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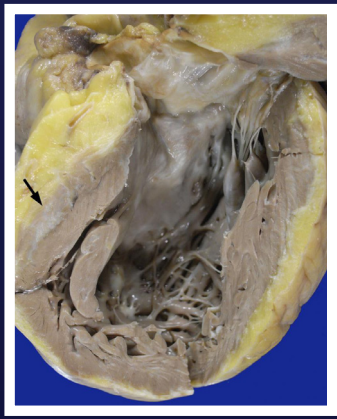

Figure 3 – *Left ventricular outflow tract. Note the moderate dilatation of the cavity, hypertrophy of the wall and area of subepicardial fibrosis (arrow). Page 199*

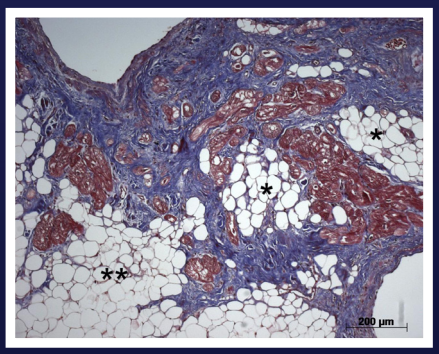

Figure 4 – *Histological section of the right ventricular inlet. The myocardium shows replacement with adipose cells (asterisks), and deposition of collagen (stained in blue) amid the cardiomyocytes (stained in red). Masson's trichrome staining. Page 200*

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What are the Characteristics of an Excellent Review of Scientific Articles?

Carlos Eduardo Rochitte[1] and Claudio Tinoco Mesquita[2]

Instituto do Coração do Hospital das Clínicas da FMUSP (InCor – HCFMUSP);[1] Hospital do Coração (HCOR),[2] São Paulo, SP; Universidade Federal Fluminense (UFF),[3] Niterói, RJ; Hospital Pró-Cardíaco,[4] Rio de Janeiro, RJ – Brazil

The selection by a scientific journal's editor-in-chief and associate editors of a manuscript for publishing is mainly, although not exclusively, based on the opinion of the manuscript's reviewers. This process is known as peer review and consists on the manuscript's assessment by experts in the area, who judge the scientific merit of the manuscript submitted to the journal. This process is expected to accept the better science for publishing, while refusing that of lower merit. Other standards and rules followed by editors of international journals contribute to improve the scientific quality of the journals.[1] One of the most important contributions of peer review is the refinement of the manuscript regarding its clarity and content. To optimize the reviewer's contribution in this process, understanding the characteristics involved is necessary.

In the peer-review system, it is crucial that the reviewer's scientific opinion be transmitted to the editors in a clear and focused way regarding the essential aspects for decision making. This information is conveyed through writing by the reviewer in the review system of a given journal. Dealing with online article submission and review systems is challenging, and most of such systems are neither intuitive nor easy to use. However, this editorial will not focus on such difficulties, which can usually be overcome with the support of assistant editors and an efficient editorial office, which we fortunately have for the Brazilian Society of Cardiology (SBC) journals: the *Arquivos Brasileiros de Cardiologia* and the *International Journal of Cardiovascular Science*. We will address the specific topics that should be clearly indicated by the reviewers to allow the editors to make their best decision possible. In addition to local specific suggestions that the SBC journals' editors consider important, we add recommendations of other editors for an excellent-quality review.[2,3]

An excellent review requires time and effort of the reviewer, in addition to a non-trivial work of checking the literature in the manuscript's specific area. That time tends to decrease as the reviewer gains more experience, but, on average, it ranges from 2 to 3 hours. The reviewer is rewarded with the knowledge and updated view of the specific area, in addition to the possibility of influencing the text that will be read by the scientific cardiovascular community. An excellent review will play a crucial role in the manuscript's acceptance or rejection, as well as significantly improve the manuscript's quality. It is a great opportunity for the reviewer not only to participate in the dissemination of innovation and new knowledge, but to directly influence it, in addition to being aware, prior to other colleagues, of the innovations that are in the pipeline, that is, in the publishing process. Usually, our reviewers are chosen based on their capability and technical knowledge in cardiovascular science and their history of publishing in that specific field, which make them highly trained in article editing, often qualifying them as excellent reviewers. However, the process of article selection usually requires specific responses focused in certain aspects of the manuscript that can pass unnoticed by the reviewer. In addition, different journals can differ in the way reviewers and editors communicate. Many reviewers never receive any formal guidance on what editors consider essential in reviews. This document will provide the reviewers with the information the *Arquivos Brasileiros de Cardiologia* and *International Journal of Cardiovascular Science* editors would like to find in an excellent review for their journals.

The scientific reviewers are invited to represent the journals in selecting articles of high scientific quality for publishing. The reviewers should protect our journals from articles with evident flaws or with methodological errors, inappropriate analysis or conclusions. In that aspect, the reviewers act as judges. In addition, they are expected to act as consultants to the authors to improve the article. Another characteristic of the process is that almost all articles that undergo peer review, whether accepted or not for publishing, end up improved.

Many reviews begin with a short summary of the manuscript. Although the editors have already read the manuscript, this summary provides them with the perspective of the reviewer, an expert in the area. Thus, the manuscript's summary, although not mandatory, is extremely useful for the editors and highly recommendable.

The essence of a review is the manuscript's assessment and how it will serve the scientific process. The reviewer should ask himself the following questions: Is there a rationale for the study's objectives? How important is the hypothesis being tested? The term 'important' here can have several meanings, depending on the subjective view of each reviewer, but a point considered critical is whether the hypothesis is original and has not been tested before in the literature. The famous gap in the literature is what we search in a manuscript to justify its publication. Metaphorically speaking, we look for a hole in the cardiovascular science wall to put a brick in it. Or, more directly speaking: Is it new? Is it true? Does anybody care about it? Or: Is the manuscript original, precise, valid and relevant?

Keywords

Authorship and Co-Authorship in Scientific Publications; Scientific and Technical Publications; Peer Review; Peer Review, Research; Journal Impact Factor.

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Editorial

Continuing with the technical questions on the manuscript being reviewed, reviewers should ask: Are the methods for data collection and analysis appropriate and accurate? Are the results significant for the area? Can the conclusions be supported by the results? We suggest such questions be divided into two types: general and specific comments. The general comments are the most important ones and should comprise the manuscript's positive and negative general aspects. For example, if there is an important methodological flaw or if the sample size is insufficient, or if originality is a strength. Those aspects should be part of the general comments. The specific comments comprise grammar or sentence corrections and suggestions of change in tables and figures, which are formal aspects to be fixed, and the reviewer should indicate their respective page and paragraph.

It is worth noting how frequent such data lack in the reviewer's comments, leaving the interpretation for the editors. Would that lack of information indicate that the article is suitable for publication?

