8 – Recommendations for intraoperative transesophageal echocardiography[9,45-46]

Recommendation	Recommendation class	Evidence level
Perioperative assessment of cardiac anatomy and function	I	A
Monitoring of surgical procedures involving risk of abnormal flows, valve reflux, residual obstructions, or myocardial ventricular dysfunction	I	A
Minimally invasive surgery, video-guided surgery, and hybrid procedures	I	A

Table 9 – Recommendations for transesophageal echocardiography in the ICU[9,45]

Recommendation	Recommendation class	Evidence level
Assessment of residual defects, pericardial hemorrhage, and ventricular function in patients with a poor transthoracic acoustic window	I	A
Postoperative monitoring in a patient with an open sternum	I	A

Table 10 – Recommendations for Transesophageal Echocardiography in the Catheterization Laboratory[9,45,47]

Recommendation	Recommendation class	Evidence level
In percutaneous closure of patent foramen ovale, interatrial and interventricular communications	I	A
Postoperative closure of fenestrations after Fontan procedures	I	A
During dilatation of Senning and Mustard procedure tunneling	I	A
During stenting of stenosis of pulmonary arteries and tubes	IIb	B
For guidance in mitral valvoplasty and percutaneous mitral valve repair (Mitraclip)	I	A
For guidance in pulmonary and aortic valvoplasties	IIa	A
Placement of aortic endoprostheses to treat aneurysms, dissections, hematoma, or parietal ulcers of the thoracic aorta	I	A
Catheter guidance for perforation and percutaneous dilatation of atretic valves	I	A
During therapeutic interventional catheterization for radio frequency ablation	I	A

8. Stress Echocardiography in Pediatric Cardiology

Echocardiography under stress (physical or pharmacological) is a well-established technique in adults.[48,49] There are not yet specific guidelines or recommendations for the pediatric age group. However, as in the adult population, applications in children and adolescents have been concentrated on investigation of ischemic disease,[50-56] but are being extended to other areas that are not necessarily ischemic[55-63] (Table 7).

Both types of stress, pharmacological and exercise, can be administered to children, with certain peculiarities.[64-66] Dobutamine is the most common pharmacological agent and is used in the same protocols as with adult patients. In general, sedation or even anesthesia is recommended for children under the age of 8. Physical exercise can be used with children over the age of 8 who are cooperative and able to exercise on a treadmill or bicycle.[67]

9. Three-dimensional Echocardiography

Three-dimensional (3D) echocardiography has been incorporated into clinical practice, providing additional information in comparison to two-dimensional (2D) echocardiography, and is primarily used for congenital defects in which the three-dimensional view offers images very close to the anatomic and surgical planes.[68] The same concept is applicable to procedures undertaken in the catheterization laboratory, in which the three-dimensional view can be used not only to guide the procedures, but also to better evaluate the anatomy when choosing which devices to employ. Assessment of ventricular volumes and function has also been performed using the 3D technology, primarily to evaluate ventricular geometry in the most diverse forms of congenital defects, including univentricular hearts.[69,70] Atrioventricular valves can be assessed not only from the point of view of anatomic details, including the subvalvular apparatus, but also in terms of functional assessment of valve ring movement, and interactions between movement of valve leaflets and chords.[71]

When dealing with pediatric patients, the larger transthoracic acoustic window is a great advantage. More recently, more advanced transducers have been developed with a smaller footprint and higher frequency (2 to 8 MHz). However, the image

quality is still not the same when a 2D-3D combination is used with the same transducer, particularly in small patients. Another significant challenge that remains to be overcome is development of a pediatric transesophageal transducer, which limits 3D TEE to use in patients weighing more than 30 kg, according to manufacturers' recommendations. In small children, use of a pediatric transducer with higher frequency is recommended, as well as the epicardial echocardiogram, for intraoperative scenarios. Three-dimensional transesophageal echocardiography should always by considered in larger patients (generally weighing more than 30 kg) if transthoracic 3D imaging does not yield sufficient information to plan surgery or other interventions.

In a variety of different congenital defects, 3D echocardiography can provide additional information on a wide range of anatomic structures, including atrial and ventricular septa, the semilunar and atrioventricular valves, and also the outflow tracts. Applications are expanding as technological progress advances and adaptations are made to suit the pediatric population. Currently, use is based more on clinical need for additional information than on randomized studies showing the advantage of 3D over 2D. Use is therefore individualized and depends on the profile of the imaging laboratory or hospital adopting the technology for specific lesions.

Valve lesions and isolated septal defects are the principal indications. However, in situations in which there are concomitant anomalies of the ventriculoarterial connection, as in double-outlet right ventricle, the position and size of the intraventricular communication can be better visualized and demonstrated with 3D echocardiography.

Depending on the area or structure assessed by transthoracic and/or transesophageal 3D echocardiography, it may provide relevant information that complements the findings of 2D echocardiography.[72-83] Little additional information is yielded by using 3D echocardiography to assess the pulmonary arteries, the pulmonary valve, and even the right ventricle outflow tract and the aortic arch (Table 12).

Three-dimensional echocardiography can provide additional information in the context of certain specific congenital heart disease in which there are connection anomalies (atrioventricular or ventriculoarterial)[76,84-86] (Table 13).

Application of 3D echocardiography in the catheterization laboratory for closure of atrial and ventricular septal defects complements 2D images for delimiting the margins of defects and related structures,[87,88] specifically in atrial communications of the type ostium secundum, which are very well demonstrated by real-time imaging with 3D transesophageal echocardiography. Closure of interventricular communications using percutaneous or transmural devices can also be guided and, primarily, assess nearby structures, such as, for example, leaflets and/or tricuspid valve chords. There are other applications in the catheterization laboratory in which 3D echocardiography can be used to guide procedures: closure of fenestrations in the Fontan procedure, coronary fistulae, ruptures of the sinus of Valsalva, paravalvular regurgitation, septal perforation, and location of electrodes for cardiac resynchronization.[89-94]

A major challenge in congenital heart disease is evaluation of ventricular volumes and function, because of reasons that are intrinsic to the congenital defects involved (position of the heart, connection anomalies, non-contractile material, and differences in ventricular preload, among others). The software packages available were developed on the basis of the left ventricular geometry of normal hearts, which can often invalidate the information obtained using 3D systems. Although measurements of volumes and ejection fractions are replicable, 3D echocardiography has shown smaller volumes than MR when quantifying volumes, which prevents one from being substituted for the other. As a result, clinical application is still complicated by the absense of values for normality in the pediatric population. It is not recommended that software developed for the normal left or right ventricle be used with congenitally malformed ventricles until new software or models have been validated.[70,95-97]

The general recommendation for use of 3D transthoracic echocardiography in pediatrics is that the decision should be taken in accordance with the type of patient and the profile of the echocardiography laboratory and/or hospital.

Table 11 – Recommendations for stress echocardiography in pediatric cardiology

Recommendation	Recommendation class	Evidence level
To investigate coronary failure in children after late heart transplantation	IIa	B
Late assessment in Kawasaki disease with coronary abnormalities in the acute phase	IIa	B
During the postoperative period after Jatene procedure and the postoperative periods of abnormal origin and course of coronary arteries, and coronary-cameral fistulae	IIa	B
Ventricular function in myocardiopathy and mitral and aortic valve failure	IIa	B
Screening for ventricular dysfunction in patients treated with chemotherapy regimens including anthracyclines and after transplant, to test myocardial function during exercise	IIa	B
To investigate coronary failure in children with pulmonary atresia with intact ventricular septum, dyslipidemia, insulin-dependent diabetes mellitus, or supravalvular aortic stenosis	IIb	B
Evaluation of pressure gradient behavior in hypertrophic cardiomyopathy and pulmonary and aortic valve stenosis	IIb	B
Evaluation of myocardial reserve in the late postoperative period after atrial switch surgery for great vessel transposition, right ventricle assessment in late postoperative period of tetralogy of Fallot surgery	IIb	B

Table 12 – Additional information yielded by 3D echocardiography on specific anatomic structures and recommendations[72-78,80-82,87,88,91]

Anatomic structure of interest	Modality	Additional information	Recommendation class	Evidence level
Interatrial septum	TTE/TEE	Dimension, format, and location of defect(s)	I – Complex or residual defects II – Central and single defects	B B
Tricuspid valve	TTE/TEE	Morphology of leaflets, subvalvular apparatus (chords), location of regurgitation jets	I	B
Mitral valve	TTE/TEE	Morphology of leaflets, subvalvular apparatus (chords), location of regurgitation jets	I	B
Interventricular septum	TTE/TEE	Dimension, format, and location of complex defect(s)	I	B
LV outflow tract	TTE/TEE	Morphology of subaortic obstruction	I	B
Aortic valve	TTE/TEE	Aortic valve measurements, morphology of leaflets, regurgitation mechanism	I	B
RV outflow tract	TTE/TEE	Morphology and visualization of site of obstruction	III	C
Pulmonary valve	TTE	Morphology	IIa	C

LV: left ventricle; RV: right ventricle; TEE: transesophageal echocardiogram; TTE: transthoracic echocardiogram.

Table 13 – Additional information yielded by 3D echocardiography on congenital defects and recommendations71,79,83-86

Congenital heart disease	Modality	Additional information	Recommendation class	Evidence level
AVSD	TTE/TEE	Dimension of atrial and/or ventricular defect; morphology of leaflets and subvalvular apparatus; assessment of regurgitation jets; dimensions of orifices and ventricles in unbalanced defects	I	B
Discordant AV connection	TTE/TEE	Morphology and function of tricuspid and mitral valves, location and dimensions of related VSD morphology of outflow tracts of the RV and LV	I	B
Complex TGA	TTE/TEE	Morphology and function of tricuspid and mitral valves, location and dimensions of the VSD, anatomy of RV and LV outflow tracts in cases of obstruction	I	B
Tetralogy of Fallot	TTE	Dimension and location of CIV and anatomy of RV outflow tract	III	C
Truncus Arteriosus	TTE/TEE	Morphology of truncal valve*	III	C
Double-outlet RV	TTE	Relationship of atrioventricular valves, position and size of the VSD with the great arteries	III	C

*AV: atrioventricular; AVSD: atrioventricular septal defect; TEE: transesophageal echocardiogram; TGA: transposition of the great arteries; TTE: transthoracic echocardiogram; VSD: ventricular septal defect. *Specifically for assessment of the truncal valve in older patients.*

There is consensus that 3D is a modality that complements rather than substitutes 2D echocardiography, irrespective of the type of disorder.

10. Myocardial Deformation Imaging in Pediatric Patients

Myocardial deformation (strain) is proving to be a useful tool for evaluation of diastolic and systolic function, in both adults and the pediatric population.[98] Myocardial strain analysis by speckle tracking imaging is a method that is independent of the angle of insonation and has low intraobserver and interobserver variability, enabling global and regional ventricular function to be quantified more accurately than with more traditional methods, such as tissue Doppler, fractional shortening, or ejection fraction.[99] Some studies have shown that strain obtained by speckle tracking has high prognostic value, underscoring its utility for both congenital and acquired pathologies.[100]

Notwithstanding, myocardial strain is subject to physiological variations caused by age, sex, heart rate, preload, arterial blood pressure, and body surface area, in addition to the type of software used for the analysis.[101] Efforts are ongoing to establish normal values for strain that can be used as a universal reference in pediatrics, so that myocardial deformation analysis can be incorporated into guidelines and start to be adopted in clinical routines.[102-104] Meanwhile, myocardial deformation imaging has recommendation class II and evidence level B for use in the many different pediatric diseases.

10.1. Ventricular Strain in Acquired Heart Diseases in Childhood

Analysis of right and left ventricular strain is particularly useful in situations in which the intention is to identify systolic and/or diastolic dysfunction while in the subclinical phase. The information obtained from strain analysis makes opportune

therapeutic intervention possible in a range of systemic diseases with myocardial involvement.

Early detection of myocardial damage secondary to use of anthracyclines is one of the most important contributions of myocardial deformation imaging to date and has been incorporated into protocols for monitoring patients in oncology.[105-108]

A correlation has been demonstrated between the degree of inflammatory activity and the values of LV strain and systolic and diastolic LV strain rate in patients with rheumatic diseases, such as childhood-onset systemic lupus erythematosus.[20]

Other studies have confirmed the efficacy of strain obtained using the speckle tracking technique for detection of myocarditis of both autoimmune and viral etiology.[109,110] In cases of dilated cardiomyopathy in children, the pattern of regional compromise of LV strain influenced the outcome of death or transplantation, as demonstrated by Forsha et al.[111] Another use for strain in cases of dilated cardiomyopathy is to detect dyssynchrony, identifying cases that could benefit from resynchronization.[111]

After orthotopic heart transplantation in children, strain analysis has reasonable sensitivity and specificity for identifying which individuals will manifest vascular graft disease in later years.[112] Some reports, including small numbers of transplanted children, suggest there is an association between reduced segmental strain and rejection in endomyocardial biopsies, suggesting the technique could become a less invasive diagnostic instrument in the near future.[113-115]

In young patients with Duchenne muscular dystrophy, studies have demonstrated a significant reduction in longitudinal and radial strain of the inferolateral and anterolateral walls of the LV, even before ejection fraction is compromised or symptoms of heart failure emerge.[116] Several studies have demonstrated improved cardiovascular performance and 10-year survival in patients with Duchenne muscular dystrophy who were put on angiotensin-converting enzyme inhibitors and beta blockers as soon as the first echocardiographic signs of myocardial deterioration were detected, while still asymptomatic from a cardiovascular point of view.[117]

Myocardial strain imaging can also contribute to detection of myocardial compromise in storage disorders such as the mucopolysaccharidoses (MPS)[118] and Pompe disease.[119] Studies have focused attention on myocardial strain as a parameter for assessment of the impact of long-term enzyme replacement on the ventricular function of patients with these diseases.[120]

Myocardial strain analysis has also emerged as a possible method for early diagnosis of myocardial inflammation and ventricular dysfunction in Kawasaki disease.[51] McCandless et al.[121] found evidence that longitudinal LV strain was reduced on initial echocardiograms of patients with Kawasaki who later developed coronary dilation or exhibited resistance to treatment with immunoglobulin. These findings suggest that LV strain could soon come to be used as a tool for risk stratification in Kawasaki patients.[121]

In cases of myocardial dysfunction induced by pediatric sepsis, LV longitudinal and circumferential strain appear to already be reduced in the initial phases, even though ejection fraction is still unimpaired.[122]

In adult patients with chronic renal failure (CRF), reduction of LV longitudinal strain has been confirmed even in initial stages of the disease and with unimpaired ejection fraction. This early compromise of myocardial deformation has been attributed to fibrosis induced by chronic inflammation and uremic toxins. Additionally, the endothelial dysfunction that occurs in CRF may cause an inappropriate vasodilator response, leading to ischemia in an already hypertrophic ventricle. Similar findings have also been documented in pediatric populations, although it remains to be established whether this reduction in longitudinal LV strain can be used as a specific predictor of morbidity and mortality in children with CRF.[123]

Cardiovascular disorders are common among people with HIV infection, but are frequently underdiagnosed and left untreated, which impacts on patients' quality of life and on long-term mortality. They have been attributed both to the direct effects of the virus and to the effects of antiretroviral medications on the myocardium and vasculature. Symptomatic systolic dysfunction is normally only observed in more advanced cases of the acquired immunodeficiency syndrome.[124] More recent studies with children and young adults confirm compromised longitudinal RV and LV strain, in patients who are still asymptomatic and have normal LV ejection fraction. In 2016, these results prompted Naami et al. to suggest that myocardial deformation imaging should be included in echocardiographic examinations of pediatric patients with HIV, with the objective of identifying patients with subclinical dysfunction and increased cardiovascular risk.[125]

In a study that enrolled adolescents and young adults with thalassemia who underwent multiple transfusions, Chen et al.[126] identified a negative correlation between serum ferritin and longitudinal LV strain. Additionally, even after correction for sex, age, serum ferritin, and ventricular mass index, longitudinal LV strain remained an independent predictor of adverse events in thalassemic patients, such as heart failure, arrhythmia, and death (HR: 6.05; $p = 0.033$).[127]

Okumura et al. investigated children and adolescents with idiopathic pulmonary hypertension (IPH), confirming the prognostic value of serial assessment of longitudinal RV strain in the pediatric population. A strain value lower than -14% on the initial echocardiogram identified patients who progressed to lung transplant or death with 100% sensitivity and 54.5% specificity. They concluded that myocardial deformation in pediatric IPH is a more sensitive tool than conventional parameters for evaluation of RV function (TAPSE – tricuspid annular plane systolic excursion, FAC – fractional area change, tricuspid S wave velocity) to detect patients with worse prognosis.[127] In a recent publication, Hooper et al.[128] confirmed the utility of longitudinal RV strain in clinical follow-up of IPH in children, demonstrating that strain values had an excellent correlation with BNP – B-type natriuretic peptide values, in the course of treatment with prostacyclin analogues.[13] Table 14 lists recommendation classes and evidence levels.