The best reviews compare the manuscript with the current literature in the specific area, in addition to providing the references that support the reviewer's opinions, especially regarding the manuscript's originality. Quite often, editors must judge a manuscript based on different opinions from different reviewers. Very likely, the opinion supported by the literature will prevail.

A common mistake in our editing management system is when reviewers repeat the comments to authors in the space reserved for comments to editors. This space is intended for confidential comments, where reviewers are free to justify directly why they accept or reject the manuscript, or even suggest its rejection or acceptance, justifying their decision. In that same space, reviewers can comment if the manuscript is suitable for our audience. Although this is a fundamental task of editors, the reviewer's opinion will be considered, and often the editors will follow the reviewer's opinion.

It is worth noting and emphasizing that, in the 'comments to authors' section, reviewers should never state whether the manuscript would or would not be accepted. The authors should only receive comments on specific scientific merits and suggestions for improvement. Nevertheless, despite the determinant role of the review in the fate of the manuscript, the final decision of acceptance or refusal is up to the editors, and, eventually, to the editor-in-chief.

It is worth noting the practical fact that the review is undoubtedly a very individual process, to which there is no formal training, and, similarly to medicine, an art. Thus, the result of the scientific review is necessarily a mix of scientific merit and the reviewer's opinion. From the editors' viewpoint, reviewers must acknowledge that our journals, whose best impact factor is 1.18, will receive manuscripts with scientific limitations inherent in any submission, but possibly more evident in our cases. In this context, the reviewer should decide whether the manuscript, despite its limitations, deserves to be published or not, and communicate that clearly to the editors, in the 'confidential comments to editors' space. Excessive rigidity is not recommended at that point. Assess and reflect. Be neither aggressive nor rude. Be technical. Remember the large amount of effort the colleagues put into the task, from the project elaboration to the manuscript's final writing. In the next step, the reviewer should act as a consultant to authors, clearly indicating which changes should be made to provide the manuscript with quality for publishing.

Finally, be concise. Short and objective texts, and even a list of items of the changes suggested, are sufficient. Do not exceed one page of text with single line spacing. We do not recommend long reviews with endless lists of changes. Even the specific comments on shape and grammar, if frequent in the manuscript, can be summarized as only one suggestion of extensive grammar review. Our journals can use writing consultants in English and Portuguese. The same is valid for the statistical analysis, for which we count on a statistical appraiser and consultant for all manuscripts submitted.

The review of scientific articles and reviewers are extremely important for the scientific community in general and for the existence of the journals. Despite the increasing trend towards previous publishing in repositories prior to peer review to accelerate the dissemination of the results, peer review is fundamental for the reliability of an article in the scientific community. Thus, the review of scientific manuscripts is a huge responsibility of inestimable value, which leads editors to keep in mind the names of the high-quality reviewers. To confirm that value, we will go beyond the prizes for the most punctual reviewer, enhancing the awards and recognition in our scientific community for reviewers who perform best. Wait and see!

The following table summarizes our recommendations for reviewers.

We hope to have contributed to foster an efficient dialogue between reviewers and editors in the coming years, in addition to yielding an increasingly suitable selection of articles for publishing in our journals.

RECOMMENDATION FOR SCIENTIFIC REVIEWERS	
STRUCTURE OF THE REVIEW	
COMMENTS TO AUTHORS	
1. Manuscript summary from the reviewer's perspective	How the reviewer "sees" the article. Describe in your own words the objectives, methods and important findings. How does the article compare in the literature?
2. General comments	**These are the most important comments that support and justify acceptance or refusal**. In this section of comments to authors, never state your opinion on whether the manuscript should or should not be accepted, not even the possibility of acceptance or rejection.
2.1. Originality	Assess originality and make a quick literature search in the topic and authors. Assess what has been published. This is the most common reason for refusal.
2.2 Validity	Check if the data are valid: sample, appropriate data collection and analysis, sound statistics. Avoid asking for more cases or analysis, unless it is possible. Are the results valid for other populations?
2.3 Relevance	State your opinion on whether the study is relevant and why. What is the importance of the findings in the specific area? How does the study suit the needs of our journals' readers?
2.4 Extras	Comment on other strengths (well written, significant sample size), weaknesses (inappropriate methodology, unreliable data analysis), severe mistakes or very important limitations, extension of the manuscript and its parts (appropriate, too short, too long).
3. Specific comments	List punctual formal and grammar mistakes, meaningless sentences, correction of tables and figures, specific questions about certain points (how participants were selected, ask more details about the methodology, ask for specific statistic methods, express doubts about data collection and analysis, and how measurements were taken). Check the references (if they correspond to the text where they are indicated and if they are in the correct order), at least some randomly. But do not exceed in detail here. What matters most is your opinion about the manuscript in the 'general comments' space.
CONFIDENTIAL COMMENTS TO EDITORS	Very important section. Do not skip it. Give your honest opinion on the manuscript. Here the reviewer can directly state to the editors his opinion on whether the manuscript should be accepted or refused. Be technical, but be aware that the manuscripts submitted to our journals usually have limitations. Avoid extreme rigidity! In your opinion, is publishing the article a priority? If approved, should there be an editorial about the article? State whether the manuscript requires minor, major or more extensive reviews. In case of rejection, can the manuscript be resubmitted after being fully rewritten (de novo submission)? Acceptance without any review is rare, but, if that is the case, justify!

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Low-Flow Low-Gradient and Low-Ejection Fraction Aortic Stenosis and Projected Aortic Valve Area Calculation: So Important but so Complicated. Let us Just Keep it Simple!

Wilson Mathias Junior

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Low-flow low-gradient aortic stenosis with low ejection fraction is still one of the main challenges not only for echocardiography but to cardiology itself. It is the very late stage of aortic stenosis that portends very poor prognosis with medical treatment, in addition to a very high operative mortality.[1] In subjects with that condition, dobutamine stress echocardiography is of paramount importance to stratify aortic stenosis status (real aortic stenosis vs pseudo aortic stenosis) and to predict surgical mortality by the evaluation of the left ventricular contractile reserve status.[1-3]

To better differentiate both parameters, the sole use of the variation of the absolute values of aortic valve area and flow through the outflow tract carries major problems due to load conditions, previous use of medication, such as betablockers, and submaximal stress. All of these limitations may impede the detection of maximal cardiac output, a marker of contractile reserve and, therefore, may underestimate the aortic valve area.

In this regard, the use of the projected aortic valve area tends to correct these limitations and helps us to better predict the patients who tend to get the best benefit from surgery and those who would be less harmed using medical management. Unfortunately, the current formula proposed initially by Blais et al. is cumbersome and of difficult use in clinical practice, especially in high volume centers.[4] Despite the fact that the current equation was already simplified,[5] the calculation of flow, in addition to burdensome, may induce to additional errors, because it involves many parameters, such as left ventricular outflow tract (LVOT) diameter and ejection time, and LVOT velocity time integral.

Keywords

Aortic Valve Stenosis / surgery; Stroke Volume; Echocardiogrphy, Stress / methods.

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In this regard we welcome the work by Ferreira et al.[6] in this issue of *Arquivos Brasileiros de Cardiologia*. By using the simplified flow rate calculation (bellow), they could reach a very high concordance with the classical approach. They found that, on average, the alternative method overestimated the projected aortic valve area in 0.037 cm^2 when comparing to the classic method (95% CI: 0.004-0.066), a variation that is clearly not clinically significant, because this error is lower than 0.1 cm^2. Their work is not final though, because their findings are mainly based on the analysis of nine patients.

Therefore, when studying a patient with low-flow, low-gradient and low-ejection fraction aortic stenosis, one should always keep in mind the formulas and the explanatory diagram below, to better stratify this very difficult group of patients.[7] Here is a situation where a carefully performed study may make a difference between life and death. It should be performed by all in all studies! So, let us just keep it simple!

Alternative flow calculation formula:

$$\mathbf{Q\_alternative = AST_{LVOT} \times (Vmean_{LVOT} \times 100)}$$

where Q is flow in mL/s, AST_{LVOT} is the sectional transverse area of the left ventricular outflow tract (LVOT) in cm^2, and $Vmean_{LVOT}$ is the mean blood flow velocity by pulsed wave Doppler at the LVOT level during left ventricular ejection, being expressed in m/s.

Alternative valve area calculation formula:

$$\mathbf{AVAproj = AVArest + (AVApeak - AVArest / Qpeak - Qrest) \times (250 - Qrest)}$$

where AVArest is the aortic valve area measured by the continuity equation at rest in cm^2, AVApeak is the aortic valve area measured by the continuity equation at peak dobutamine infusion in cm^2, Q_{rest} is the alternative measurement of flow at rest expressed in mL/s, and Q_{peak} is the alternative measurement of flow at peak dobutamine infusion expressed in mL/s.

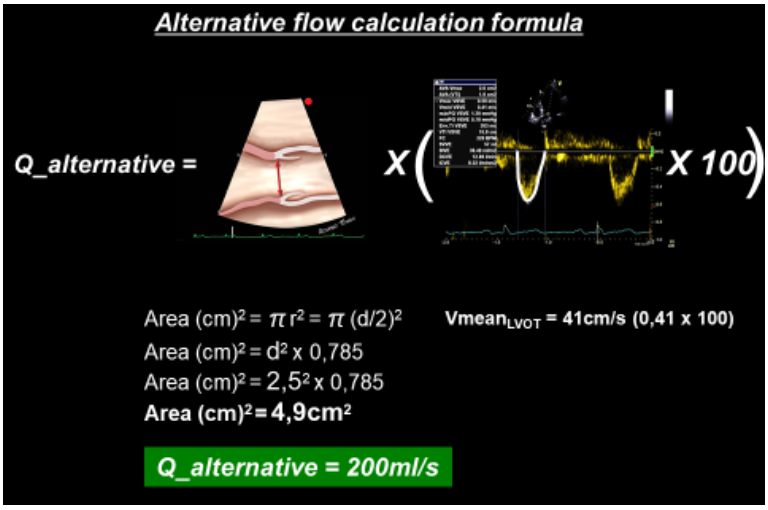

Figure 1 – *Alternative flow calculation formula where: $Q_{alternative}$ is flow in mL/s, AST_{LVOT} is the sectional transverse area of the left ventricular outflow tract (LVOT) in cm^2, and $Vmean_{LVOT}$ is the mean blood flow velocity by pulsed wave Doppler at the LVOT level during left ventricular ejection, being expressed in m/s.*

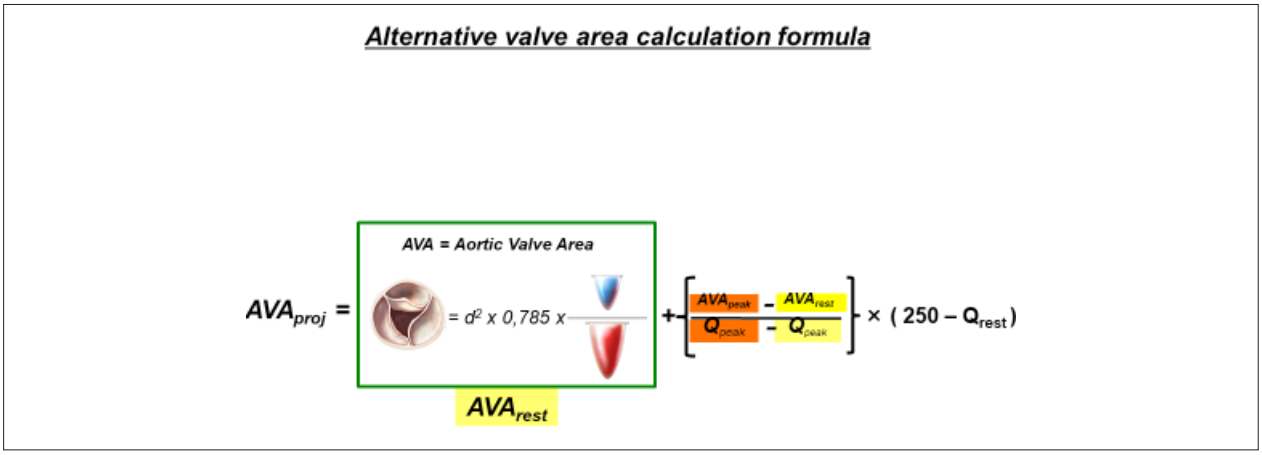

Figure 2 – *Alternative valve area calculation formula where: AVArest is the aortic valve area measured by the continuity equation at rest in cm^2, AVApeak is the aortic valve area measured by the continuity equation at peak dobutamine infusion in cm^2, Q_{rest} is the alternative measurement of flow at rest expressed in mL/s, and Q_{peak} is the alternative measurement of flow at peak dobutamine infusion expressed in mL/s.*

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The Indeterminate Form of Chagas Disease

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The presence of diffuse fibrosis in the myocardial tissue is a characteristic of Chagas heart disease.[1] The mechanisms proposed to explain such fibrosis areas vary and include direct injury by *Trypanosoma cruzi* to the cardiac tissue, as well as tissue ischemia due to microcirculation changes and microvascular thrombosis mediated by inflammatory[2] and immune[3] processes. The myocardial fibrosis not only reveals important aspects of the pathophysiology of the disease, but has a clinical significance,[4] because its progression can lead to injury to the heart conduction system, contributing to generate arrhythmia, as well as systolic and diastolic ventricular dysfunction, in addition to favoring the appearance of thromboembolic phenomena from the hypokinetic or akinetic areas.