10.2. Ventricular Strain in Congenital Heart Disease

Analysis of longitudinal RV strain in a subpulmonary position proved feasible and reproducible for perioperative assessment of several congenital heart disorders.[129] However, in the presence of significant residual obstruction during the postoperative period (PO), parameters for evaluation of the longitudinal RV systolic function, such as TAPSE, S wave velocity, and longitudinal peak systolic strain, did not exhibit adequate correlations with ejection fraction according to MR. In situations with residual pulmonary stenosis or a combination of stenosis and pulmonary failure, RV hypertrophy causes a predominance of circumferential fibers, changing the deformation pattern of this chamber, which is habitually more dependent on longitudinal fibers.[130] Hayabuchi et al.[131] evaluated RV free wall circumferential peak systolic strain in the subcostal view, specifically in children with congenital heart disease with RV pressure overload. Using this method, they found a better correlation between strain values and ejection fraction in the RV.[131] Studies with asymptomatic children in the late postoperative period after surgery for tetralogy of Fallot (T4F) identified compromised biventricular longitudinal systolic peak strain. Some authors found a negative correlation between RV longitudinal systolic peak strain and RV ejection fraction and the pulmonary regurgitation fraction, both estimated by MR.[132] Other studies have documented a negative correlation between LV longitudinal strain and the degree of pulmonary regurgitation, emphasizing the importance of ventricle interdependence.[133] Although myocardial deformation imaging can detect subclinical systolic dysfunction in postoperative T4F patients who progress to pulmonary regurgitation, unfortunately there is not yet any consensus on a strain cutoff value that can indicate the best timing for pulmonary valve replacement.

Table 14 – Recommendations for ventricular strain analysis in acquired heart diseases of childhood[20,51,105-128]

Indication	Recommendation class	Evidence level
Cardiotoxicity in pediatric oncology	IIa	B
Autoimmune and viral myocarditis	IIa	B
Dilated cardiomyopathy: selection for resynchronization therapy	IIa	B
Vascular graft disease after heart transplantation	IIb	B
Rejection after heart transplantation	IIb	B
Muscular dystrophies (e.g. Duchenne)	IIa	B
Storage diseases (e.g. Pompe and MPS)	IIa	B
Kawasaki disease	IIa	C
Sepsis	IIb	B
Chronic renal failure	IIb	B
HIV/AIDS infection	IIa	B
Chronic anemias (e.g. thalassemia)	IIa	B
Pulmonary hypertension	IIa	B

AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; MPS: mucopolysaccharidoses.

Patients with the RV in the systemic position also exhibit abnormal myocardial deformation patterns, with predominance of contraction of circumferential fibers. In this condition, the discrete reduction of longitudinal strain is indicative of changes to right ventricular geometry, and not of true systolic dysfunction. This is an adaptive mechanism, which makes contractility of the systemic RV similar to LV contractility. Recent publications therefore suggest a normal range of longitudinal systolic peak strain values in systemic RV that are below those expected for subpulmonary RV (–10% to –14.5%).[130] Longitudinal RV strain values below –10% have been associated with occurrence of adverse events, in the late PO after Senning procedures.[134]

Selection of patients with a single ventricle (SV) for Fontan procedure surgery takes into consideration pulmonary vascular resistance and end-diastolic ventricular pressure. However, current indication criteria have proved fallible for a considerable proportion of these patients, who are subject to complications and extended hospital stays. When associated with pulmonary vascular resistance and end-diastolic ventricular pressure, the preoperative circumferential strain rate improves risk stratification for patients with SV who are candidates for Fontan surgery, irrespective of whether the ventricle has right or left morphology.[135]

In the case of Ebstein's anomaly, myocardial deformation imaging has little to contribute to right ventricular function assessment, since strain has a weak correlation with ejection fraction measured with MR.[136]

Castaldi et al.[137] have demonstrated the utility of left ventricle longitudinal strain to diagnosis of patients with coronary obstruction in late PO after correction of anomalous origin of the left coronary artery. A strain value < –14.8% on echocardiography identified myocardial segments with fibrosis on MR, with sensitivity of 92.5% and specificity of 93.7%.[137]

10.3. Right and Left Atrial Strain in Pediatrics

Analysis of right atrial mechanics using speckle tracking was recently introduced in pediatrics, emerging as a promising tool for detection of right ventricular dysfunction. Hope et al.[139] found a significant reduction in right atrium longitudinal strain in children with IPH. Atrial strain proved more sensitive and specific than conventional right ventricular function assessment parameters for identifying patients with IPH who would later develop unfavorable outcomes (death, pulmonary and/or cardiac transplant).[139]

Several studies have described the clinical implications of left atrial strain measurements using the speckle tracking technique. Left atrium strain in the reservoir phase proved more accurate for estimation of end-diastolic pressure of the LV than classical echocardiographic parameters such as left atrial volume and the E/E' ratio and was also inversely correlated with plasma NT-ProBNP levels.[140]

10.4. Prospects for Utilization of Ventricular Strain in the Fetus

Recent studies have suggested that analysis of myocardial deformation can also contribute to evaluation of biventricular systolic and diastolic function in fetuses. For example, Miranda et al. documented reduced early and late diastolic strain rate in the longitudinal axes of RV and LV in fetuses with diabetic mothers. Additionally, they also observed reductions in right ventricle longitudinal systolic peak strain in comparison with normal fetuses of the same gestational age. These authors pointed out that diastolic deformation compromise was irrespective of the presence of septal hypertrophy. They concluded that myocardial deformation analysis could detect subclinical changes in the fetuses of diabetic mothers before classical echocardiographic parameters are able to do so.[141]

Dusenbery et al.[138] confirmed the association between reduced LV longitudinal strain and presence of myocardial fibrosis, assessing children and young adults with aortic valve stenosis and preserved LV ejection fraction.[138] It is known that adults with aortic stenosis who have late enhancement on MR with gadolinium and reduced LV longitudinal strain values have higher mortality rates after valve interventions.[138] See Table 15 for recommendation classes and evidence levels.

Table 15 – Recommendations for ventricular strain in congenital heart disease[129-135,137]

Indication	Recommendation class	Evidence level
Functional evaluation of subpulmonary RV (e.g. T4F)	IIb	B
Functional evaluation of systemic RV (e.g. PO of Senning procedure, CCTGA)	IIb	B
Evaluation of SV before Fontan procedure	IIb	B
Evaluation of SV after Fontan procedure	IIb	B
Assessment of LV after ALCAPA surgical repair	IIa	B
Evaluation of LV function in aortic stenosis	IIb	B

ALCAPA: anomalous left main coronary artery from the pulmonary artery; CCTGA: congenitally corrected transposition of the great arteries; LV: left ventricle; PO: postoperative; RV: right ventricle; SV: single ventricle; T4F: tetralogy of Fallot.

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Brazilian Cardio-oncology Guideline – 2020

Development: Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC)

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Brazilian Cardio-oncology Guideline – 2020	
The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these update, 2020.	
Expert	**Type of relationship with industry**
Ana Oliveira Hoff	FINANCIAL DECLARATION A - ECONOMICALLY RELEVANT PAYMENTS OF ANY KIND MADE TO (i) YOU, (ii) YOUR SPOUSE/PARTNER OR ANY OTHER PERSON LIVING WITH YOU, (iii) ANY LEGAL PERSON IN WHICH ANY OF THESE IS EITHER A DIRECT OR INDIRECT CONTROLLING OWNER, BUSINESS PARTNER, SHAREHOLDER OR PARTICIPANT; ANY PAYMENTS RECEIVED FOR LECTURES, LESSONS, TRAINING INSTRUCTION, COMPENSATION, FEES PAID FOR PARTICIPATION IN ADVISORY BOARDS, INVESTIGATIVE BOARDS OR OTHER COMMITTEES, ETC. FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Bayer: thyroid cancer - Exelixis: thyroid cancer - Eli Lilly: thyroid cancer - United B - RESEARCH FUNDING UNDER YOUR DIRECT/PERSONAL RESPONSIBILITY (DIRECTED TO THE DEPARTMENT OR INSTITUTION) FROM THE BRAZILIAN OR INTERNATIONAL PHARMACEUTICAL, ORTHOSIS, PROSTHESIS, EQUIPMENT AND IMPLANTS INDUSTRY: - Exelixis: thyroid cancer - Eli Lilly: thyroid cancer
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João Cesar Nunes Sbano	Nothing to be declared
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Content

1. Introduction

Cardiovascular disease (CVD) and cancer are currently the leading causes of mortality worldwide and in Brazil.[1-3] The recent demographic and epidemiological transitions in Brazil have determined an increase in the population's life expectancy, today around 76 years, and a change in the health profile, in which chronic diseases and their complications prevail.[4]

These factors pose important challenges and require the development of a health policy agenda for the management of the ongoing transitions. The technological advances, the shortage of cost-effectiveness analyses and, in higher education settings, the little value attributed to health access and promotion, as well as to disease prevention, require the implementation of guidelines and consensus statements. These guidelines and consensus statements are aimed at helping the use of systematized protocols to adapt the clinical practice regardless of the geographic location of the health facilities and the heterogeneity of their resources.

Recent advances in cancer detection and treatment have resulted in an exponential increase in the number of cancer survivors around the world. According to a recent estimate, by 2026, the United States will have 20 million cancer survivors, 50% of whom will be older than 70 years.[5,6] The care of an older population with history of cancer and CVD, compounded by the potential cardiovascular toxicity of the oncological treatment, requires specialists in the 'cancer-CVD' interaction.[7]

In 1967, anthracycline-induced cardiotoxicity was first described.[8] In 1971, a study reported that anthracycline-induced cardiotoxicity was dose-dependent and that the cardiac damage might be irreversible.[9] Some years later, risk factors for chemotherapy-related ventricular dysfunction were identified, and biomarkers, such as troponin and B-type natriuretic peptide (BNP), were related to the prediction of cardiovascular events.[10,11] Those findings were the cornerstone of cardio-oncology.

Cardio-oncology is the field of science devoted to the early diagnosis and proper management of CVD in patients with the current or previous diagnosis of cancer. Furthermore, cardio-oncology comprises the analysis of not only the cardiovascular risks related to the oncological diagnosis, but also the patient's needs before, during and after the treatment. Cardio-oncology specialists should follow patients up since their diagnosis, through all treatment phases, and even after their cure, when the patients are called cancer survivors. The need for expansion of cardio-oncology relates directly to the epidemiology of cancer and CVD, the risk factors they share, and the multiplicity of treatments with distinct toxicities to the cardiovascular system (Figure 1).[12,13]

In 2011, the Brazilian Society of Cardiology (SBC) and the Brazilian Society of Clinical Oncology (SBOC) pioneered in joining forces to publish the I Guideline on Cardio-Oncology.[14] In 9 years, cardio-oncology has significantly grown as a discipline because of the following factors: a) remarkable advances in cancer treatment; b) understanding of multidisciplinarity and integration of cardiology, oncology and hematology as essentials for the care of cancer patients; c) implementation of fellowship programs across the world and insertion of 'cardio-oncology' in the curriculum of some cardiology residency training programs; d) growth of research in basic and clinical areas; and e) creation of important journals dedicated to the subject, such as *JACC CardioOncology* and *Cardio-Oncology*.[15,16]

It is worth noting that, in 2019, Brazil hosted the *V Global Cardio-Oncology Summit*, to which specialists from several countries and approximately 600 professionals (cardiologists, oncologists, hematologists, nurses, physical therapists, pharmacists, physical educators) attended. The journal *Frontiers in Cardiovascular Medicine* published 89 abstracts, and the *JACC CardioOncology* published *"Proceedings From the Global Cardio-Oncology Summit - The Top 10 Priorities to Actualize for CardioOncology"*.[17,18]

The SBC and the SBOC, aiming at knowledge updating and promotion of a rational and systematic approach to cardiovascular complications in oncology patients, have gathered a team of experts to create new strategies, issue evidence-based recommendations, and develop multiprofessional healthcare, which will provide the proper management of that increasing category of patients.

The goals of the *Brazilian Cardio-Oncology Guideline - 2020* are as follows: 1) to demystify the belief of CVD as a barrier to the effective treatment of cancer patients; 2) to prevent and reduce the risks of treatment-related cardiotoxicity; 3) to promote the interaction among medical specialties (cardiology, hematology and oncology) to agree the best strategy for

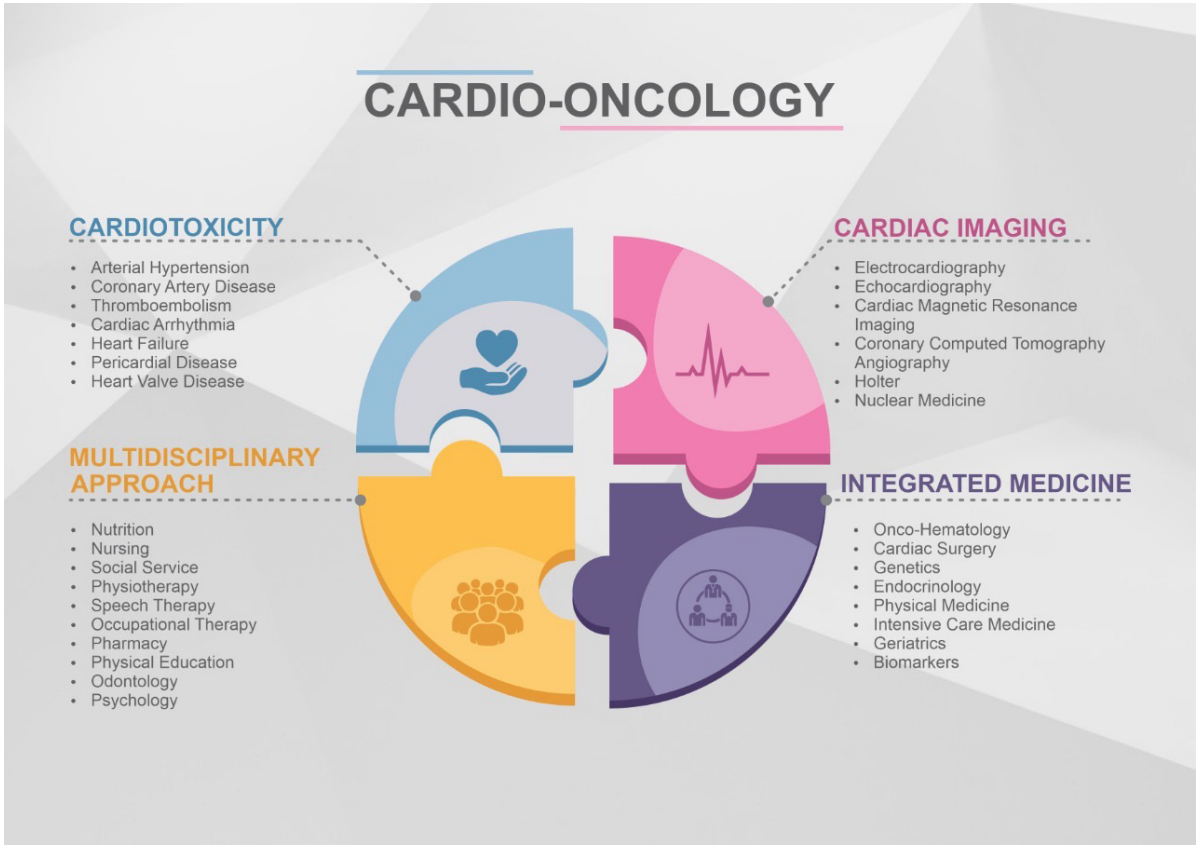


Figure 1 – *The current frontiers of cardio-oncology.*

patient's care, weighing the risks and benefits of the treatment; 4) to propose the unification of terminologies and definitions of the cardiovascular complications of cancer patients, aiming at homogenizing care and research; 5) to disclose the evidence available on the management of cardiovascular complications in oncology patients, aiming at their early diagnosis by use of cardiovascular function monitoring before, during and after the treatment; 6) to promote proper treatment, with the participation of oncologists and hematologists, based on scientific evidence, risk analysis and care personalization, considering the patient's preferences; and 7) to boost research and knowledge spread in cardio-oncology (Figure 1).

The *Brazilian Cardio-Oncology Guideline - 2020* gathers evidence on the cardiovascular complications of cancer patients available up to 2020.

2. Methods

The *Brazilian Cardio-Oncology Guideline - 2020* abided by the ongoing recommendations. A team of experts in cardiology, hematology and oncology formed a committee to elaborate this manuscript. Participants were chosen based on their prominence in their fields, their participation in the International Cardio-Oncology Society (ICOS), SBC and SBOC, in addition to their scientific production.

A bibliographic search was conducted in PubMed in the period from 1975 to July 2020 with the following keywords: *cardiotoxicity, cancer, immunotherapy, cardiooncology, cardiovascular complications, targeted therapy, radiotherapy, vascular toxicity, heart failure, ventricular dysfunction, pericardial disease, coronary disease, thromboembolism, arrhythmias, hypertension, individual drug names*. The manuscript was sent electronically to all participants, and, after they all agreed on its content, it was formatted and sent to publication.

The classes of recommendation and levels of evidence used in this guideline were as follows:

Classes of recommendations:

Grade I – there is conclusive evidence, or, failing that, a consensus that the procedure is safe and useful/effective.

Grade II – there is conflicting evidence and/or divergent opinions on the safety and utility/effectiveness of the procedure:

- Grade IIA: weight of the evidence/opinion is in favor of the procedure. Most experts approve;
- Grade IIB: safety and utility/effectiveness are less well established, with no predominance of opinions in favor.

Grade III – there is evidence and/or expert consensus that the procedure is not useful/effective and, in some cases, can even be harmful.

Levels of Evidence:

Level A – data obtained from multiple, large, concordant randomized studies and/or robust meta-analyses of randomized clinical studies.

Level B – data obtained from a less robust metaanalysis, based on a single randomized trial or on non-randomized (observational) studies.

Level C – data obtained from consensus expert opinions.