This issue of the *Arquivos Brasileiros de Cardiologia* presents the results of a study jointly conducted by three different centers in the city of Salvador, Bahia state, about the clinical significance of the fibrosis found in patients with Chagas disease, in both the indeterminate and heart disease (with and without left ventricular dysfunction) stages. The search for fibrosis was performed by use of late enhancement cardiac magnetic resonance imaging. The authors have reported late enhancement compatible with fibrosis in 41% of the patients with the indeterminate form, a figure similar to that found in patients with heart disease without ventricular dysfunction. In addition, it is worth noting the similar findings in the other groups regarding the clinical characteristics and the levels of type B natriuretic peptide, troponin, interleukins 2, 4, 6 and 10, tumor necrosis factor alpha and gamma interferon.[5]

Previous studies have identified myocardial fibrosis in patients with Chagas disease and correlated its intensity with the severity of ventricular dysfunction and symptoms. A study of 51 patients with Chagas disease using late enhancement technique has identified images compatible with myocardial fibrosis in 20% of the 15 patients with the indeterminate form.[6] Similar results have been found by using other imaging techniques: a study of 40 patients with the indeterminate form of Chagas disease, using echocardiography and single photon emission computed tomography (*gated*-SPECT) myocardial perfusion imaging, has detected some changes in perfusion and myocardial motion in 25% of the individuals, including perfusion defects, reduced ejection fraction and intraventricular dyssynchrony.[7]

The finding by Rabelo et al.[5] of similar phenotypes in patients with the indeterminate form and those with heart disease (and normal left ventricular function) draws attention to the discussion on the meaning of the indeterminate form definition. This concept has been applied to patients with positive serology for *Trypanosoma cruzi* and neither gastrointestinal disease nor myocardial injury identified on clinical assessment, chest X-rays and electrocardiogram. However, the value of that definition has been questioned based on the current methods to assess cardiac function and morphology. One way to estimate the value of those findings is to assess the long-term outcome of patients.[8] A study from 2001 of 160 patients with the indeterminate form, followed up for 98 months, and based on clinical, electrocardiographic and echocardiographic findings (two-dimensional and M mode) has reported stable ejection fraction during follow-up despite the appearance of electrocardiographic changes.[9] A study with a 10-year follow-up of blood donors with positive serology for *Trypanosoma cruzi* has estimated the incidence of the progression to heart disease in 1.85 per 100 individuals-year, with heart disease diagnosis based on electrocardiographic and two-dimensional echocardiographic changes.[10] However, studies assessing the long-term follow-up of patients with the indeterminate form of Chagas disease by using the currently available techniques for analysis of myocardial function and morphology and mortality data still lack.

Finally, despite the progression over the last decades of the methods to identify the patients at higher risk or with subclinical morphological changes, the likelihood of the patients' prognostic improvement still faces the limitations of therapy, especially considering the negative results of the etiological treatment of Chagas disease's chronic forms.[11] Those and other difficulties that persist in the management of patients with Chagas disease are a constant challenge for the doctors and researchers who cope with such a severe condition.

Keywords

Chagas Disease/physiopathology; Chagas Cardiomyopathy; Ventricular Dysfunction; Endomyocardial Fibrosis; Diagnostic Imaging, Epidemiology.

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Is There Any Relationship between TSH Levels and Prognosis in Acute Coronary Syndrome?

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Abstract

Background: **Some small studies have related higher levels of thyrotropin (TSH) to potentially worse prognosis in acute coronary syndromes. However, this relationship remains uncertain.**

Objective: **To analyze the outcomes of patients with acute coronary syndromes in relation to the value of TSH at admission.**

Methods: **Observational and retrospective study with 505 patients (446 in group I [TSH ≤ 4 mIU/L] and 59 in group II [TSH > 4 mIU/L]) with acute coronary syndromes between May 2010 and May 2014. We obtained data about comorbidities and the medications used at the hospital. The primary endpoint was in-hospital all-cause death. The secondary endpoint included combined events (death, non-fatal unstable angina or myocardial infarction, cardiogenic shock, bleeding and stroke). Comparisons between groups were made by one-way ANOVA and chi-square test. Multivariate analysis was determined by logistic regression. Analyses were considered significant when $p < 0.05$.**

Results: **Significant differences between groups I and II were observed regarding the use of enoxaparin (75.2% vs. 57.63%, $p = 0.02$) and statins (84.08% vs. 71.19%, $p < 0.0001$), previous stroke (5.83% vs. 15.25%, $p = 0.007$), combined events (14.80% vs. 27.12%, OR = 3.05, $p = 0.004$), cardiogenic shock (4.77% vs. 6.05%, OR = 4.77, $p = 0.02$) and bleeding (12.09% vs. 15.25%, OR = 3.36, $p = 0.012$).**

Conclusions: **In patients with acute coronary syndromes and TSH > 4 mIU/L at admission, worse prognosis was observed, with higher incidences of in-hospital combined events, cardiogenic shock and bleeding. (Arq Bras Cardiol. 2018; 110(2):113-118)**

Keywords: **Acute Coronary Syndrome; Thyrotropin/metabolism; Euthyroid Sick Syndromes; Hospital Mortality.**

Introduction

Patients with severe nonthyroidal illness often experience concomitant disorders in thyroid function. In severe illness of nonthyroidal origin, including acute myocardial infarction (AMI), the thyroid hormone system may be down-regulated. These conditions can induce changes in one or more aspects of thyroid hormone economy, leading to findings referred to as sick euthyroid syndrome, which poses a diagnostic and therapeutic challenge for the clinician. The cardiovascular system is very sensitive to thyroid hormones, and a wide spectrum of cardiac changes has long been recognized in overt thyroid dysfunction.[1-3]

The real value of thyrotropin (TSH) as marker of prognosis in acute coronary syndromes (ACS) is still uncertain. Therefore, the objective of this study was to analyze the outcomes of patients with ACS related with the TSH value measured in the emergency department.

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Methods

Study population

This was an observational, retrospective databank analysis study performed in a tertiary health centre with 505 patients with ACS included between May 2010 and May 2014. They were divided in two groups: TSH ≤ 4 mIU/L (group I, n = 446) and TSH > 4 mIU/L (group II, n = 59). Patients with known thyroid disorders were excluded.

All patients were diagnosed and treated according to the AHA/ESC Task Force guidelines.[4,5] All patients underwent percutaneous coronary intervention less than 24 hours after onset of ACS.

The primary outcome was in-hospital all-cause mortality. The secondary outcome was major adverse cardiac events (MACE) including death (of any cause), non-fatal unstable angina or AMI/target vessel revascularization, cardiogenic shock, bleeding (major and minor), and stroke.

The study was approved by the ethics and research committee.

Analytical methods

The following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoking habit, dyslipidemia, family history of premature coronary artery disease, heart failure, previous coronary artery disease, previous stroke, hematocrit, creatinine, higher troponin, systolic blood pressure, left ventricular ejection fraction and medications used (within the first 24 hours) (Table 1).