3. Diagnosis and Management of Cardiovascular Complications in Cancer Patients

3.1. Initial Cardiological Assessment

The different types of cancer treatment, such as chemotherapy, immunotherapy, and radiotherapy, can result in damage to the cardiovascular system. Patients with previous CVD or cardiovascular risk factors have the highest likelihood of complications from cancer treatment. Thus, the treatment and control of cardiovascular risk factors in cancer patients are recommended.[19-21]

The consultation of cancer patients with a cardiologist should comprise the control of cardiovascular risk factors, cardioprotective measures, adhesion to treatment, and a strategy to enable the early diagnosis of cardiac damage (I, B).

Patients with cardiovascular risk factors or already established CVD and who will undergo a potentially cardiotoxic treatment [anthracyclines, anti-HER2 (human epidermal growth factor receptor 2) agents, alkylating agents, inhibitors of vascular endothelial growth factor (VEGF) signaling, proteasome inhibitors and immune checkpoint inhibitors (ICIs)] should be assessed by a cardiologist at the beginning of therapy and followed up according to specific protocols (I, B). Table 1 shows the antineoplastic treatments most associated with cardiovascular toxicity. Figure 2 shows the factors associated with a higher risk for cardiotoxicity.

The multiprofessional team assessing the cancer patient should weigh the risks and supposed benefits of the therapy and implement strategies to prevent cardiovascular damage (IIa, C).

Measuring and approaching the cardiovascular risk factors according to consensus and guidelines are recommended (I, A).

In the initial cardiological assessment, the following are recommended: anamnesis, physical examination, electrocardiogram (ECG), chest X-ray, complete blood count, measurement of electrolytes and biomarkers [N-terminal pro-BNP (NT-proBNP) and troponin I or high-sensitivity troponin T], folic acid, vitamins D and B12, glycemia, lipid profile, as well as kidney, liver and thyroid function (I, A) (Figure 3).

In addition, in baseline and serial assessment according to the treatment regimen, transthoracic echocardiography with color Doppler, ideally three-dimensional, is recommended, with analysis of left ventricular ejection fraction (LVEF), diastolic function, and myocardial deformation with strain quantification by use of the speckle tracking technique (I, A).

Collaboration between cardiologists, oncologists and hematologists is recommended to ensure the proper and beneficial treatment to cancer patients (IIa, A).

3.2. Diagnosis of Cardiotoxicity in Cancer Patients

Cardiotoxicity can be diagnosed by confirming the presence of a new cardiovascular alteration (clinical and/or in biomarkers and/or in imaging) during or after treatment, once other etiologies have been excluded (I, B).

Echocardiography is the method of choice to detect myocardial dysfunction related to the oncological treatment. Three-dimensional echocardiography is the best echocardiographic method to measure LVEF in cancer patients. When not available or in the presence of limitations, biplane Simpson method is recommended (I, A).

Ventricular dysfunction related to cancer therapy is defined as a reduction ≥ 10% in LVEF to a value below the lower limit of the normal range (LVEF < 50%). A new cardiovascular imaging test should be performed in 2 to 3 weeks (I, B).

That LVEF reduction occurs in the course of treatment, and can be classified as symptomatic or asymptomatic and reversible or irreversible (I, B).

Global longitudinal strain (GLS) is a highly sensitive tool to predict later LVEF reduction. A GLS reduction ≥ 15% in regard to baseline is considered abnormal and an early marker of ventricular dysfunction (I, B).

Diastolic function analysis is recommended in oncological patients, both before therapy starts and during follow-up (IIa, C). However, there is no evidence that the treatment should be interrupted based on diastolic function.

Radionuclide ventriculography is not recommended for ventricular function assessment in cancer patients (III, B).

Cardiac magnetic resonance imaging (CMRI) is the gold-standard method to assess cardiac function. It enables structural assessment and tissue characterization, being recommended when echocardiography cannot be performed, in the presence of infiltrative diseases, for pericardial and myocardial evaluation, and for the detection of masses and tumors (IIa, B). In addition, CMRI can assess prognosis by analyzing myocardial fibrosis.

The routine use of biomarkers during a potentially cardiotoxic treatment has not been well established. Monitoring cardiotoxicity by measuring biomarkers can be considered for the early detection of myocardial damage in patients at high risk due to previous factors or those exposed to drugs, such as anthracyclines and trastuzumab (IIa, B). Neither the best time for measuring biomarkers regarding chemotherapy (during chemotherapy, 24 hours after, 48 hours after or later) nor the best management when high levels of biomarkers are detected are known. In addition, in the course of treatment, the same analysis kits of biomarkers, such as high-sensitivity troponin and NT-proBNP assays, should be used (IIa, C).

High levels of biomarkers (NT-proBNP and troponin) indicate increased risk for cardiotoxicity (I, A).

On initial assessment and throughout treatment, ECG should be performed. The QTc should be calculated by using Bazett's [QT / $(RR)^{1/2}$] or Fridericia's [QT / $(RR)^{1/3}$] formula, and the same method should be used for the patient's serial assessment. In cancer

Table 1 – Antineoplastic therapies associated with cardiovascular toxicity

Classes of antineoplastic drugs	Cardiovascular toxicity
Radiotherapy	Myocardial ischemia and infarction Pericardial disease Heart valve disease Myocarditis Cardiac arrhythmia
Anthracyclines (doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone)	Heart failure Asymptomatic ventricular dysfunction Myocarditis Pericarditis Atrial and ventricular arrhythmias
Alkylating agents (cyclophosphamide, ifosfamide, melphalan)	Arrhythmias Ventricular dysfunction Coronary artery disease
Platinum drugs (cisplatin, carboplatin, oxaliplatin)	Coronary thrombosis Myocardial ischemia Arterial hypertension
Antimetabolite drugs (5-fluorouracil, capecitabine)	Myocardial ischemia Coronary vasospasm Atrial and ventricular arrhythmias
HER2-targeted therapies (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)	Heart failure Asymptomatic ventricular dysfunction Arterial hypertension
Inhibitors of VEGF signaling: • Tyrosine kinase inhibitors (sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib) • Monoclonal antibodies (bevacizumab, ramucirumab)	Arterial hypertension Heart failure Asymptomatic ventricular dysfunction Myocardial ischemia and infarction QTc prolongation
• Multi-targeted tyrosine kinase inhibitors: Second- and third-generation BCR-ABL tyrosine kinase inhibitors (ponatinib, nilotinib, dasatinib, bosutinib)	Arterial thrombosis (myocardial infarction, stroke and occlusive peripheral vascular disease*) Venous thromboembolism Arterial hypertension Heart failure Asymptomatic ventricular dysfunction Atherosclerosis** QTc prolongation** Pulmonary hypertension***
Other multi-targeted tyrosine kinase inhibitors: • ALK inhibitors (crizotinib, ceritinib) • PI3-AKT-mTOR inhibitors (everolimus, sirolimus) • Bruton's tyrosine kinase inhibitors (ibrutinib) • EGFR tyrosine kinase inhibitor (osimertinib)	Bradycardia, QTc prolongation Hyperglycemia, dyslipidemia Atrial fibrillation Heart failure, atrial fibrillation, QTc prolongation Atrial fibrillation, heart failure
Therapy of multiple myeloma: Proteasome inhibitors (carfilzomib, bortezomib, ixazomib) Immune modulators (lenalidomide, thalidomide, pomalidomide)	Heart failure**** Asymptomatic ventricular dysfunction**** Myocardial ischemia and infarction Atrial and ventricular arrhythmias Venous thromboembolism Arterial thrombosis Arterial hypertension
BRAF and MEK inhibitors: (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)	Heart failure Asymptomatic ventricular dysfunction Arterial hypertension QTc prolongation*****
Antiandrogen therapies: • GnRH agonists (goserelin, leuprolide) • GnRH antagonists (degarelix) • Antiandrogens (abiraterone)	Atherosclerosis Myocardial ischemia and infarction Diabetes mellitus Arterial hypertension
Immune checkpoint inhibitors: (nivolumab, ipilimumab, durvalumab, pembrolizumab, atezolizumab, avelumab)	Myocarditis Heart failure Atrial and ventricular arrhythmias Myocardial ischemia

**Associated with ponatinib, **Associated with ponatinib and nilotinib, ***Associated with dasatinib, ****Associated with carfilzomib, *****Associated with vemurafenib and cobimetinib. EGFR: epidermal growth factor receptor; GnRH: gonadotropin releasing hormone; HER2: human epidermal growth factor receptor 2; QTc: corrected QT; T-DM1: ado-trastuzumab emtansine; VEGF: vascular endothelial growth factor.*

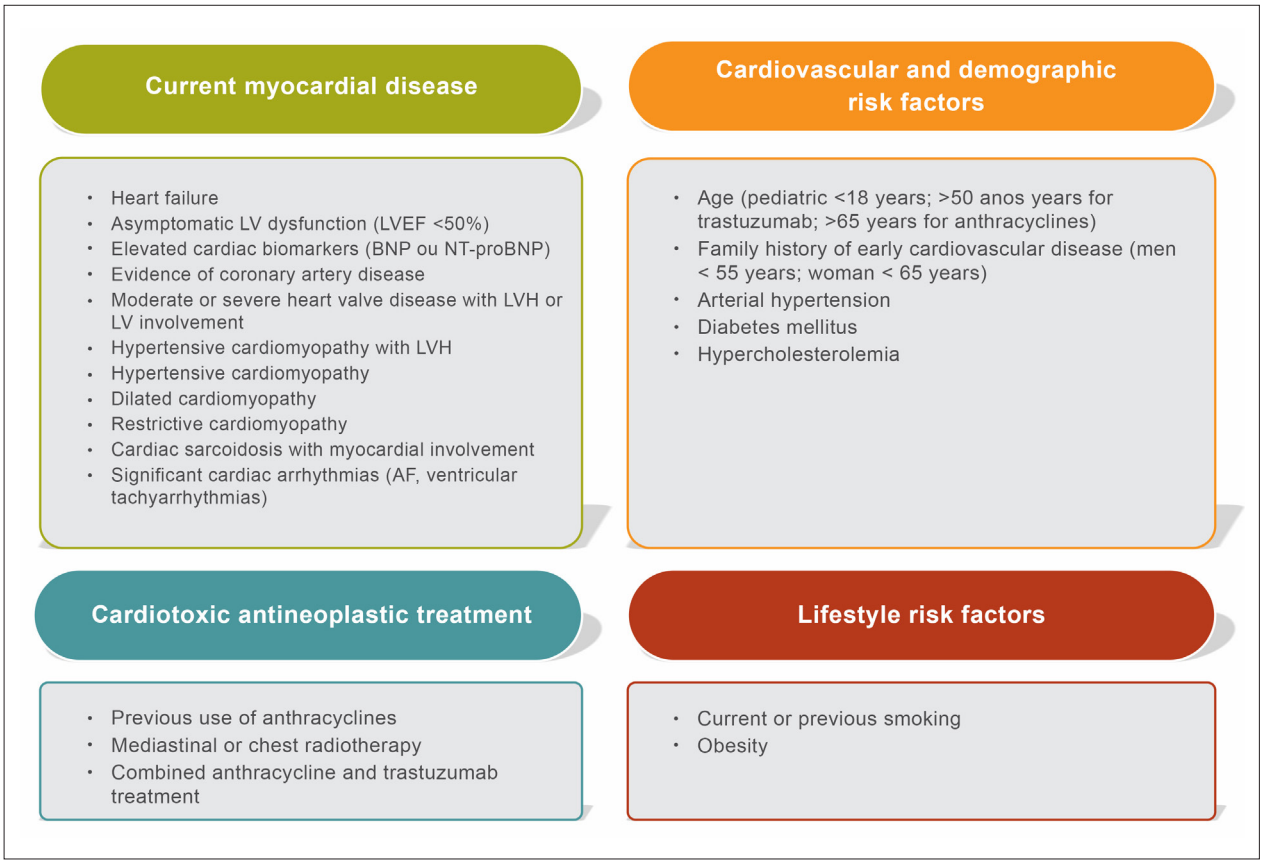


Figure 2 – *Predisposing factors for the development of cardiotoxicity in cancer patients. Adapted from Zamorano et al.[22]*
AF: atrial fibrillation; BNP: B-type natriuretic peptide; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

patients, the Fridericia's formula is preferred, because it undergoes less change in the presence of tachycardia or bradycardia (IIa, C).

Table 2 describes the cardiovascular diagnostic methods and their major advantages, uses, and limitations.

4. Ventricular Dysfunction

Ventricular dysfunction is one of the most severe complications from cancer treatment, characterized by high morbidity and mortality rates. It may appear during therapy or years after completion of therapy and even so be consequent to drug toxicity.[23] The classic model of ventricular dysfunction as a form of cardiotoxicity is secondary to the use of anthracyclines, which are widely used to treat sarcoma, lymphoma, leukemia, and breast cancer.[24,25]

The different chemotherapy and immunotherapy drugs associated with ventricular dysfunction result in different phenotypes in patients, ranging from asymptomatic mild and reversible dysfunction to severe, clinically manifest and irreversible heart failure (HF). Pediatric cancer survivors are up to 15 times more likely to develop HF than controls matched for other risk factors.[26]

Predicting cardiotoxicity is a challenge, because of the multiplicity of drugs to which patients are exposed throughout life, in addition to the often-present cardiovascular risk factors. It is worth noting the multiple drug interactions of the different therapeutic regimens, such as those of anthracyclines with cyclophosphamide and anthracyclines with trastuzumab.

In recent years, with the introduction of new chemotherapy drugs and the advent of immunotherapy, in addition to the introduction of protocols for early detection of cardiotoxicity, ventricular dysfunction has been increasingly diagnosed. Table 3 shows the antineoplastic drugs more often associated with ventricular dysfunction.

4.1. Anthracyclines

Anthracyclines consist in a group of antineoplastic drugs known to be effective in treating sarcoma, lymphoma, leukemia, and breast cancer. Their clinical use is limited by cardiotoxicity characterized by ventricular dysfunction and HF, which are the main causes of mortality in cancer survivors.

The toxicity of anthracyclines is highly variable and can occur in up to 50% of the patients, depending on the patient's risk factors and the pharmacological properties of the chemotherapy drugs, such as cumulative dose. For example, doxorubicin is associated with a 5% incidence of HF at the cumulative dose of up to 400 mg/m^2, and that incidence can reach 50% if the dose exceeds 700 mg/m^2.[27] A recent study with 2625 patients in a 5-year follow-up has shown a 9% overall incidence of anthracycline-induced

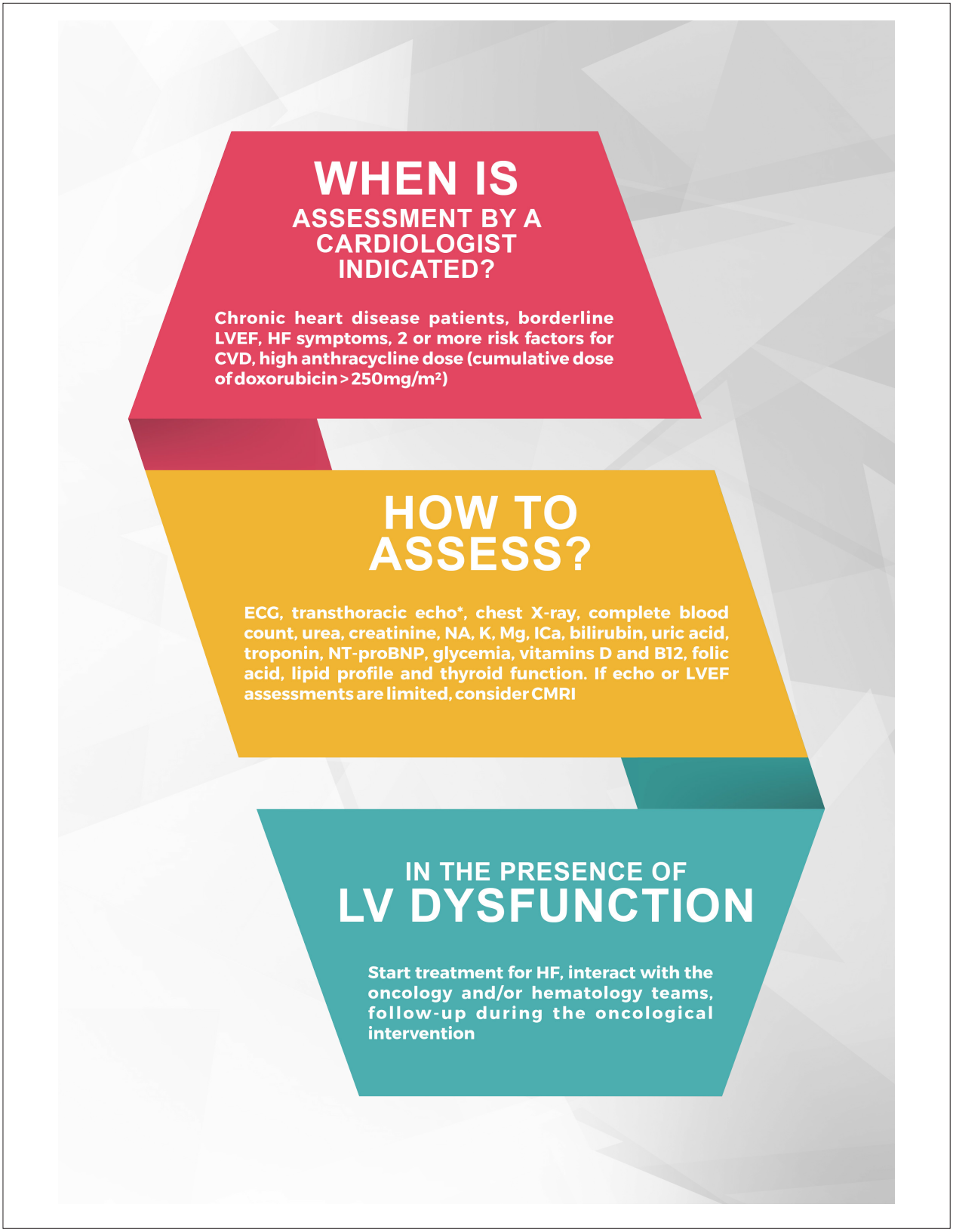


Figure 3 – *Initial cardiologist assessment. *Ideally combined with LVEF three-dimensional assessment and myocardial strain quantification by speckle tracking. CMRI: cardiac magnetic resonance imaging; CVD: cardiovascular disease; ECG: electrocardiogram; echo: echocardiography; HF: heart failure; Ica: serum ionic calcium; K: serum potassium; LV: left ventricular; LVEF: left ventricular ejection fraction; Mg: serum magnesium; Na: serum sodium; NT-proBNP: N-terminal pro-B-type natriuretic peptide; X-ray: radiography.*

Table 2 – Cardiovascular diagnostic methods and their major advantages, uses, and limitations

DIAGNOSIC METHOD	USES	ADVANTAGES	LIMITATIONS
Troponin I or T	• High levels are associated with cardiotoxicity • Can be used for patients at high risk for cardiotoxicity	• Availability • Low cost • High sensitivity	• The ideal time for collection is not clear
BNP or NT-proBNP	• Extremely high levels may suggest decompensated HF • Can be used for patients at high risk for cardiotoxicity	• Availability • Low cost	• Several factors of cancer patients can rise NT-proBNP levels
Electrocardiography	• Indicated for all patients undergoing a potentially cardiotoxic therapy • QTc should be calculated using Bazett's or Fridericia's formula	• Low cost • Availability • May aid the differential diagnosis	• Limited role in cancer patients
2D echocardiography	• Indicated for all patients undergoing a potentially cardiotoxic therapy • LVEF should be assessed using Simpson method • Adding 2D-STE can predict LVEF drop • Contrast medium use enhances diagnostic accuracy	• Low cost • Availability • Allows to assess diastolic function and valves	• Acoustic window • May overestimate LVEF
3D echocardiography	• Effective method for serial assessment of LVEF in cancer patients on cardiotoxic therapy	• Similar accuracy to that of CMRI	• Limited availability • High cost • Requires trained professionals
Cardiac magnetic resonance imaging	• Gold-standard method to assess LVEF • Indicated for diagnostic confirmation, patients with borderline LVEF or with limitation on echocardiographic assessment	• Allows tissue characterization by use of sequences, such as T1/T2 mapping and extracellular volume • Provides the differential diagnosis with other cardiomyopathies • The presence of fibrosis has prognostic implications	• Limited availability • High cost
Radionuclide ventriculography	• Indicated for LVEF confirmation in patients with limited echocardiographic window	• High accuracy • Reproducibility	• Exposure to radiation

2D: two-dimensional; 3D: three-dimensional; LVEF: left ventricular ejection fraction; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; HF: heart failure; STE: Speckle Tracking Echocardiography.

cardiotoxicity, and 98% of the cases were asymptomatic and occurred in the first year.[24]

Cardiotoxicity can be acute, early or late, reversible or irreversible. Acute toxicity is characterized by the presence of supraventricular arrhythmia, left ventricular dysfunction and electrocardiographic changes, which appear right after anthracycline infusion in up to 1% of the patients, being usually reversible. Acute ventricular dysfunction can be a predictor of HF, which can be subacute or chronic. Early cardiotoxicity appears in the first year of treatment, while late cardiotoxicity appears years after treatment, on average, 7 years after completion of treatment.[28]

There is no predictor of the reversibility/irreversibility of the anthracycline-induced toxicity. However, the elevation in the levels of biomarkers and its persistence can identify patients at high risk for irreversibility.[29]

The tendency towards cardiotoxicity varies with the different treatment regimens, and doxorubicin is the anthracycline most associated with ventricular dysfunction. Cardiotoxicity is dose-dependent, and reducing the cumulative dose is a way to minimize it. Changes in infusion, such as prolonging its duration, splitting the dose and using liposomal formulations, can prevent cardiotoxicity.[24] A recent experimental study has suggested that ischemic preconditioning might prevent doxorubicin-induced cardiotoxicity.[30]

Mechanistic studies have shown that anthracycline-induced ventricular dysfunction is associated with: 1) damage to the sarcoplasmic reticulum and mitochondria; 2) changes in myofibrillar structure and function; 3) total or partial loss of matrix interspersed with collagen plaques in the interstitium; 4) change in the excitation-contraction coupling and calcium flow; 5) apoptosis; 6) changes in iron metabolism; and 7) loss of the regeneration capacity of the cardiac muscle and coronary endothelial cells. The consequence is dysfunction and hypertrophy of the remaining myocytes.[31] The common trigger for those events seems to be related to the oxidative stress caused by the production of reactive oxygen species, in addition to the inhibition of topoisomerase 2β, resulting in damage to membranes, proteins and DNA. The following observations support the importance of oxidative stress in anthracycline-induced cardiotoxicity: a) over-expression of metallothionein, a free radical scavenger, in the heart of transgenic mice minimizes the doxorubicin-induced injury; b) inhibition of the formation of peroxynitrite, a reactive oxidant produced from nitric oxide and superoxide, improves the cardiac function of mice exposed to doxorubicin; c) probucol, a strong antioxidant, prevents glutathione peroxidase reduction and reduces doxorubicin-related myocardial lipid peroxidation in a murine model; d) dexrazoxane is a chelating agent like EDTA that can prevent anthracycline damage via iron binding, which acts as a cofactor for free radicals.[32] Diastolic dysfunction due to cumulative dose-dependent toxicity can be observed with a cumulative dose of 200 mg/m^2, while systolic dysfunction is usually observed with doses over 400 mg/m^2, with variability according to an individual threshold. However, impaired diastolic function has been observed with the cumulative dose of only 120 mg/m^2.[33]

Table 4 shows the risk factors associated with a higher likelihood of anthracycline-induced toxicity, of which previous heart disease, cumulative dose and fast drug infusion stand out. However, in the presence of the same risk factors, there is an important variability in the occurrence of cardiotoxicity among patients, which might be related to genetic factors and interactions with unknown factors.

Polymorphisms in ATP-binding cassette (ABC) transporter genes are associated with anthracycline cardiomyopathy. Those transporters play an important role in drug resistance via cellular efflux of drugs, including anthracyclines. Reduced activity can lead to intracellular accumulation of anthracycline and cellular toxicity. Variants in that family of genes replicated in cohorts of

Table 3 – Chemotherapy drugs associated with ventricular dysfunction

Chemotherapy drugs	Incidence (%)
Anthracyclines (dose-dependent)	
Doxorubicin (Adriamycin) 400 mg/m^2 550 mg/m^2 700 mg/m^2	 3-5 7-26 18-48
Idarubicin > 90 mg/m^2	5-18
Epirubicin > 900 mg/m^2	0.9-11.4
Mitoxantrone > 120 mg/m^2	2.6
Liposomal doxorubicin >900 mg/m^2	2
Alkylating agents	
Cyclophosphamide	7-28
Ifosfamide < 10 g/m^2 12.5-16 g/m^2	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3-13
Paclitaxel	< 1
HER2 targeted therapies	
Trastuzumab	1.7-20.1
Pertuzumab	0.7-1.2
Monoclonal antibodies	
Bevacizumab	1.6-4
Tyrosine kinase inhibitors	
Sunitinib	2.7-19
Pazopanib	7-11
Sorafenib	4-8
Dasatinib	2-4
Imatinib	0.2-2.7
Lapatinib	0.2-1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11-25
Bortezomib	2-5

HER2: human epidermal growth factor receptor 2. Adapted from Zamorano et al.22

childhood cancer patients include *ABCC5* (A-1629T, rs7627754), associated with a significant LVEF reduction in T-allele homozygous survivors.[34] In addition, a variant in histamine methyltransferase *HNMT* (rs17583889) confers risk in young patients exposed to anthracyclines.[35] Table 5 shows the pharmacogenetic variants that predispose to anthracycline-related cardiotoxicity.

During treatment with anthracyclines, clinical and echocardiographic monitoring is recommended at a pre-established frequency or out of protocol in the presence of HF signs and symptoms.[21] Ideally, the echocardiographic assessment should comprise biventricular systolic and diastolic function analysis (I, A) (Figure 4).

4.2. HER2-targeted Therapies

Trastuzumab is a monoclonal antibody targeted at the human epidermal growth factor receptor 2 (HER2 or ErbB2). For 15-20% of the patients with breast cancer whose tumors over express HER2, therapy with trastuzumab significantly reduces mortality.[36,37]

Table 4 – Risk factors for anthracycline-related cardiotoxicity

Risk factors	High risk in the presence of	
Age	<18 years or >65 years	
Gender	Female	
Type of administration	Bolus injection	
Cumulative dose	Daunorubicin	550 - 800 mg/m²
	Doxorubicin	≥ 250 mg/m²
	Epirubicin	900 - 1000 mg/m²
	Idarubicin	150 - 225 mg/m²
Mediastinal irradiation	Early or concomitant mediastinal irradiation	
Previous cardiovascular diseases	Ischemic or non-ischemic cardiomyopathy, coronary artery disease, arterial hypertension	
Electrolyte disorders	Hypocalcemia, hypomagnesemia	
Ejection fraction	<50%	
Concomitant therapy	Trastuzumab, alkylating agents, signaling inhibitors	

Its use is associated with a considerable risk of cardiotoxicity, clinically manifested by an asymptomatic decline in LVEF and, less commonly, by symptomatic HF.[38] After the introduction of trastuzumab, three other anti-HER2 agents were developed: lapatinib, a tyrosine kinase inhibitor of the epidermal growth factor (EGFR), ERBB1 and HER2; ado-trastuzumab emtansine (T-DM1), a conjugated antibody composed by trastuzumab, a thioester linker and an antimitotic maytansine derivative; and pertuzumab, a monoclonal antibody that binds to the subdomain II of the HER2 extracellular domain and prevents HER2 homo- and heterodimerization with other HER receptors. Although data on those new drugs are scarce, there is evidence that T-DM1 and pertuzumab are less cardiotoxic than trastuzumab.[39]

The LVEF decline rate consequent to trastuzumab use varies in the literature. Recent studies have reported, in 15% to 40% of the patients on trastuzumab, a LVEF reduction of at least 10%, and, in 18% of the patients, a LVEF drop to less than 53%.[40,41] Symptomatic HF has been reported in 0.6% to 8.7% of patients.[40]

One difference between the toxicity of anti-HER2 agents and that of anthracyclines is the reversibility of the former in most cases. The determinants of reversibility are previous cardiovascular function and the extent of LVEF decline related to treatment. A recent study has shown that all LVEF declines smaller than 10% were reversible. However, for LVEF declines greater than 10%, reversibility was observed in 91% of the patients with normal baseline cardiovascular function as compared to only 71.4% of those with reduced LVEF prior to exposure.[42] Some studies have reported that, even in the presence of cardiotoxicity, 70% to 80% of patients continue receiving trastuzumab and that the highest likelihood of cardiovascular toxicity and mortality related to treatment is observed in patients with previously reduced LVEF.[43]

Trastuzumab-induced ventricular dysfunction and clinically manifest HF are usually reversible after chemotherapy interruption and/or after beginning HF treatment. The mechanisms of the anti-HER2 therapy-induced cardiotoxicity include structural and functional changes in contractile proteins and mitochondria, but rarely lead to cellular death, explaining the potential reversibility. The interruption of trastuzumab treatment is associated with an increase in cancer recurrence, and cardiotoxicity is the major responsible for drug suspension.[44]

Table 6 shows the risk factors for cardiotoxicity induced by anti-HER2 therapy.

During treatment with trastuzumab, clinical and echocardiographic monitoring is recommended according to protocol or in the presence of HF signs and symptoms (I, A) (Figure 5).

Tabela 5 – Variantes farmacogenéticas associadas à cardiotoxicidade das antraciclinas

Gene	rs	Biological process
ABCB1	rs1128503	Drug transportation
ABCC1	rs5511401 rs60782127 rs4148356	Drug transportation
CAT	rs10836235	Oxidative stress
CBR3	rs8133052	Drug metabolism
NCF4	rs1800566	Oxidative stress
NQO1	rs1800566	Energy use
NR1/2	NA	Regulation of drug metabolism and/or transportation and apoptosis
RARG	rs2229774	Derepression of the key genetic determinant Top2b, increasing oxidative stress
SLC22A16	rs714368	Higher exposure to drugs
TOP2A	NA	Regulation of DNA
HAS3	rs2232228	Oxidative stress
CELF4	rs1786814	Expression of abnormally spliced TNNT2 variants

4.3. VEGF Inhibitors

The inhibition of VEGF signaling pathways benefits thousands of cancer patients, but some chemotherapy drugs of that class are associated with the risk of cardiotoxicity, which can be reversible or irreversible, particularly in the presence of concomitant or previous use of other chemotherapy drugs.[45-47]

The relative risk of congestive HF in bevacizumab-treated patients was 4.74 (95% CI: 1.6-11.18; p = 0.001) compared to that of the placebo group.[45] In addition, other drugs, such as sunitinib, pazopanib and axitinib, have been associated with the development of ventricular dysfunction. A meta-analysis including 10 553 patients has reported congestive HF incidence of 3.2% (95% CI: 1.8% - 5.8%) with the use of VEGF tyrosine kinase inhibitors.[47]

Systemic arterial hypertension (SAH) is a common complication of that class of chemotherapy drugs, and some studies have suggested that the proper treatment of SAH might reduce the risk of HF.[48] The prognosis of patients who develop cardiotoxicity associated with VEGF inhibitors is hard to assess, because candidates for treatment with such drugs usually have metastatic disease and reduced life expectancy. Most cases reverse with the treatment of ventricular dysfunction. Table 7 shows the risk factors for cardiotoxicity.

4.3.1. BCR-ABL Tyrosine Kinase Inhibitors

The BCR-ABL tyrosine kinase inhibitors have changed the prognosis of patients with chronic myeloid leukemia and gastrointestinal stromal tumors. The cardiotoxicity of imatinib has not been confirmed; however, nilotinib and ponatinib may be associated with cardiotoxicity involving HF, SAH, arrhythmias and thromboembolism.[49]

4.4. Therapies for Multiple Myeloma

Proteasome inhibitors are relatively new drugs to treat multiple myeloma. Bortezomib and carfilzomib belong to this class of drugs and can cause cardiovascular dysfunction. Proteasomes are protein complexes responsible for degrading dysfunctional proteins, being essential for the cardiomyocyte survival. The incidence of bortezomib-related HF is 4% and it can be compounded by the use of steroids.[50] In addition to being irreversible, carfilzomib is

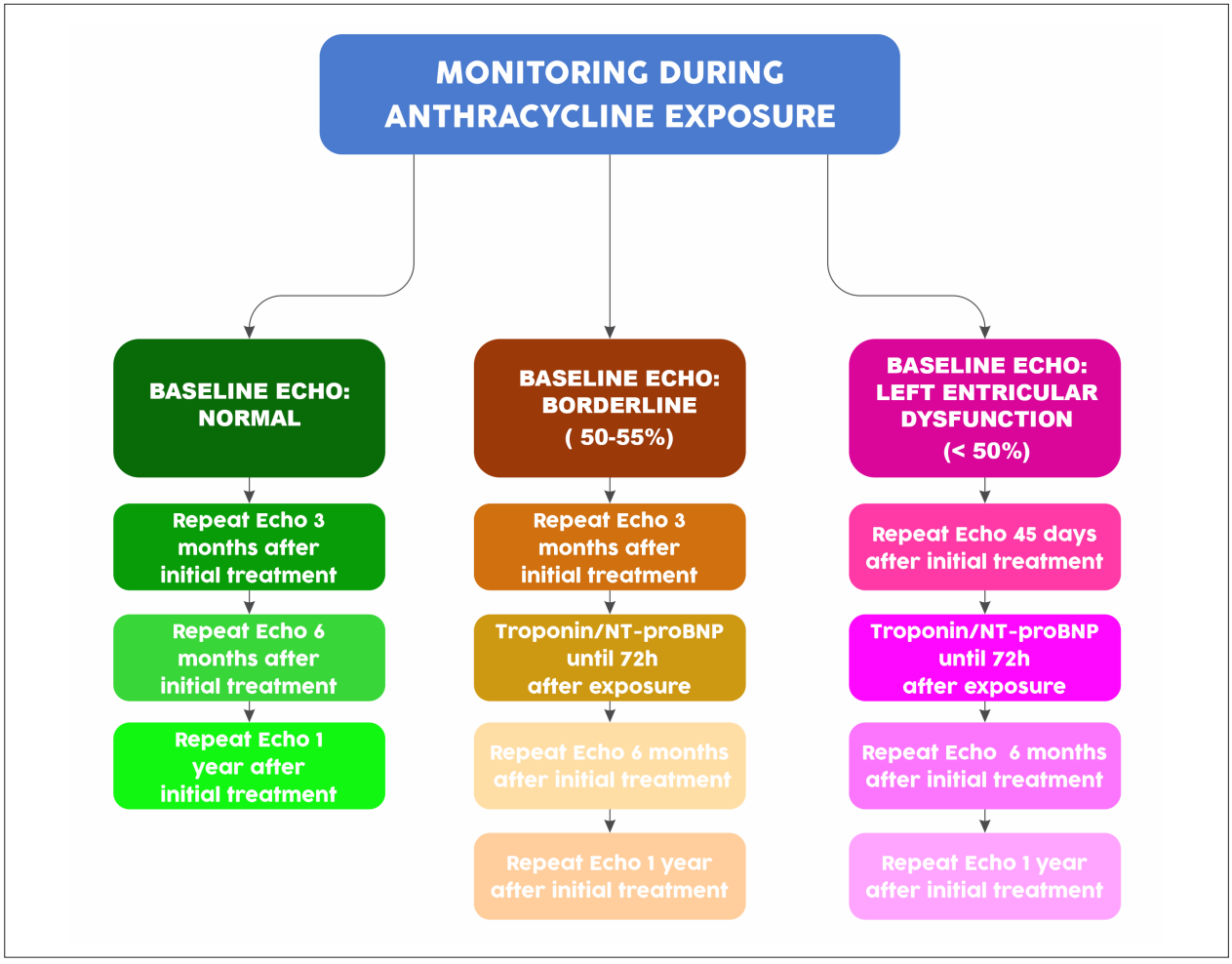


Figure 4 – *Echocardiographic monitoring and analysis of biomarkers in patients using anthracyclines. Echo: echocardiogram; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QT: chemotherapy.*