Blood was sampled immediately after admission, prior to administration of medications (baseline) and daily, according to institution protocol. TSH was obtained routinely in all patients with ACS. Cardiac markers such as troponin-I were measured using standard clinical chemistry. Laboratory upper limits of normal were 0.04 ng/mL (99th percentile) for troponin-I measured by *Elecsys 2010* (*Siemens Healthcare Diagnostics Inc., USA)* 4th generation immunoassay.

Major bleeding was defined using BARC[6] score types 3 and 5, and minor bleedings, types 1 and 2. Post-operative bleeding events were not considered.

Statistical analysis

Descriptive analyses of data collected included median, minimum and maximum values. Categorical variables were described as percentages. Comparisons between groups were made by ANOVA one-way and chi-square test (to categorical variables), and a p value < 0.05 was considered significant. If Kolmogorov-Smirnov tests confirmed a normal distribution, continuous variables were presented as mean ± standard deviation, and were compared using Student t test for independent samples. Mann-Whitney U test was used to compare not normally distributed continuous variables, which were presented as median and interquartile range.

Multivariate analysis was determined by logistic regression, and a p value < 0.05 was considered significant. The patients' baseline characteristics are shown in Table 1.

All statistical procedures were performed using the statistical software SPSS, version 10.0.

Results

The median age was 63 years, and approximately 59% of patients were male. Baseline characteristics and univariate analysis are shown in Table 1. ST-elevation myocardial infarction (STEMI) was observed in 18% of group I versus 24% of group II (p = 0.08) (Figure 1).

Multivariate analysis is shown in Table 2 and describes the differences between groups I and II in combined events

Table 1 – Baseline characteristics of patients according with TSH levels.

	TSH ≤ 4 mIU/L	TSH > 4 mIU/L	p
Age (mean)	62.5	66.3	0.86*
Male (%)	61%	51%	0.14#
Diabetes Mellitus (%)	39%	48%	0.38#
Hypertension (%)	80%	76%	0.49#
Smoking habit (%)	40%	37%	0.72#
FH of CAD (%)	13%	10%	0.56#
Dyslipidemia (%)	47%	48%	0.9#
Heart failure (%)	8%	10%	0.62#
Previous stroke (%)	6%	15%	0.007#
Previous AMI (%)	38%	48%	0.14#
Previous CABG (%)	18%	27%	0.08#
Previous PCI (%)	25%	32%	0.21#
Ht (%) (mean)	42.2	41.5	0.08*
Cr (mg/dL) (mean)	2.18	2.99	0.51*
SBP (mm Hg) (median)	134.5	133.8	0.24π
EF (%) (median)	42.5	33.7	0.62π
Troponin (higher) (ng/dL) (mean)	4.68	7.37	0.52*
ASA (%)	99%	93%	0.12#
Beta-blocker (%)	68%	54%	0.12#
Enoxaparin (%)	72%	58%	0.021#
ACE inhibitor (%)	51%	48%	0.64#
Statin (%)	83%	71%	< 0.001#

*TSH: thyrotropin; FH: family history; CAD: coronary artery disease; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; Ht: hematocrit; Cr: creatinine; EF: ejection fraction; ASA: acetylsalicylic acid; ACE: angiotensin-converting-enzyme; #: Q-square test; *: Student t test for independent samples; π = Mann-Whitney U test.*

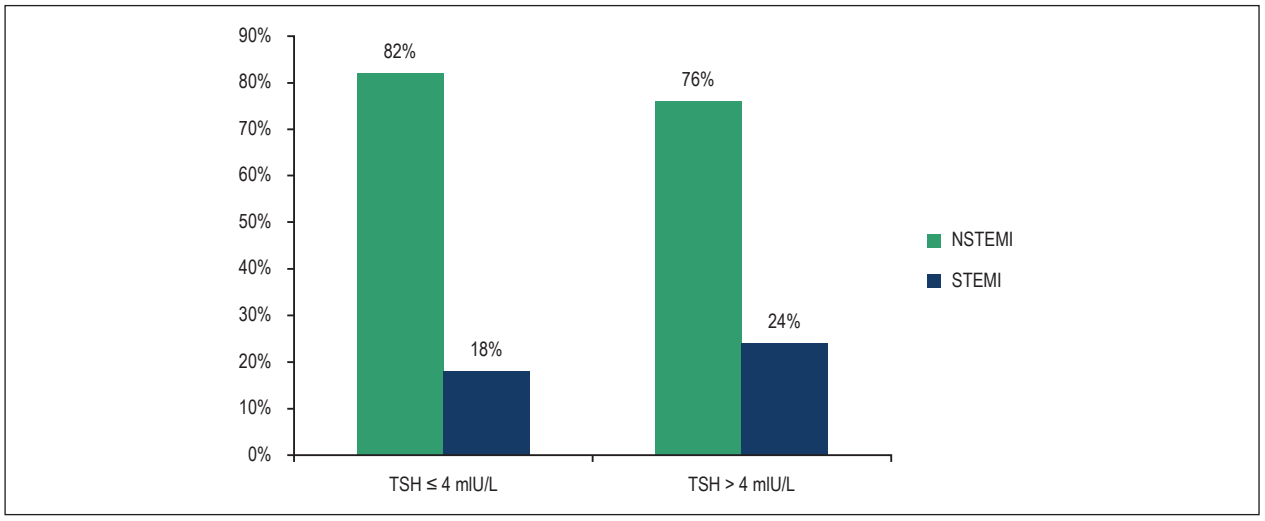

Figure 1 – *Classification of ACS according to TSH levels. NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; TSH: thyrotropin.*

Table 2 – Results of multivariate analysis of in-hospital outcomes comparing groups I and II

	TSH ≤ 4 mIU/L	TSH > 4 mIU/L	OR	95% CI	p
Reinfarction	1.3%	0%	0.2	0.11 – 3.45	0.37
Cardiogenic Shock	6.1%	13.6%	1.72	1.25 – 4.68	0.029
Bleeding	6.5%	15.3%	3.36	1.31 – 8.65	0.012
Stroke	0.9%	0%	0.9	0.15 – 9.32	0.9
Mortality	3.1%	8.5%	2.32	0.63 – 8.48	0.2
MACE	17.9%	37.4%	3.05	1.43 – 6.42	0.004

CI: confidence interval; MACE: major adverse cardiac events; TSH: thyrotropin.

(14.80% vs. 27.12%, respectively, OR = 3.05, p = 0.004), cardiogenic shock (4.77% vs. 6.05%, respectively, OR = 4.77, p = 0.02) and bleeding (12.09% vs. 15.25%, respectively, OR = 3.36, p = 0.012).

Discussion

The major finding of this study supports data previously published, showing that in-hospital MACE of patients with ACS were associated with higher levels of TSH. In addition, we also showed a relationship between TSH and cardiogenic shock and bleeding.

There are many possible pathophysiological explanations for the uncertain relationship between worse prognosis and thyroid hormones in cardiovascular diseases. Numerous studies have focused on the impact of subclinical thyroid dysfunction on the development of cardiovascular disease, especially ACS. However, we do not know if the TSH levels are higher prior to ACS or if they become higher at the moment of ACS.[2,3,7-11]

Triiodothyronine functions through interactions with isoform type α receptors, α1 or α2, and type β receptors, β1, β2 or β3.[2,3,12,13] Regarding their cardiac distribution, these receptors are located both on atrial cells, as well as on ventricular cells.[2,3,12-14] By binding to these receptors, thyroid hormones accelerate myosin synthesis and influence sarcoplasmic reticulum activity, movement through the ionic Ca and K channels, response of adrenergic receptors, transmembrane ion gradients, and the levels of ATP and of atrial natriuretic peptide.[2,3,12-14] The effects of thyroid hormones can be categorized as genomic or non-genomic, and can structurally and functionally influence cardiovascular proteins.[2,3] Acting on α receptors, triiodothyronine plays a role in the process of increasing myocardial contractility and enhancing myosin production. Acting on β receptors, they influence diastolic processes and left ventricular relaxation. The main mechanism is that of reducing the high levels of cytosolic calcium during systole. On a vascular level, triiodothyronine plays an essential role in the maintenance and renewal of endothelial integrity, in peripheral arterial resistance and in modulating the arterial response to the renin-angiotensin-aldosterone mechanism activation.[2,3,15] This hormone also controls the macrophage response to the deposition of lipids in the vascular wall.[2,3] Apart from these direct effects, thyroid hormones play an important role in the development of cardiovascular pathology by other mechanisms, such as influencing the coagulation process by controlling the levels of activated factor VII and the ratio of activated factor VII and anti-activated factor VII antibody.[2,3]

Specifically, hypothyroidism reduces cardiac output, blood volume, chronotropism and inotropism, and increases systemic vascular resistance, diastolic blood pressure, vascular wall thickness and stiffness, and afterload. The increase in peripheral resistance mainly induces left ventricular systolic dysfunction and abnormal relaxation, without modification of heart rate. Changes in arterial wall elasticity are involved in the progression of atherosclerotic processes. Effects on vascular endothelial function alter blood flow, and nitric oxide plays an important role in this process. Hypothyroidism decreases glomerular filtration rate, which influences circulating cholesterol levels and favors the development of type II diabetes complications.[2,3,16,17] These findings could partially justify the higher occurrence of ACS in this group of patients, and perhaps their worse prognosis. In addition, this mechanism could be associated with the development of cardiogenic shock, well described in our study.

In 2005, Walsh et al.[18] studied the relationship between thyroid hormone and cardiovascular events in 1,981 healthy individuals in Australia. In a cross-sectional study, they examined the prevalence of coronary heart disease in subjects with and without subclinical thyroid dysfunction. In a longitudinal study, they examined the risk of cardiovascular mortality and coronary heart disease events (fatal and nonfatal). Subjects with subclinical hypothyroidism (n = 119) had a significantly higher prevalence of coronary heart disease than euthyroid subjects (OR = 1.8; 95% CI: 1.0 - 3.1; p = 0.04). In the longitudinal analysis of subjects with subclinical hypothyroidism, 33 coronary heart disease events were observed as compared to 14.7 expected (HR = 1.7; 95% CI: 1.2 - 2.4; p = 0.01).[18]

Another study[1] in 2005 investigated whether thyroid hormone levels had any predictive value for mortality in patients presenting to the emergency department with AMI. Three groups of patients admitted to the emergency department within the 11-month study period: 95 patients with chest pain and diagnosed AMI; 26 patients with chest pain and no AMI; and 114 controls with no evidence of any major disease. Cardiac enzymes and thyroid hormones were analyzed and compared between groups to examine the effects of historical and demographic factors. Sixteen patients with AMI (16.8%) died within the study period. Troponin and creatine kinase M-type subunit levels were significantly higher among non-survivors as compared with survivors. Survivors in the AMI group had higher levels of triiodothyronine and total thyroxine and lower free thyroxine levels, while non-survivors in the AMI group had higher TSH and lower triiodothyronine, total thyroxine and free thyroxine levels than controls. In logistic regression, TSH levels were not significantly different between survivors and non-survivors (1.08 mIU/L vs. 1.84 mIU/L, p = 0.1). The conclusion was that triiodothyronine and lower free thyroxine appeared to be independent prognostic factors in patients with AMI.[1] In our study, we showed a trend towards higher levels of troponin and TSH. However, correlation until this moment was not significant. Differences might appear with a larger sample.

On the other hand, in 2014, Him et al.[19] retrospectively reviewed the relationship between thyroid hormone levels and AMI severity in 40 patients with STEMI, and the extent of transmural involvement was evaluated via contrast-enhanced cardiac magnetic resonance imaging. The high triiodothyronine group (≥ 68.3 ng/dL) exhibited a significantly greater transmural involvement (late transmural enhancement > 75% after administration of gadolinium contrast agent) than did the low triiodothyronine group (60% vs. 15%, p = 0.003). However, a significant difference was not evident between the high- and low-TSH and free thyroxine groups. When the triiodothyronine cut-off level was set to 68.3 ng/dL using a receiver operating characteristic curve, the sensitivity was 80% and the specificity was 68% in terms of differentiating between those with and without transmural involvement.[19]

Friberg et al.[20] have described a possible rapid down-regulation of thyroid hormones in patients with AMI. Forty-seven consecutive euthyroid patients with AMI were studied prospectively during the first 5 days, and again 6 and 12 weeks after AMI. They observed that the thyroid system was rapidly down-regulated with maximal changes appearing 24 to 36 hours after onset of symptoms. Levels of TSH declined 51% (p < 0.001) between the first 6 hours and the 24 to 36-hour period. The authors also described a strong relationship between inflammation (high levels of C-reactive protein and cytokine interleukin 6) and a greater down-regulation of the thyroid system. Alternatively, MACE were high among patients with the most pronounced TSH depression, indicating that the down-regulation observed after AMI may be maladaptive. Lower TSH levels measured at 5 days significantly correlated with mortality in one year (1.0 mIU/L vs. 1.6 mIU/L, p = 0.04, respectively, between dead and alive patients).[20] This difference from our results may be because we did not assess TSH levels on the first and fifth days after ACS in our study. Our analysis of only the initial sample at hospital admission was not included in that study by Friberg et al.[20]

Another study has investigated whether changes in plasma thyroid hormone levels were associated with the recovery of cardiac function in patients with AMI. A total of 47 patients with AMI and early reperfusion therapy were included in this study. Cardiac function was assessed by echocardiography; left ventricular ejection fraction and function recovery were evaluated 48 hours and 6 months after AMI. A strong correlation was found between function recovery and total triiodothyronine levels ($r = 0.64$, $p = 10^{-6}$) 6 months after AMI. Furthermore, multivariate regression analysis revealed that triiodothyronine at 6 months was an independent determinant of ventricular function recovery. TSH levels were not significantly different between the two groups (with and without ventricular function recovery) during the acute phase of myocardial infarction, but at 6 months, TSH levels were significantly higher in the group without recovery as compared with the group with better recovery of ventricular function (2.9 vs. 1.46, p < 0.05).[21]

A study published in 2016 assessed a prospective 3-year cohort with 2430 patients submitted to percutaneous coronary intervention with *versus* without hypothyroidism. The authors related a higher number of MACE (myocardial infarction, stroke, revascularization) in patients with hypothyroidism or TSH > 5.0 mIU/L (HR = 1.28, p = 0.0001).[22] These data were similar to our findings, but they evaluate long-term prognosis. However, the association with worse prognosis was the same, including the similar value of TSH described.