Table 6 – Anti-HER2 therapy and risk factors for cardiotoxicity

Agents	Risk factors for cardiotoxicity
Anti-HER2	• Previous or concomitant treatment with anthracycline
• Trastuzumab	• Age > 50 years
• Pertuzumab	• Body mass index > 30 kg/m^2
• T-DM1	• Previous left ventricular dysfunction
	• Arterial hypertension
	• Previous mediastinal radiotherapy

HER2: human epidermal growth factor receptor 2; T-DM1: ado-trastuzumab emtansine.

the most potent proteasome inhibitor and can cause HF in up to 25% of the patients.[51,52]

4.5. BRAF and MEK Inhibitors

The combined BRAF-MEK inhibitor therapy is currently the first choice for metastatic BRAF-mutant melanoma, because it significantly improves patients' survival. So far, three BRAF inhibitors (dabrafenib, vemurafenib and encorafenib) and three MEK inhibitors (trametinib, cobimetinib and binimetinib) have been approved for the treatment of melanoma.[53-55]

Several studies have reported cardiovascular adverse effects associated with those inhibitors, mainly LVEF reduction (5-11%), SAH (10-15%), and QT interval prolongation.[56,57] The inhibition of BRAF and MEK interferes with cardiovascular MAPK signaling, resulting in oxidative stress, cardiac myocyte apoptosis, and angiogenesis inhibition.[56,57]

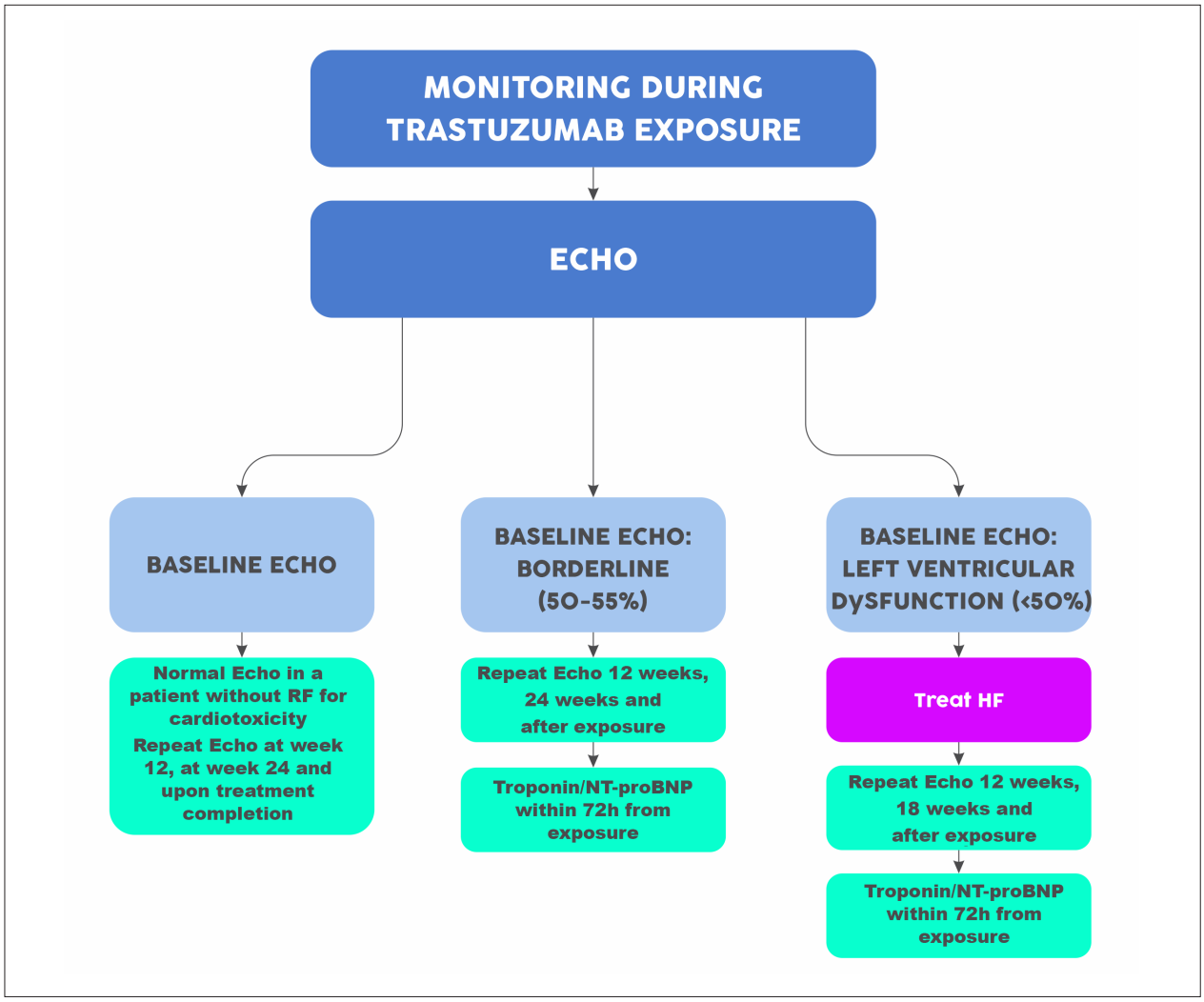


Figure 5 – *Echocardiographic monitoring and analysis of biomarkers in patients using anti-HER2 drugs. Echo, echocardiogram; RF, risk factors; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.*

A recent meta-analysis, including five randomized clinical trials and 2317 patients with melanoma and receiving BRAF and MEK inhibitors, has shown that the concomitant treatment with those inhibitors is associated with an increased risk for pulmonary embolism (4.4x), LVEF reduction (3.72x), and SAH (1.5x). There was no increase in the occurrence of arrhythmias, myocardial infarction, and QT prolongation. A higher risk for HF was detected in patients under the age of 55 years.[58]

4.6. Taxanes

Paclitaxel and docetaxel are used to treat several solid neoplasms. Cardiotoxicity is not frequent with this group of drugs, occurring in 12 out of 100 (RR: 0.9 [0.53 -1.54]).[59] Docetaxel, in particular, seems to be associated with an increase in the occurrence of ventricular dysfunction. Some reports have suggested that taxanes should be avoided in patients with previous ventricular dysfunction, and the same non-use criteria of anthracyclines apply. Taxanes have been reported to cause sinus bradycardia, atrioventricular blocks, ventricular tachycardia, and ventricular extrasystoles. However, because taxanes are used in combination with anthracyclines, determining their cardiotoxicity potential is challenging.[36,60]

4.7. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have revolutionized cancer treatment. The ICIs modulate the immune system, inhibiting the apoptosis of T lymphocytes, restoring the antitumor cell response. Their anti-apoptotic action comprises the inhibition of CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PDL-1 (atezolizumab, durvalumab, avelumab) (Figure 6).[61]

The cardiotoxicity of ICIs can be divided into two categories: inflammatory adverse effects (myocarditis, pericarditis, and vasculitis) and non-inflammatory cardiovascular toxicity (Takotsubo-like syndrome, asymptomatic non-inflammatory ventricular dysfunction, and arrhythmias). Most cases reported

Table 7 – Therapy with VEGF inhibitors and risk factors for cardiotoxicity

VEGF Inhibitors	
Antibodies • Bevacizumab • Ramucirumab	Pre-existing HF, coronary artery disease, heart valve disease, ischemic heart disease Previous use of anthracycline
Tyrosine kinase inhibitors • Sunitinib • Pazopanib • Axitinib • Neratinib • Afatinib • Sorafenib • Desatinib	Arterial hypertension Pre-existing heart disease

HF: heart failure.

are severe, with mortality rates of 50% in myocarditis, 21% in pericardial disease, and 6% in vasculitis.[62] The major causes of mortality from myocarditis are arrhythmias and cardiogenic shock.[62-64]

The adverse events usually occur after the first or second dose of ICIs, but sporadic cardiovascular events have been reported up to 32 weeks after treatment. The prevalence of cardiovascular involvement is higher in patients on combined therapy, of the female sex, and older than 75 years. The prevalence of myocarditis varies from 0.06% to 0.3%.[62,63]

For patients who develop new cardiovascular symptoms during or right after treatment with ICIs or who have arrhythmia, conduction system abnormality or ventricular dysfunction on the echocardiogram, initiating cardiovascular investigation with measurement of biomarkers (troponin, NT-proBNP and C-reactive protein), ECG, viral panel test, strain echocardiography and CMRI is recommended to confirm the diagnosis and exclude viral myocarditis (IIa, C).

Endomyocardial biopsy should be considered in case of diagnostic suspicion even when the initial investigation is negative (IIa, C).

5. Radiotherapy

The current incidence of radiation-induced cardiotoxicity is hard to estimate, among other reasons, because of the long interval between exposure and the clinical manifestation of cardiotoxicity, the concomitant use of cardiotoxic chemotherapy, and the progressive improvement in radiation techniques in recent years with the consequent reduction in the incidence of cardiac structural damage. Some studies have reported relative risk of fatal cardiovascular events varying from 2.2% to 12.7% in lymphoma survivors and from 1% to 2.2% in breast cancer patients.[65,66] Among survivors exposed to radiotherapy, the risk of ventricular dysfunction increases 4.9 times.[66] Radiation-related cardiotoxicity is more frequent in patients with left-sided breast cancer[67] and in those on the concomitant use of anthracyclines. The radiation-induced injury can affect the cardiac muscle, valves, pericardium, coronary arteries and conduction system,[68] and can be diagnosed 10 to 15 years after radiotherapy.

6. Cardiotoxicity Prevention and Treatment

a) Cardiotoxicity should be prevented in all cancer patients and the cardiovascular risk factors should be recognized since the initial consultation. The following measures are recommended: smoking and alcoholism cessation, implementation of a regular diet aimed at maintaining a proper weight (body mass index between 18 and 24 kg/m^2), physical exercise practice (moderate aerobic activity for 30 minutes per day at least 5 times per week), SAH control, treatment of diabetes and dyslipidemia (I, B).

b) Angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the drugs of choice to treat SAH. Statins are recommended to treat dyslipidemia, aiming at maintaining LDL levels below 100 mg/dL. Metformin is the drug of choice to treat diabetes and, when HF is associated, SGLT2 inhibitors (empaglifozin, dapaglifozin, canaglifozin) should be used. In the presence of coronary artery disease (CAD), GLP-1 agonists (liraglutide, dulaglutide and semaglutide) should be preferred (IIa, C).

c) When assessing the therapeutic proposal, the risk factors for cardiotoxicity should be identified and specific measures implemented according to the regimen (IIa, C).

d) For patients with subclinical cardiotoxicity [troponin elevation or SLG reduction (absolute ≥ 5% or relative ≥ 15%)]:

• the use of ACEI or ARB or beta-blocker can be considered, aiming at preventing ventricular dysfunction and cardiovascular events (IIa, B);

• repeat strain echocardiography every 3 months and measurement of biomarkers every cycle, if asymptomatic, or at any time, if symptoms appear (IIa, C);

• chemotherapy should not be suspended based on alterations in strain and biomarkers (IIa, C);

consider referring the patient to the cardio-oncologist (IIa, C);

• consider ruling ischemic heart disease out (IIa, C);

• consider initiating dexrazoxane in patients who will undergo high doses of anthracyclines and at high risk for cardiotoxicity (IIa, B).

e) For patients with LVEF ≤ 50% and ≥ 40%, therapy with ACEI/ARB and beta-blocker is recommended before initiating a cardiotoxic treatment (I, A).

f) Patients with LVEF ≤ 40% should not receive therapy with anthracycline unless there is no effective treatment option (IIa, A).

g) Patients on chemotherapy or immunotherapy, who develop HF and LVEF < 40% during treatment, should have their antineoplastic treatment suspended temporarily based on the discussion with the cardiologist and the oncologist, and therapy for HF should begin based on guidelines and consensus statements (I, A).

h) Patients on potentially cardiotoxic drugs, who develop HF signs or symptoms, should be referred to the cardio-oncologist for clinical assessment, echocardiography, and measurement of biomarkers (IIa, C).

i) Figures 7 and 8 show the algorithms that should be considered for the management of ventricular dysfunction induced by anthracyclines and anti-HER2 (IIa, B).

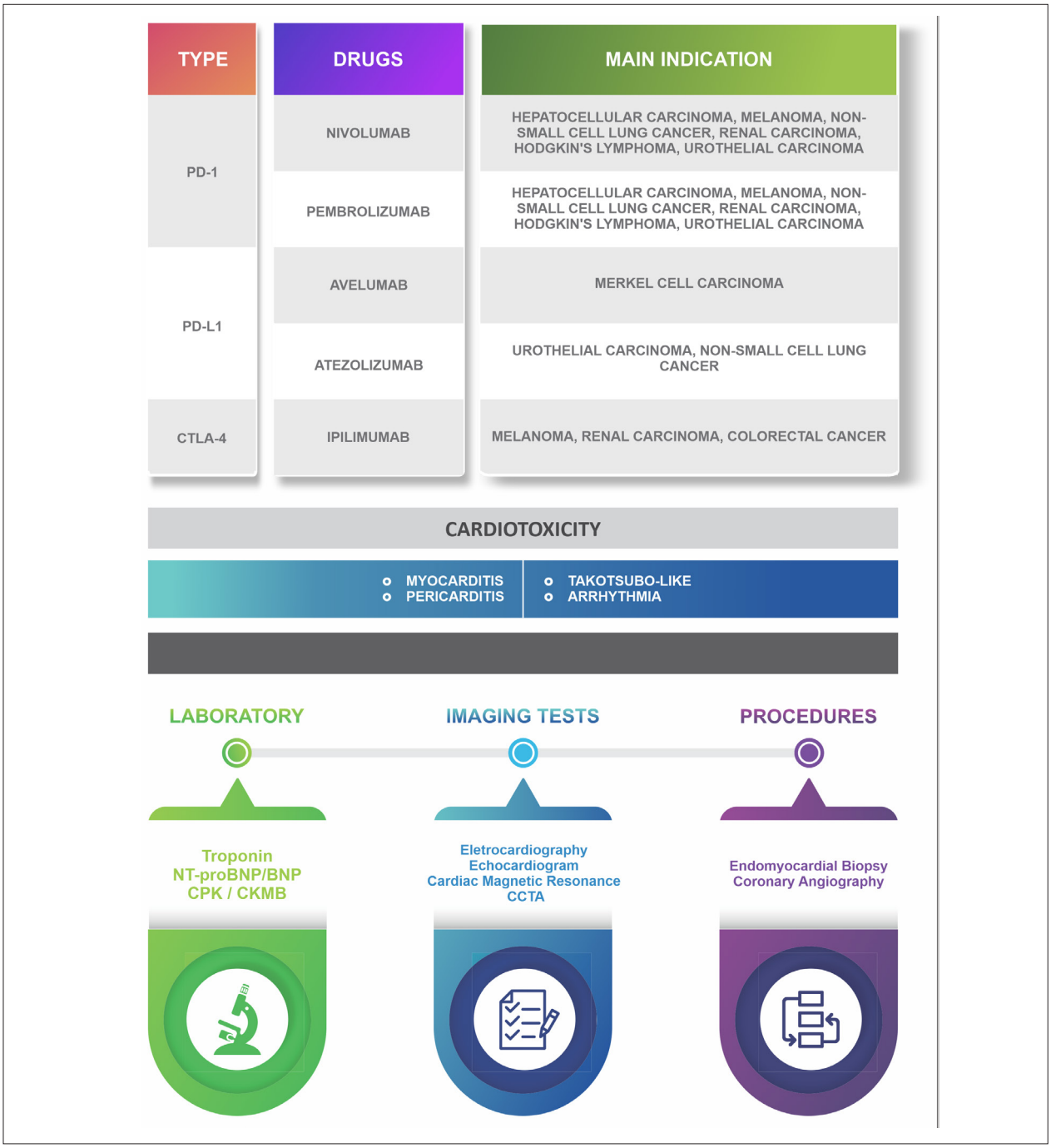


Figure 6 – *Major immune checkpoint inhibitors related to cardiotoxicity and its management.*

j) For patients with trastuzumab-induced cardiotoxicity, after symptom stabilization and LVEF recovery to > 40%, trastuzumab reintroduction should be considered, provided that the patient is followed up by a cardio-oncologist, with serial assessment by use of echocardiography and biomarkers (IIa, B).

k) For patients with trastuzumab-induced cardiotoxicity, if symptoms do not improve and LVEF persists below 40%, trastuzumab should only be reintroduced if there is no therapeutic alternative and after thorough discussion with the oncologist (IIa, C).

l) For patients on sunitinib or other anti-VEGF drug, SAH assessment and proper control are recommended (IIa, C).

m) For patients on monoclonal antibodies or anti-VEGF tyrosine kinase inhibitors (bevacizumab, sunitinib, sorafenib, axitinib and pazopanib), the highest risk for HF occurs at the beginning of therapy. In the presence of signs and symptoms, the patient should be assessed with echocardiography and

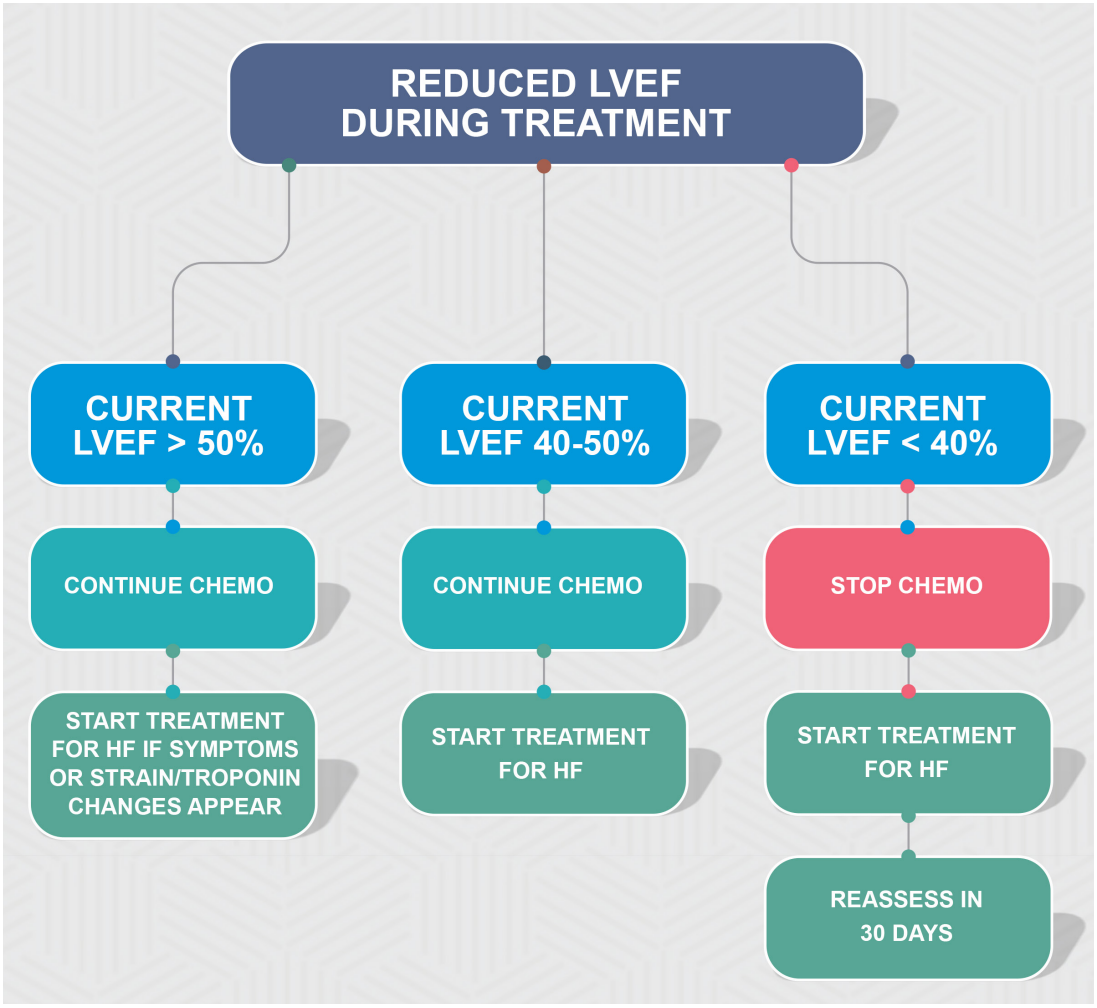


Figure 7 – *Algorithm for the management of heart failure and ventricular dysfunction induced by anthracyclines. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

measurement of biomarkers (IIa, B). Cardio-oncologist consultation, HF treatment initiation, and discussion of drug suspension with the oncologist are recommended (IIa, C). After clinical and LVEF recovery, consider resuming chemotherapy (IIa, C).

n) For patients with HF or ventricular dysfunction, drug treatment should be instituted according to guidelines (I, A).

o) The indication for circulatory assistance device or heart transplantation follows the Brazilian Guideline on Acute and Chronic Heart Failure recommendations. Before the indication, the patient's *status* and oncological prognosis should be discussed with the oncologist, always considering the patient's preferences.

p) The indication for heart transplantation of cancer patients follows the Brazilian Guideline on Acute and Chronic Heart Failure recommendations (Table 8). However, patients with acute or chronic HF should only be considered for transplantation when meeting criteria of cancer remission or cure for more than 3 years (IIa, C).

q) If myocarditis due to ICIs is suspected or confirmed, the therapy with ICIs should be interrupted and corticosteroid initiated immediately (intravenous methylprednisolone, 1g per day, for 3 to 5 days, followed by prednisone, 1-2 mg/kg/day). Corticosteroid should be kept until resolution of the symptoms and normalization of troponin, systolic function and conduction abnormalities (IIa, C). In cases of pericarditis, oral corticosteroid is recommended (IIa, C). For Takotsubo syndrome, pulse therapy can be considered (IIa, C), and, for dilated cardiomyopathy, support treatment is recommended (Table 9).

r) For patients with refractory myocarditis or in severe situations with cardiogenic shock, other immunosuppressant therapies, such as antithymocyte globulin, infliximab (except for patients with HF), mycophenolate mofetil, cyclophosphamide or abatacept, should be considered (IIa, C).

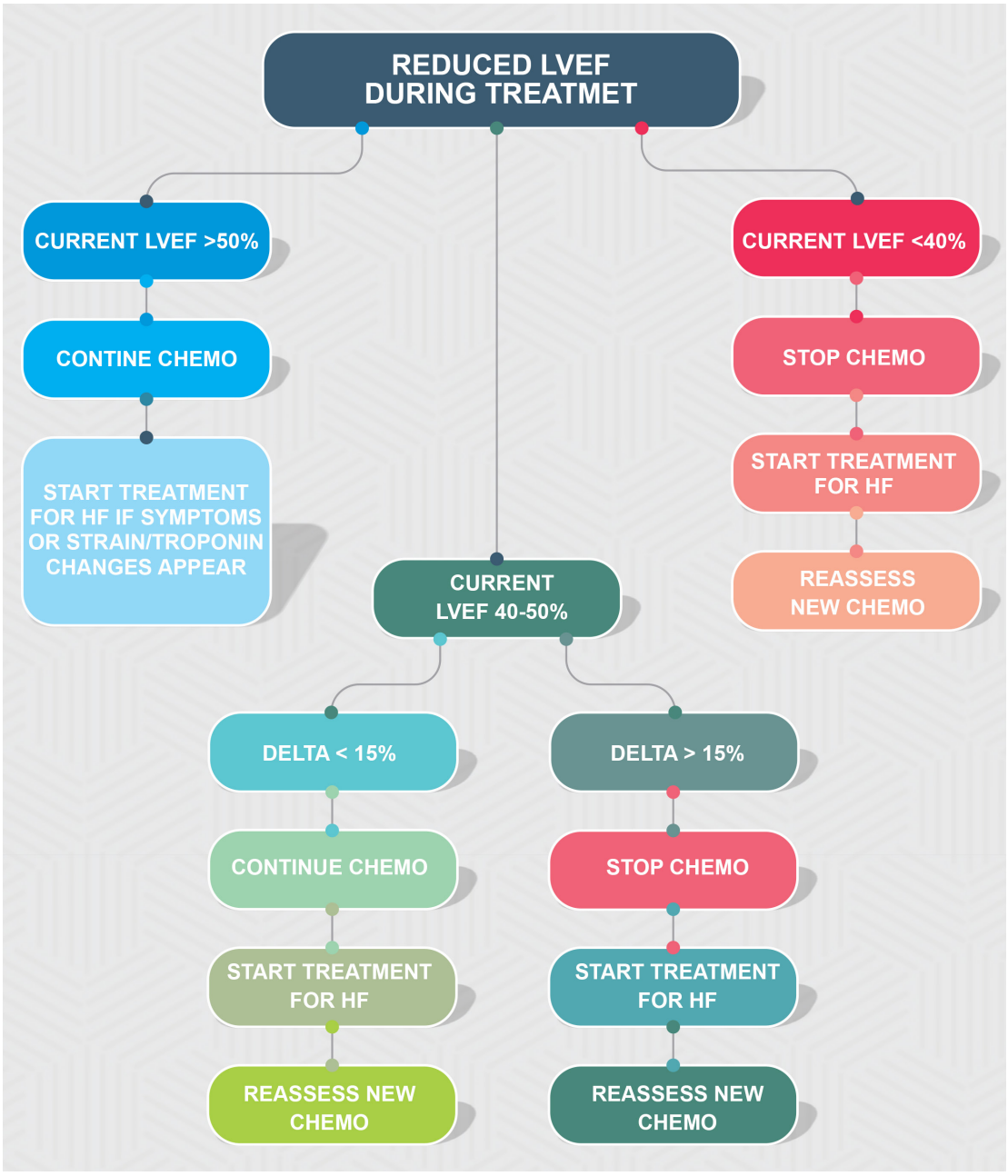


Figure 8 – *Algorithm for the management of heart failure and ventricular dysfunction induced by anti-HER2 therapy. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

Table 8 – Recommendations for heart transplantation. Coordinating Committee of the Brazilian Guideline on Acute and Chronic Heart Failure[69]

Recommendation	Class	Level of evidence
For patients with acute heart failure and/or cardiogenic shock with low recovery potential, assessment of heart transplant candidacy should begin early and be as thorough as possible, including psychosocial assessment, even in the presence of difficulties inherent in acute findings.	I	C
For patients with refractory cardiogenic shock and no proper myocardial function recovery, heart transplant candidacy should consider the hemodynamic instability grade, presence of multiorgan dysfunctions, comorbidities, and the transplant center experience. Prognostic scores might help estimate the post-transplant mortality risk in the short and long run.	IIa	C

Table 9 – Adverse effects of the use of immune checkpoint inhibitors and therapeutic strategies

Potential CV events related to ICIs	Diagnostic methods	Potential initial approach for treatment	Potential additional therapy if stable and not responding to initial approach	Potential additional therapy if unstable
Myocarditis	Non-invasive: CMRI, troponin, ECG Invasive: biopsy and pathology	Methylprednisolone, 1g/day for 3-5 days, followed by prednisone, 1.5mg/kg, with ambulatory troponin monitoring. Standard therapy for HF with neuro-hormonal blocker, if LVEF is reduced.	Mycophenolate, 500-750mg 2x/day Plasmapheresis Intravenous immunoglobulin	Antithymocyte globulin Abatacept Alemtuzumab Mechanical circulatory support
Pericarditis	Non-invasive: echocardiography Invasive: fluid analysis	Prednisone, 1.5mg/kg/day, with ambulatory dose reduction for 2 months.	Methylprednisolone, 1g/day for 3-5 days Mycophenolate, 500-750mg 2x/day	Pericardial drainage if huge pericardial effusion with signs of hemodynamic instability is present
Takotsubo syndrome	Non-invasive: echocardiography, CMRI Invasive: coronary cineangiography and ventriculography	Standard therapy for HF with neuro-hormonal blocker, if LVEF is reduced. Consider methylprednisolone, 1g/day for 3-5 days, followed by oral prednisone with dose reduction for 4-6 weeks.	Mycophenolate, 500-750mg 2x/day	Mechanical circulatory support
Dilated cardiomyopathy	Non-invasive: CMRI, echocardiography, troponin, natriuretic peptide Invasive: coronary cineangiography and ventriculography	Standard therapy for HF with neuro-hormonal blocker, if LVEF is reduced.	Cardiac resynchronization therapy Implantable cardioverter defibrillator	

This table details the CV toxicities associated with ICIs and potential management strategies. Many strategies listed for toxicities other than myocarditis have been extrapolated from the literature on myocarditis and based on small case series or case reports. CMRI: cardiac magnetic resonance imaging; CV: cardiovascular; ECG: electrocardiogram; HF: heart failure; ICIs: immune checkpoint inhibitors; LVEF: left ventricular ejection fraction. Table adapted from: Lenihan DJ et al. Proceedings.[18]

s) For patients with tachyarrhythmia or bradyarrhythmia induced by ICIs, proper drug therapy and pacemaker should be considered according to the clinical characteristics (IIa, C).

t) Therapy with ICIs should be discontinued in cases of myocarditis. The decision on resuming therapy should be individualized according to cancer *status*, response to treatment and cardiotoxicity severity, and analyzing the risks and benefits. If ICIs are resumed, monotherapy with one anti-PD1 drug and cardiovascular surveillance are recommended (IIa, C).

u) Consider the use of dexrazoxane for patients with metastatic breast cancer and a planned high dose of anthracycline (doxorubicin > 250 mg/m^2) (I, A), for patients with sarcoma and for pediatric patients with lymphoma/leukemia (IIa, A).

7. Arterial and Venous Thromboembolism

Thromboembolic disease is common in cancer patients, being considered the second cause of mortality in that population.

7.1. Venous Thromboembolism

Venous thromboembolism (VTE) comprises deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). It is a severe complication in cancer patients, being their second cause of death. Neoplasms are associated not only with an increase in the risk for VTE and in its severity, but also with thrombosis recurrence, which result in higher rates of treatment-related complications. Moreover, cancer patients have a 2- to 9-times higher chance of recurrence of thromboembolic events.[70-72]

Cancer induces a pro-thrombotic state because of the following: production of thrombogenic microparticles; platelet activation; its antifibrinolytic properties; and thrombin production. In addition, thrombogenesis is intensified by factors related to cancer type, disease *status*, concomitant use of drugs,[73] such as erythropoiesis-stimulating agents, presence of anemia and leukocytosis, obesity and thrombogenic laboratory phenotype, such as high levels of D-dimer and prothrombin fragment 1+2.[74]

In the past 5 years, some clinical trials on the cancer population were published, allowing the expansion of the therapeutic arsenal (Table 10).[75,76]

The recommendations for VTE management in cancer patients are:

a) The multiprofessional team caring for oncological patients should instruct them on the risk for VTE, particularly in high-risk situations, such as large surgeries and during chemotherapy (IIa, C).