In summary, different studies have shown a relationship between prognosis and the level of thyroid hormones in ACS. However, the best cut-off, the ideal moment to evaluate TSH levels, and the expected changes after ACS are not known. Combining our results with others from the literature, we postulate that the value of TSH on hospital admission could be helpful and that the prognosis is worse if TSH levels are high at that timepoint. In addition, including the evaluation of other thyroid hormones could be beneficial.

Limitations

This study showed some limitations, such as the small number of patients evaluated. In addition, we did not measure other thyroid hormones. In addition, this is a retrospective study, and the group with higher TSH levels had worse baseline characteristics, such as higher troponin levels and lower ejection fraction. However, this is an original and novel observation, and other prospective studies will be required.

Conclusion

In patients with ACS and TSH > 4 mIU/L on hospital admission, worse prognosis was observed, with higher incidences of in-hospital MACE, cardiogenic shock and bleeding events.

Author contributions

Conception and design of the research: Soeiro AM, Araújo VA, Vella JP, Oliveira Junior MT; Acquisition of data: Soeiro AM, Araújo VA, Vella JP, Bossa AS, Biselli B, Leal TCAT, Soeiro MCFA; Analysis and interpretation of the data: Soeiro AM; Análise estatística: Soeiro AM, Bossa AS; Writing of the manuscript: Soeiro AM, Araújo VA, Vella JP; Critical revision of the manuscript for intellectual content: Soeiro AM, Soeiro MCFA, Serrano Jr. CV, Mueller C, Oliveira Junior MT.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number 38511114700000068. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Clinical, Anthropometric and Biochemical Characteristics of Patients with or without Genetically Confirmed Familial Hypercholesterolemia

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Abstract

Background: Familial hypercholesterolemia (FH) is a common autosomal dominant disorder, characterized by a high level of low-density lipoprotein cholesterol (LDL-C) and a high risk of premature cardiovascular disease.

Objective: To evaluate clinical and anthropometric characteristics of patients with the familiar hypercholesterolemia (FH) phenotype, with or without genetic confirmation of FH.

Methods: Forty-five patients with LDL-C > 190 mg/dl were genotyped for six FH-related genes: LDLR, APOB, PCSK9, LDLRAP1, LIPA and APOE. Patients who tested positive for any of these mutations were considered to have genetically confirmed FH. The FH phenotype was classified according to the Dutch Lipid Clinic Network criteria.

Results: Comparing patients with genetically confirmed FH to those without it, the former had a higher clinical score for FH, more often had xanthelasma and had higher LDL-C and apo B levels. There were significant correlations between LDL-C and the clinical point score for FH (R = 0.382, p = 0.037) and between LDL-C and body fat (R = 0.461, p = 0.01). However, patients with mutations did not have any correlation between LDL-C and other variables, while for those without a mutation, there was a correlation between LDL-C and the clinical point score.

Conclusions: LDL-C correlated with the clinical point score and with body fat, both in the overall patient population and in patients without the genetic confirmation of FH. In those with genetically confirmed FH, there were no correlations between LDL-C and other clinical or biochemical variables in patients. (Arq Bras Cardiol. 2018; 110(2):119-123)

Keywords: Hyperlipoproteinemia Type II; Body Weights and Measurements, LDL Lipoproteins, Dyslipidemias, Mutation, Phenotype.

Introduction

Familial hypercholesterolemia (FH) is characterized by a high level of low-density lipoprotein cholesterol (LDL-C) and a high risk of premature cardiovascular disease.[1] It is a common autosomal dominant disorder, affecting up to 1 in 200–250 people in its heterozygous form.[2] According to the Dutch Lipid Clinic Network, the clinical diagnosis of FH (FH phenotype) is based on high LDL-C and a score in which points are assigned for family history of hyperlipidemia or heart disease, clinical characteristics such as tendinous xanthomata, elevated LDL cholesterol, and/or an identified mutation. A total point score greater than eight is considered "definite" FH, 6–8 is "probable" FH, and 3–5 is "possible" FH.[3]

Despite being helpful as they provide a standardization of the diagnosis of the FH phenotype, scores may not necessarily result in consistent diagnoses of FH, as cholesterol levels for FH patients overlap with those of the general population. Genetic diagnosis is considered evidence of definite FH according to some criteria.[1] Mutations in 3 genes- the LDL-receptor gene (LDLR), the gene coding for apolipoprotein B and the gene encoding the proprotein convertase subtilisin/kexin type 9-are usually responsible for FH.[4-6] However, other mutations have been identified in the LDLR gene, as well as mutations in other genes leading to the clinical FH phenotype, and there is also evidence that some mutations lead to more severe manifestations of FH than others. Additionally, a large proportion of the patients with a clinical diagnosis of FH do not have a detectable mutation in any of these genes.[7,8]

In view of the complexity of this scenario, there is continuing need for additional information on the clinical and laboratory profile of patients with either genetically defined FH or with only the phenotype of FH, since such data might help optimize patient management, in the sense of their cardiovascular risk burden. Therefore, this study sought to evaluate clinical and anthropometric characteristics of patients with or without genetic confirmation of FH.

Methods

Study population

This was a cross-sectional study of adult outpatients with severe hypercholesterolemia recruited at the National

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Institute of Cardiology in Rio de Janeiro, Brazil. Subjects with LDL-C > 190 mg/dl and in use of lipid-lowering drug were selected after review of the lipid panel results over 6 months. These patients were invited by phone call to take part in the study, and those with acute coronary syndromes or myocardial revascularization in the previous 30 days, autoimmune diseases, thyroid disorders, chronic renal failure, liver diseases, malignancy, using steroids, or pregnant or breastfeeding were excluded. For this study, a convenience sample was used, including all patients who had been genetically screened to date. Once considered eligible, all participants read and signed an informed consent document approved by the institutional Ethics Committee. The study was undertaken in accordance with the Helsinki Declaration of 1975, revised in 2000.