Table 10 – Clinical studies on venous thromboembolism in cancer patients

Study	Population	Intervention	Primary efficacy outcomes	Primary safety outcome
Primary prevention				
CASSINI trial*	841 ambulatory cancer patients at high risk for VTE	Rivaroxaban 10mg vs placebo 6 months	DVT or PE or VTE-related death HR: 0.66; 95%CI: 0.4-1.09	Major bleeding 1.0% vs 2.0% HR: 1.96; 95%CI: 0.59-6.49
AVERT trial*	574 ambulatory cancer patients at high risk for VTE	Apixaban 2.5mg 2x/day vs placebo	Documented VTE 4.2% vs 10.2% HR: 0.41; 95%CI: 0.26-0.65	Major bleeding 3.5% vs 1.8% HR: 2.0; 95%CI: 1.0-3.95
Treatment				
HOKUSAI VTE	1050 cancer patients with acute symptomatic or incidental VTE	LMWH for 5 days + edoxaban 60mg vs dalteparin Treatment: 6 months	VTE recurrence or major bleeding 12.8% vs 13%	Major bleeding 6.9% vs 4% HR: 1.77; 95%CI: 1.03-3.04
SELECT-D	406 cancer patients with symptomatic PE or VTE	Rivaroxaban vs dalteparin Treatment: 6 months	VTE recurrence: 4% vs 11% HR: 0.43; 95%CI: 0.19-0.99	Major bleeding 6% vs 4% HR:1.83; 95%CI: 0.68-4.96
ADAM-VTE trial	300 patients with VTE associated with cancer	Apixaban 10mg 2x/day for 7 days followed by 5mg 2x/day vs dalteparin	VTE recurrence: 0.7% vs 6.3% HR: 0.099; 95%CI: 0.013-0.78	Major bleeding 0% vs 1.4% HR: 1.96; 95%CI: 0.59-6.49
Caravaggio Study*	1055 cancer patients with symptomatic or incidental VTE or PE	Apixaban 10mg for 10 days followed by 5mg/day vs dalteparin	VTE recurrence: 5.6% vs 7.9% HR: 0.63; 95%CI: 0.37-1.07	Major bleeding 3.8% vs 4% HR: 0.82; 95%CI: 0.4-1.69

*Randomized clinical trial; CASSINI = rivaroxaban in ambulatory cancer patients at high risk for VTE; AVERT = apixaban for VTE prevention in cancer patients; HOKUSAI VTE = edoxaban *versus* dalteparin to treat symptomatic VTE; SELECT-D = anticoagulation in patients at high risk for VTE recurrence; ADAM VTE = apixaban and dalteparin in VTE associated with active neoplasm; Caravaggio Study = apixaban to treat VTE associated with cancer. CI: confidence interval; DVT: deep venous thrombosis; HR: hazard ratio; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; VTE: venous thromboembolism; Table adapted from: Lenihan DJ *et al*. Proceedings.[18]

b) In-patients should receive pharmacological prophylaxis, in the absence of contraindications (IIa, B).

c) Pharmacological prophylaxis should not be routinely performed for patients admitted for small procedures or chemotherapy infusion or transplantation (IIa, C).

d) For low-risk outpatients, routine anticoagulation to prevent VTE is not recommended (III, B).

e) Outpatient pharmacological prophylaxis with apixaban, rivaroxaban or enoxaparin should be provided to those at high risk for VTE, assessed with the Khorana score (≥ 2) or the CAT score (D-dimer level and cancer type) (IIa, A).

f) For outpatient pharmacological prophylaxis assessment, consider the patients' risk for bleeding (higher in gastrointestinal tumors) and their preferences (IIa, C).

g) Patients with multiple myeloma on thalidomide or lenalidomide or dexamethasone should be assessed for the use of aspirin or enoxaparin (IIa, C).

h) Patients undergoing large oncological surgeries should receive pharmacological prophylaxis against VTE (enoxaparin or low-molecular-weight heparin), starting in the preoperative period, except for those with active bleeding or at high risk for bleeding (I, A). Mechanical methods can be added to pharmacological prophylaxis; however, they should only be used as monotherapy for patients with contraindication for heparin (IIa, B).

i) The combined regimen of pharmacological and mechanical prophylaxis can improve efficacy, especially in patients at higher risk (IIa, B).

j) The pharmacological prophylaxis against thrombus for patients undergoing large oncological surgery should be extended for 7 to 10 days, and be prolonged for 4 weeks in the postoperative period in cases of open abdominal or laparoscopic surgery and of pelvic surgery in the presence of other risk factors, such as obesity, immobility, and history of VTE (IIa, B).

k) For smaller surgeries, the duration of prophylaxis should be decided on a personalized basis (IIa, C).

l) In the oncology patient, VTE can be initially treated with low-molecular-weight heparin (enoxaparin), unfractionated heparin, fondaparinux, apixaban or rivaroxaban. For patients starting treatment with parenteral anticoagulation, low-molecular-weight heparin, rather than unfractionated heparin, is preferred in the first days of treatment, provided the patient has no kidney dysfunction (creatinine clearance should be > 40 mL/min/m^2) (I, A).

m) Long-term anticoagulation can be performed preferably with low-molecular-weight heparin, edoxaban, apixaban or rivaroxaban for at least 6 months (I, A).

n) Warfarin can be used in cancer patients when other drugs are not available or when other anticoagulants are contraindicated, such as for chronic kidney failure requiring dialysis (IIa, B).

o) Direct oral anticoagulants (DOACs), such as rivaroxaban and apixaban, are associated with higher bleeding rates, especially in gastrointestinal and genitourinary neoplasms (IIa, B).

p) In cancer patients, drug interactions with DOACs should be analyzed on a case-by-case basis (I, A).

q) Anticoagulation for more than 6 months should be offered to patients with active cancer, such as metastatic ones, or on chemotherapy, provided the risks and benefits are analyzed (IIa, C).

r) Based on expert opinions, in the absence of randomized studies, vena cava filters should not be inserted in patients with chronic or established (for more than 4 weeks) thrombosis or temporary contraindications for anticoagulant therapy (IIa, C).

s) Warfarin is the first option for anticoagulation in patients with chronic kidney failure requiring dialysis (IIa, B).

t) Vena cava filters can be considered for patients with high-risk acute VTE (in the past 4 weeks) and absolute contraindication for anticoagulation (IIa, C).

u) Incidental PTE and DVT should be treated the same way symptomatic VTE is, because they have similar outcomes (IIa, C).

v) The treatment of subsegmental PTE or of visceral or splanchnic venous thrombosis should be considered on a case-by-case basis, analyzing the potential benefits and risks of anticoagulation (IIa, C).

w) Cancer patients should have their risk for VTE assessed on an outpatient basis with the Khorana or the CAT score, and the benefits and risks of that strategy should be analyzed on a case-by-case basis, because they are associated with a reduction in thromboembolic events but not in mortality (IIa, B).

x) For clinically significant bleeding associated with warfarin, the treatment of choice is intravenous vitamin K (10 mg) and intravenous prothrombin complex (500 U/kg) (IIa, B).

y) For bleeding associated with rivaroxaban, edoxaban and apixaban, no specific antidote is available. Thus, the use of antifibrinolytics (intravenous tranexamic acid, 1g to 2g) and prothrombin complex (500 U/kg, intravenous) is recommended. For refractory cases, plasma (15 mL/kg), cryoprecipitate (1 U/kg) and platelet (1-2 units), by use of apheresis, are recommended (IIa, C).

There is a substantial variation in the risk for VTE in cancer patients and different clinical situations. Cancer patients should have their risk for VTE analyzed in the baseline assessment and then periodically, particularly at the beginning of antineoplastic therapy and on hospital admission. Individual risk factors, including biomarkers or cancer site, do not accurately identify cancer patients at risk for VTE. On an outpatient basis, the assessment should include the Khorana and the CAT scores (IIa, C) (Tables 11 and 12, respectively).

7.2. Arterial Thrombosis

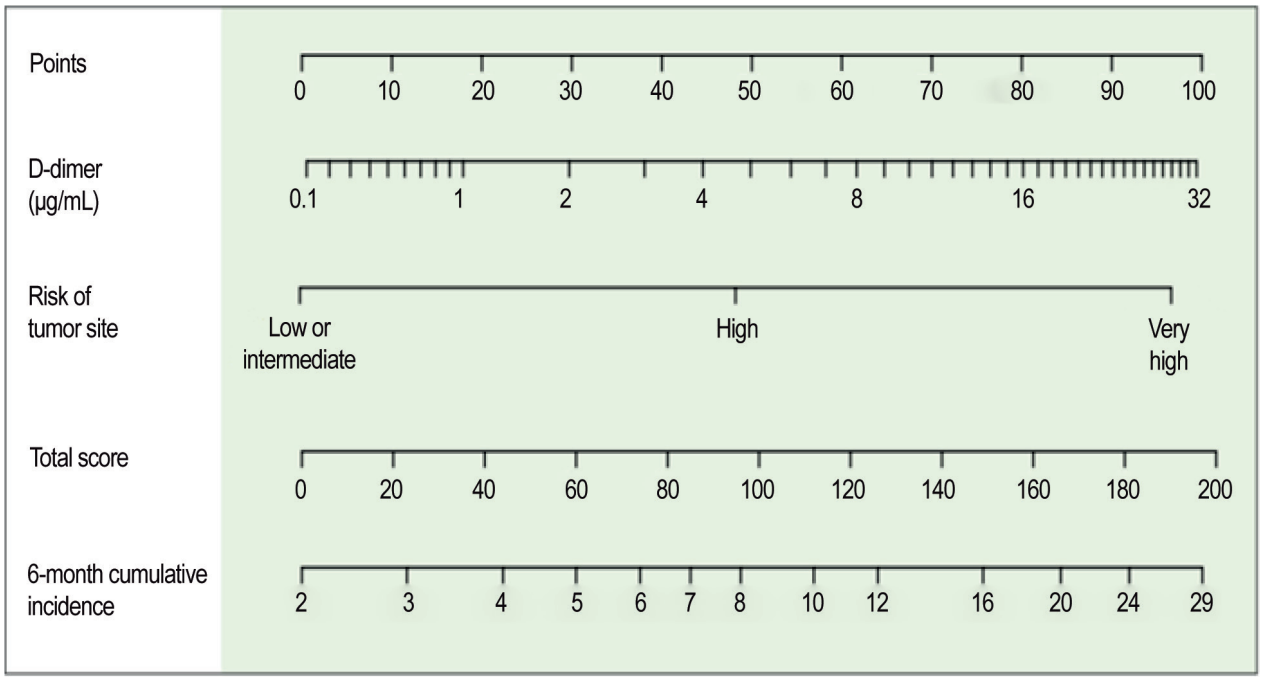
In an epidemiological study with 279 719 participants and comparing patients with neoplasm and controls without neoplasm, the incidence of arterial events was 4.7% in the former and 2.2% in the latter in 6 months.[79] Usually, these events occur in individuals with metastatic pancreas, breast, colorectal and lung neoplasms, who are on anthracyclines, taxanes and platins. The pro-thrombotic state may favor the occurrence of embolic events secondary to atrial fibrillation. Some antineoplastic drugs, especially VEGF inhibitors, may induce thromboembolic complications. In patients on hormone therapy, higher rates of arterial thrombotic events are more often observed with aromatase inhibitors than with tamoxifen. In several cases, kinases and their pathways play a critical role in vascular and metabolic cell homeostasis. The inhibition of these kinases can cause cardiovascular sequelae, depending on the kinase type. The most worrisome vascular toxicities that might occur with the new agents include arterial ischemic events, such as acute myocardial infarction, stroke and ischemia of a limb, as well as venous thromboembolic events.[79]

Recent reports have shown that the VEGF-inhibitor therapy results in adverse vascular events, such as aortic dissection, stroke, and arterial and venous thrombosis. Of the VEGF inhibitors, bevacizumab is associated with the highest VTE rate, around 12%, as compared to 2% with the other drugs.[49,80]

Table 11 – Khorana score[77]

Patient's characteristic	
Site of cancer	
Very high risk (stomach and pancreas)	2
High risk (lung, lymphoma, gynecological, urinary bladder, testicles, kidney)	1
Pre-chemotherapy platelet count ≥ 350 000 / μL	1
Hemoglobin < 10 g/dL and/or use of erythropoiesis-stimulating agents	1
Pre-chemotherapy leukocyte count > 11 000 / μL	1
Body mass index ≥ 35 kg/m^2	1
Calculate the total score by adding the points for each criterion of the model	
Score interpretation:	
High risk: ≥ 3 points	
Intermediate risk: 1-2 points	
Low risk: 0 point	

Table 12 – Nomogram (CAT score) to predict risk for venous thromboembolism in 6 months[78]



8. Metabolic Syndrome Associated with Androgen Deprivation Therapy

The treatment of locally advanced prostate neoplasms is based on the hormonal control of testosterone. This blockade can be obtained surgically (orchiectomy) or through androgen deprivation therapy. Gonadotropin releasing hormone (GnRH) agonists (leuprolide, goserelin and triptorelin) and antagonists (degarelix) cause central blockade with a reduction in the levels of luteinizing and follicle stimulating hormones and testosterone. In addition, adrenal androgen receptor inhibitors (abiraterone) and direct androgen inhibitors (enzalutamide) reduce testosterone. These drugs are used with curative intention in high-risk patients with non-metastatic disease and as standard therapy for metastatic disease. Understanding the impact of these drugs on cardiovascular risk is important because many risk factors that lead to prostate cancer can result in cardiovascular disease, such as advanced age, smoking, diet, and obesity. Some studies have reported a higher prevalence of those risk factors among prostate cancer patients.

The recognized antiandrogen therapy leads to metabolic changes characterized by hyperinsulinemia, hypercholesterolemia, and body composition changes, with an increase in predominantly visceral fat and a reduction in lean mass. The metabolic syndrome resulting from the antiandrogen therapy is associated with an increase in cardiovascular complications. Modification of risk factors is recommended with lipid-lowering therapy, antihypertensive treatment, strict control of glycemia, and use of antiplatelet drugs (IIa, B).

9. Cardiac Arrhythmia

Several factors present in cancer patients, such as infection, electrolyte imbalance, dehydration, surgical procedures, and oncological and adjuvant therapies, predispose to the occurrence of cardiac arrhythmias.[81] These arrhythmias are relatively frequent complications in cancer patients, estimated to occur in 16-36% of those patients.[82,83]

The types of cardiac arrhythmias in oncology patients comprise a wide range: sinus tachycardia, bradyarrhythmias, tachyarrhythmias, and conduction disorders. Of the supraventricular arrhythmias, the most common is atrial fibrillation. Ventricular tachycardia and ventricular fibrillation are rare, but can occur especially in the presence of QT prolongation and in patients with hypokalemia or hypomagnesemia.[84,85] Table 13 lists the major drugs related to cardiac arrhythmias and their incidences.

9.1. QT Prolongation

The diagnosis of QT prolongation is electrocardiographic, and QTc should be calculated by use of the Bazett's formula [QT / $(RR)^{1/2}$] or Fridericia's formula [QT / $(RR)^{1/3}$]. Normal QTc values are as follows: ≤ 440 ms in men; between 450 and 460 in women. Both congenital and acquired factors can be responsible for QT prolongation, and the most cited conditions are as follows: female sex, bradycardia, electrolyte abnormalities, drug effects, myocardial ischemia, HF, myocarditis, hypothermia, and channelopathies.[86]

The QT prolongation is a concern in cancer patients, because the oncological treatment, electrolyte disorders and concomitant medications can contribute to that prolongation and predispose to complex arrhythmias.[83] Monitoring the

Table 13 – Major drugs related to cardiac arrhythmias and their incidences

Drug	Incidence
Anthracyclines	ECG changes: 38.6% AF: 2-10%
Antimicrotubule agents (Paclitaxel)	Sinus bradycardia: 29% 1st degree AVB: 25%
Antimetabolites (5-Fluorouracil and Capecitabine)	ECG changes: 68% Arrhythmias (AF, SVT, VT): 5%
Platins (Cisplatin)	SVT: 12-32%
Thalidomide	Bradycardia: 27%
Arsenic trioxide	QT prolongation and ventricular arrhythmias: up to 50%
Tyrosine kinase inhibitor	
Crizotinib	QT prolongation and arrhythmias: 3.5%
Dasatinib	QT prolongation and arrhythmias: 0.6-3%
Sunitinib	QT prolongation and arrhythmias: 1-4%
Vandetinib	QT prolongation and arrhythmias: 12-15%

AF: atrial fibrillation; AVB: atrioventricular block; ECG: electrocardiographic; SVT: supraventricular tachycardia; VT: ventricular tachycardia.

QT interval and correcting the factors that contribute to QT prolongation should be considered in patients on medications that prolong the QT interval. Cardiotoxicity is defined in the presence of QTc prolongation > 500 ms and/or QT variation > 60ms from baseline (Table 14).[87,88]

The QT interval and the risk factors associated with QT prolongation should be assessed before and after treatment with drugs known to be related to cardiac arrhythmias, such as tyrosine kinase inhibitors (crizotinib, dasatinib, sunitinib) and arsenic trioxide. Electrolyte and ECG assessments should be performed during treatment at baseline, 7-15 days after the beginning of therapy, after changes in doses in the first 3 months, and depending on the therapy frequency. Before postponing chemotherapy, the suspension of other medications related to QT prolongation, such as antiemetics, antidepressants, antiarrhythmics, antifungal drugs, antipsychotics, should be considered. In addition, correction of electrolyte disorders should be performed. Patients on arsenic trioxide should be monitored with ECG every week.[22]

The QT prolongation increases the incidence of ventricular arrhythmias and *torsades de points*.[88] Ventricular tachycardias are usually associated with structural cardiomyopathies [CAD, dilated cardiomyopathy, right ventricular heart diseases, congenital abnormalities, hypertrophic cardiomyopathy, and channelopathies].[89] The objective of the treatment of ventricular arrhythmias is to reduce morbidity and sudden death events, and the assessment of triggering factors is paramount. Pharmacological therapy is indicated for refractory and/or symptomatic cases.[90]

9.2. Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia of the oncology patient. Its occurrence is related to the pro-inflammatory state of these patients, the inflammatory response to oncological surgery, and the cardiotoxic effects of antineoplastic therapy.[91] Understanding the mechanisms that trigger and sustain atrial fibrillation is important for prevention.

Atrial fibrillation can be induced by several mechanisms, such as myocardial change due to electrolyte disorder, liposomal and mitochondrial injury, inflammation, pericardial disease, and increased oxidative stress inducing cell apoptosis.[92]

There is great difficulty in establishing the causal relationship between arrhythmic events and each chemotherapy drug. The small number of studies published and the simultaneous administration of many drugs make it difficult to relate drug and effect. The chemotherapy drugs most commonly associated with arrhythmias are anthracyclines (doxorubicin, epirubicin), antimicrotubule agents (paclitaxel and docetaxel), antimetabolites (5-fluorouracil, capecitabine and gemcitabine), alkylating agents (cisplatin and cyclophosphamide), tyrosine kinase inhibitors (ibrutinib, ponatinib, sorafenib and sunitinib), and monoclonal antibodies (trastuzumab and cetuximab), in addition to immunotherapy drugs.

Cancer is associated with a pro-thrombotic state and can increase the risk for embolic events in patients with atrial fibrillation, who also have more bleeding complications due to treatment, and, therefore, higher morbidity and mortality. There is no consensus/guideline-based recommendation on the use of antithrombotic drugs for patients with atrial fibrillation.[85,93]

The choice of antithrombotic therapy for cancer patients should be individualized, analyzing pharmacokinetic and pharmacodynamic factors, drug interactions, and risks for thrombosis and bleeding (IIa, B).

Warfarin should be avoided in the oncology patient with atrial fibrillation, because that drug is associated with lower efficacy and higher risk of bleeding due to drug interactions,

Table 14 – Recommendations for patients on drugs that can prolong the QT interval

Avoid using drugs related to QTc prolongation for patients with pre-treatment QTc > 470ms
Discontinue drugs related to QTc prolongation if QTc > 500ms, or, if QTc > 550ms when baseline QRS duration is prolonged (> 120ms secondary to pacemaker or bundle-branch block)
Reduce dose or discontinue drug if QTc increases more than 60ms from pre-treatment value
Maintain serum electrolyte (potassium, magnesium, and calcium) concentrations within the normal range
Prevent drug interactions
In patients with acute renal injury or chronic renal disease, adjust the drugs with renal clearance that prolong QTc to kidney function
Avoid rapid intravenous infusion of drugs that prolong QTc
Avoid the concomitant administration of more than one drug that prolongs QTc
Avoid drugs that prolong QTc for patients with history of drug-induced *torsade de points* or patients resuscitated from cardiac sudden death
Avoid drugs that prolong QTc for patients with congenital diseases
Perform ECG at a frequency depending on the therapy, dose administered, and concentration of drugs

ECG: electrocardiogram; QTc: corrected QT interval. Source: Adapted from Porta-Sanchez et al.[88]

higher occurrence of liver dysfunction, dietary changes, cachexia, and malnutrition (IIa, B).

The DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) are superior to warfarin in terms of efficacy and bleeding in the general population with atrial fibrillation; however, the evidence for their use in cancer patients derives from analyses of substudies and observational data (IIa, B).

Although there is no validation of the classic scores for the cancer population, anticoagulation should be initiated in those patients according to the same criteria adopted for the population without cancer: $CHADS_2$ and CHA_2DS_2-VASc scores above 2 indicate anticoagulation (IIa, C) (Table 15).

Antithrombotic therapy in cancer patients should be personalized, analyzing the patient's profile, cancer type, and risk for thrombosis and bleeding, the last, for example, by use of the HAS-BLED score (IIa, C) (Table 16).

There is no prospective randomized study on DOACs in cancer patients with atrial fibrillation. Analysis of substudies from randomized clinical trials have shown those drugs to be safe and effective in cancer patients. This evidence and the results from studies on VTE and cancer, which confirm the superiority of DOACs as compared to low-molecular-weight heparin, suggest that DOACs are a feasible option of antithrombotic therapy in cancer patients with atrial fibrillation (IIa, C).

The routine use of DOACs can be considered for patients with atrial fibrillation and gastrointestinal or genitourinary tract tumors, and the potential risk for bleeding should be analyzed (IIb, B).

The management of cancer patients with atrial fibrillation should include a cardiologist since the beginning, because of the higher rates of anticoagulation use and lower incidence of ischemic and hemorrhagic complications (IIa, C).

10. Coronary Artery Disease

Cancer and CAD have several risk factors in common and often coexist in the same patient (Figure 9). The presence of risk factors, such as advanced age, smoking, diabetes, SAH, sedentary lifestyle and dyslipidemia, is elevated in cancer patients.[94] Other common factors in those patients that contribute to the development of CAD are endothelial dysfunction, oxidative stress, genetic predisposition and chronic inflammation.[95]

In addition, the oncological treatment contributes to the high prevalence of CAD in cancer patients.[49] Patients with lung cancer undergoing chemotherapy have a 5.3-time (95% CI: 2.002-14.152) increase in the risk of important coronary injury, which suggests that the treatment may be associated with anatomic complexity.[96] The major mechanisms of CAD related to oncological therapy are: vasospasm, thrombosis, and accelerated atherosclerosis.[49]

In patients on cisplatin isolated or associated with vincristine or bleomycin, coronary thrombosis has been observed in coronary angiography without previous atherosclerosis. These drugs can induce endothelial dysfunction/lesion, which seems to be the basic mechanism of the vasoactive alteration caused by these drugs.[97-99] Cisplatin leads to the death of endothelial cells via the production of procoagulant microparticles.[100]

Another class of chemotherapy drugs typically related to CAD in cancer patients are the antimetabolites, especially 5-fluorouracil and capecitabine. The incidence of angina or acute findings ranges from 3.9% to 12.5%.[101] The mechanism through which these drugs cause toxicity has not been completely established and several hypotheses have been raised to explain those findings, such as acute vasospasm, direct toxicity to myocytes, endothelial dysfunction, and hypercoagulable state causing thrombosis.[101,102] Acute vasospasm is often observed and experimental studies have suggested that vasoconstriction caused by 5-fluorouracil is related to protein kinase C and endothelin-1.[103,104] Similarly to 5-fluorouracil, taxanes are another class of drugs that induce angina secondary to coronary spasms. The incidence of chest pain reported by patients on paclitaxel is approximately 0.2-4%.[105,106]

Accelerated atherosclerosis has been observed in patients being treated with second- and third-generation tyrosine

Table 15 – Risk score of thromboembolism associated with atrial fibrillation

CHA_2DS_2-VASc		
	Description	Points
C	Heart failure	1
H	Arterial hypertension	1
A_2	Age (≥ 75 years)	2
D	Diabetes mellitus	1
S_2	Previous TIA or stroke	2
V	Vascular disease (prior AMI, peripheral artery disease or aortic plaque)	1
A	Age (65-74 years)	1
Sc	Female sex	1

AMI: acute myocardial infarction; TIA: transient ischemic attack.

Table 16 – Risk score of bleeding associated with anticoagulation (HAS-BLED). Score 1 for each item

☐	Arterial hypertension (1 point)
☐	Abnormal liver function (1 point)
☐	Abnormal kidney function (1 point)
☐	Stroke (1 point)
☐	Bleeding tendency or predisposition (1 point)
☐	Labile INRs in patients on warfarin (1 point)
☐	Elderly: age > 60 years (1 point)
☐	Drugs: concomitant antiplatelet agent(s) or NSAIDs (1 point)
☐	Alcohol abuse (1 point)

INR: international normalized ratio; NSAIDs: non-steroidal anti-inflammatory drugs.

0 point: 1.02 bleeding per 100 patients/year
1 point: 1.13 bleeding per 100 patients/year
2 points: 1.88 bleeding per 100 patients/year
3 points: 3.74 bleedings per 100 patients/year
4 points: 8.70 bleedings per 100 patients/year
points: insufficient data (high risk)

kinase inhibitors. These drugs have an increased risk of coronary occlusion as compared to imatinib (OR = 3.45; 95% CI: 2.30-5.18).[107] Of the tyrosine kinase inhibitors, ponatinib seems to be the one most often related to vascular toxicity. Arterial and venous thromboses have been reported in 27% of the patients on ponatinib, regardless of the presence of cardiovascular risk factors.[107] Patients treated with bevacizumab have high risk for coronary ischemia as compared to a control group (RR: 2.47; 95% CI: 1.4-4.36).[108] Patients on ICIs have an altered inflammatory cell composition of the atherosclerotic plaque (increased ratio of CD3+ T cells to CD68+ macrophages), which may predispose to plaque progression and/or clinical coronary events.[109]

Radiotherapy is classically related to the development of CAD, usually reported later after exposure to radiation. The incidence varies in the literature, with a decreasing tendency in recent decades because of the most modern techniques that reduce direct radiation emission to the heart. The pathogenesis of CAD is multifactorial, resulting in direct myocardial injury, vascular tonus alteration, inflammatory activation, and oxidative stress.[110,111]

Because of the complexity of cancer patients with CAD, their mortality is higher than that of patients without cancer in the long run.[112,113] When approaching those patients, it is important to know the oncological prognosis, the therapeutic perspectives and the program of oncological surgeries. The control of risk factors should be reinforced in

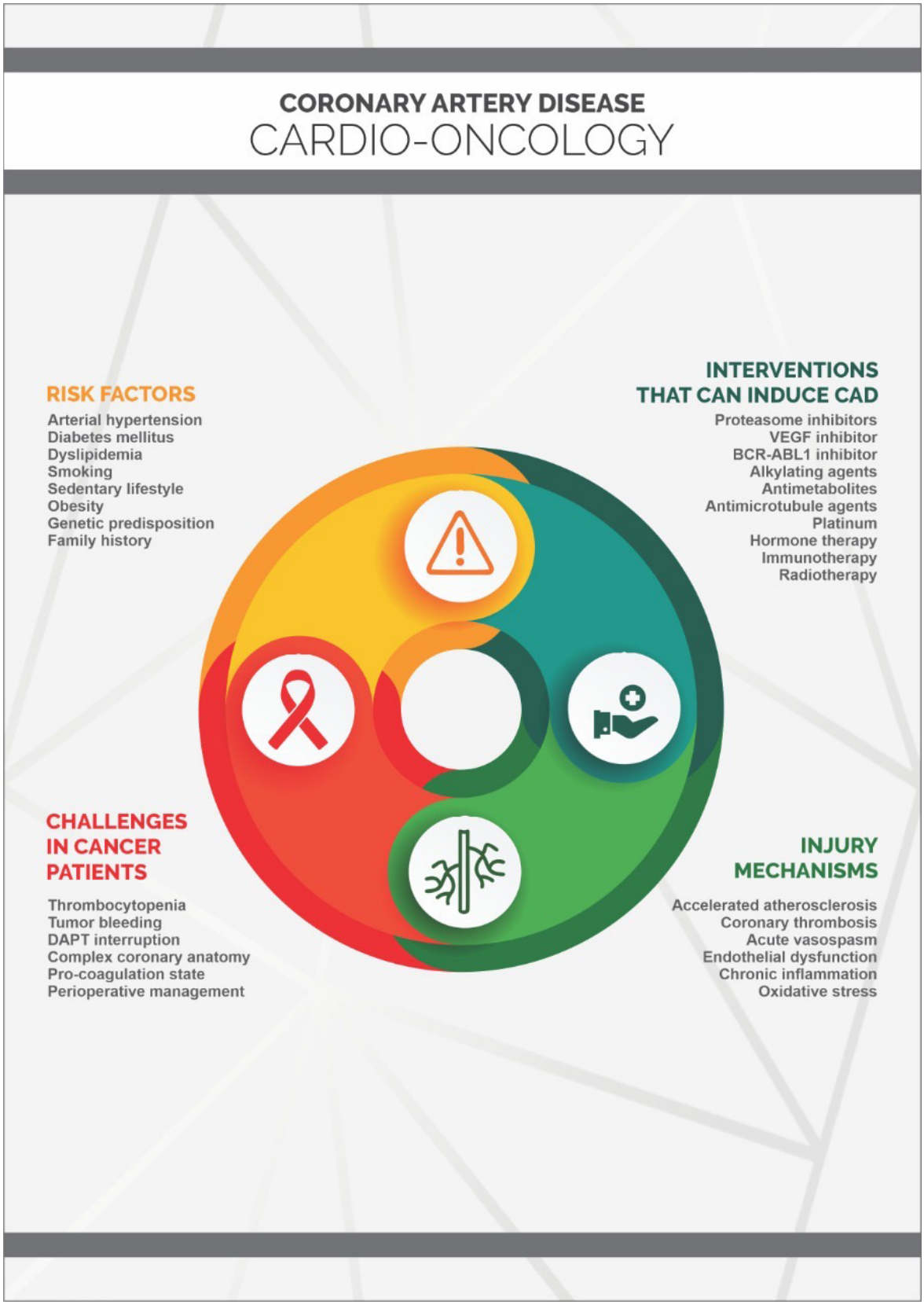


Figure 9 – *Coronary artery disease in cardio-oncology. CAD: coronary artery disease; DAPT: dual antiplatelet therapy; VEGF: vascular endothelial growth factor.*

patients with evidenced CAD. The use of drug-eluted stent should be preferred in those patients when the therapeutic intervention is indicated.[114] Therapy with antiplatelet agents should be maintained according to the guidelines on CAD and acute coronary syndrome management, unless contraindicated, such as in the presence of tumor bleeding.[115-117]

Recommendations:

a) The control of risk factors (SAH, diabetes, dyslipidemias) and of body weight loss, smoking cessation and dietary guidance should be provided to all patients who will receive drugs that predispose to CAD (I, A).

b) Drug-eluted stent should be preferred in these patients (IIa, B).

c) Dual antiplatelet therapy can be maintained in patients with platelet count > 30 000, in the absence of contraindication (IIa, B).

d) The investigation of CAD is indicated in patients 5 years after mediastinal exposure to a dose of at least 30 gy (IIa, B).

e) For patients who developed acute coronary syndrome with 5-fluorouracil, assessment of the coronary anatomy and by the cardio-oncology team should be considered (IIa, B).

f) Re-exposure can be considered for patients with mild events, who are asymptomatic and whose benefit with 5-fluorouracil impacts the prognosis. The use of nitrates and vasodilators can be considered in this scenario (IIb, B).

11. Arterial Hypertension

The prevalence of SAH is higher in cancer patients and survivors as compared to that of the general population.[118] In these patients, SAH is the major modifiable risk factor for cardiovascular events.[119] Chronic kidney disease, SAH, cardiovascular disease, and cancer have risk factors in common, such as smoking, obesity, and diabetes. Many types of cancer and their treatments cause or aggravate preexisting SAH, because of vascular, endothelial and renal effects.[22]

Periodical blood pressure measurement is recommended in cancer patients (IIa, C).

The selection of anti-hypertensive agents should consider individual risk factors, effects of the antineoplastic treatment and drug interactions. It is estimated that 35% of cancer patients will develop SAH during the treatment. Patients with history of cancer have a higher prevalence of SAH than that of the general population.[94] Patients with renal, gastric and ovarian cancer have higher blood pressure levels than those with other tumor sites. Exposure to chemotherapy is an independent risk factor for SAH.[120]

11.1. SAH and Chemotherapy

Therapy with anti-VEGF tyrosine kinase inhibitors and multi-targeted tyrosine kinase inhibitors aggravates and induces SAH.[121] The mechanisms are a reduction in the production of nitric oxide and in angiogenesis, leading to an increase in systemic vascular resistance. Anti-VEGF therapy leads to fluid retention because of natriuresis impairment, in addition to inducing endothelin-1-mediated vasoconstriction and thrombotic microangiopathy, similarly to the pathophysiology of eclampsia.[121] In a recent meta-analysis, the use of anti-VEGF tyrosine kinase inhibitors increased the risk for cardiotoxicity, such as SAH, bleeding and ventricular dysfunction. The most common vascular cardiotoxicity was SAH.[122]

The alkylating agents seem to induce SAH through nephrotoxicity, but there is not much evidence of their real effect on blood pressure. Cyclophosphamide has been associated with multiple vascular complications, such as pulmonary and hepatic veno-occlusive disease, thromboembolic disease, and myocardial ischemia. Pre-clinical evidence has shown endothelial injury and renin-angiotensin-aldosterone system abnormalities in animals treated with cyclophosphamide.[21,22] Both ifosfamide and cisplatin apparently induce SAH by causing nephrotoxicity.[123] The antimicrotubule agents affect mitosis, acting on tubulin to prevent microtubule polymerization. Experimental studies have shown that vinblastine acts on the endothelium and apoptosis, but its effect in SAH is unkonwn.[124,125] Gemcitabine and proteasome inhibitors can trigger SAH associated with thrombotic microangiopathy. Adjuvant medications associated with SAH used for cancer patients are: corticosteroids, erythropoietin, calcineurin inhibitors, and anti-inflammatory drugs.

11.2 Cancer-Induced SAH

Systemic arterial hypertension can be a paraneoplastic manifestation of hepatocellular carcinoma, renal cancer, and carcinoid disease. It results from the production of renin, angiotensinogen, angiotensin I or catecholamines. Among individuals with renal cell carcinoma, the SAH prevalence exceeds 75%, and SAH is due to the nephrectomy-related loss of nephrons and particularly to the treatment with VEGF inhibitors. In addition, renal cell carcinoma can secrete vasoactive peptides, mainly endothelin-1. The presence of SAH in renal cell carcinoma may indicate more aggressive disease, with a negative impact on prognosis.[126,127] Pheochromocytoma and paraganglioma are neuroendocrine tumors of the chromaffin cells, with an annual incidence of 0.8 per 100 000 individuals. The SAH related to those tumors is caused by secretion of catecholamines (norepinephrine, epinephrine, and dopamine) and can be associated with symptoms, such as headache, palpitations, and sweating.[128]

Patients with cancer and SAH have a higher incidence of heart and kidney failures, and SAH is an independent risk factor for CAD, HF, and arrhythmia, being the major modifiable risk factor to prevent HF.[47,129]

Blood pressure should be properly and regularly measured in cancer patients (I, A).

Patients on anti-VEGF tyrosine kinase inhibitors, multi-targeted tyrosine kinase inhibitors, alkylating agents or high doses of steroids should undergo more frequent blood pressure monitoring (IIa, C).

The blood pressure goal in cancer patients follows the recommendations for patients without cancer: < 130 x 80 mm Hg (IIa, B).

The drug treatment should be personalized, but the presence of proteinuria or ventricular dysfunction determines the indication of ACEI or ARB (IIa, B).

If there is neither proteinuria nor ventricular dysfunction, a dihydropyridine calcium-channel blocker (amlodipine) can be initiated (IIa, C).

Diuretics should be used following a well-defined criterion and considering the risk for hypovolemia as well as for fluid and electrolyte imbalance (IIa, C).

Non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) in cancer patients (III, B). Because these drugs are metabolized via CYP3A4, they can alter the serum levels of antineoplastic drugs.

Secondary causes of SAH, such as hypovolemia and pain, should be investigated (IIa, C).

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