The study patients underwent clinical evaluation and peripheral blood collection. The FH phenotype was classified according to the Dutch Lipid Clinic Network criteria.[3] Prior cardiovascular disease was defined as a history of myocardial infarction, evidence of obstructive coronary artery disease at coronary angiography (> 50% stenosis of any epicardial coronary artery), myocardial revascularization (either percutaneous or coronary artery bypass surgery) or stroke. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or antihypertensive drug use. Diabetes mellitus was defined by history and use of insulin or oral hypoglycemic medications, or fasting glucose levels > 126 mg/dl.

Anthropometric measurement

All patients underwent assessment of body composition. Body mass index (BMI) was calculated as weight in Kg/ (height)^2. Body composition (body fat percentage [%], visceral fat area [cm^2] and phase angle [degrees]) was estimated by bioelectrical impedance, using the multifrequency analyzer octopolar (In-Body 720; Biospace). The measurements were made with the patient in the supine position, with the arms lying parallel and separated from the trunk and with the legs separated, so that the thighs were not touching. Two electrodes were placed on the hand and wrist and another two were positioned on the foot and ankle of the non-dominant side of the body. An electrical current measured at six different frequencies (1, 5, 50, 250, 500 and 1000 KHz) was introduced into the subject, and resistance and reactance were measured. The phase angle was calculated according to the following equation: Phase Angle = arctangent (inductance / resistance) × 180º/ π.[9]

Laboratory measurements

For biochemical testing, venous blood samples were obtained in the morning after 12 h of fasting. The patients took their usual medications on the morning of the tests. Laboratory evaluations were performed by an automated method (ARCHITECT ci8200, Abbott ARCHITECT®, Abbott Park, IL, USA) using commercial kits (Abbott ARCHITECT c8000®, Abbott Park, IL, USA). Serum triglyceride levels, total cholesterol, LDL cholesterol (LDL-C), HDL-cholesterol (HDL-C), apolipoproteins A (apo A) and B (apo B) and C-reactive protein (CRP) were evaluated.

Genomic DNA was extracted from peripheral blood following a standard salting-out procedure. All DNA stock samples were quantified with Qubit dsDNA BR Assay Kit (Thermo Fisher) and diluted to 10 ng/ul for enrichment with Ion AmpliSeq Custom Kit (Thermo Fisher). Samples were enriched for six FH-related genes: LDLR, APOB, PCSK9, LDLRAP1, LIPA and APOE.

Patients who tested positive for any of these mutations were considered to have genetically confirmed FH. Target regions were considered as coding exons plus 10bp of introns up and downstream. Templates were prepared on Ion One Touch System and sequenced in Ion Torrent PGM ® platform, with 32 samples per run in a 316v2 Ion Chip. All FASTQ files were imported to CLC Genomics Workbench 9.5 (QIAGEN) and analyzed in a custom pipeline.

Minimum quality requirements for variant call were: Base quality of PhredQ ≥ 20; Target-region coverage ≥ 10x; Frequency of variant allele ≥ 20% and bidirectional presence of variant allele. After polymorphism filtering with control populations (NHLBI-ESP6500, ExAC and 1000Genomes), all potential mutations were consulted for previous description in ClinVar, Human Genome Mutation Database (HGMD), British Heart Foundation and Jojo Genetics databases. Functional impact prediction was performed with SIFT, PROVEAN and PolyPhen-2 and mutations without previous description should be pointed as damaging in at least two algorithms to be considered as potentially pathogenic. Individuals with negative results were also screened for large insertions and deletions via MLPA (MRC-Holland).

Statistical analysis

Continuous data were analyzed using two-tailed unpaired Student's t test or Mann-Whitney´s test, and categorical variables with *chi*-squared test. *Kolmogorov-Smirnov test was performed to* determine whether sample data was normally distributed. Continuous variables are reported as means ± standard deviations, and categorical variables are presented as percentages. Correlations between continuous variables were analyzed with Pearson`s test. Analyses were performed with SPSS software, version 21.0, and p values < 0.05 were considered statistically significant. Statistical review of the study was performed by a biomedical statistician.

Results

Forty-five patients with LDL-C > 190 mg/dl were studied, of which fifteen had positive testing for familial hypercholesterolemia and thirty had negative. Comparing patients with genetically confirmed FH to those without it (Table 1), the former had a higher clinical score for FH, were more frequently considered to have definite FH, and more often had xanthelasma. Of note, the prevalence of prior coronary artery disease or stroke were not significantly different between patients with or without the genetic diagnosis of FH. Mean LDL-C and apo B levels were higher in patients with a molecular diagnosis of FH (Table 2).

When the correlations between LDL-C levels and other clinical, demographic and anthropometric variables were examined, there was a weak, although significant correlation between LDL-C and the clinical point score (R = 0.382, p = 0.037) and a moderate and significant correlation between LDL-C and body fat (R = 0.461, p = 0.01).

Table 1 – Demographic, anthropometric and clinical characteristics of patients with positive or negative genetic testing for familial hypercholesterolemia

	Positive (n = 15)	Negative (n = 30)	p-value
Age (years)	51.7 ± 14.4	55.6 ± 12.6	0.376
Weight	71.4 ± 16.1	70.8 ± 15.7	0.906
Body mass index (Kg/m²)	27.9 ± 6.1	28.3 ± 5.1	0.784
Body fat (%)	39.1 ± 9.4	35.6 ± 8.2	0.262
Visceral fat area (cm²)	110.3 ± 34.0	104.6 ± 34.3	0.639
Waist circumference (cm)	95.6 ± 10.6	96.5 ± 11.9	0.589
Hip circumference (cm)	104.4 ± 11.6	102.8 ± 12.1	0.676
Women	14 (93.3)	18 (60.0)	0.019*
Clinically defined FH	10 (66.7)	4 (13.3)	0.001*
Score	9.64 ± 2.16	4.35 ± 1.58	0.001*
Risk factors and clinical data			
Hypertension	8 (53.3)	20 (71.4)	0.197
Diabetes	3 (20.0)	6 (21.4)	0.619
Obesity	7 (46.7)	9 (30.0)	0.219
Smoking	0	3 (10.7)	0.265
Corneal arch	3 (20.0)	1 (3.7)	0.122
Xanthomata	0	0	
Xanthelasma	3 (20.0)	0 (0)	0.04*
Angina	6 (40.0)	12 (42.0)	0.559
History of stroke	0 (0)	1 (3.6)	0.651
History of myocardial infarction	3 (20.0)	11 (39.3)	0.173
Prior coronary angioplasty	3 (20.0)	11 (40.7)	0.153
Prior coronary bypass	4 (26.7)	5 (17.9)	0.381

Numbers are n (%), for categorical variables, or mean ± SD, for continuous variables; (*) p < 0.05; FH: familial hypercholesterolemia.

Table 2 – Laboratory data of patients with positive or negative genetic testing for familial hypercholesterolemia

	Positive (n = 15)	Negativo (n = 30)	p-value
Total cholesterol (mg/dL)	263.1 ± 93.1	231.0 ± 57.4	0.417
LDL-C (mg/dL)	208.1 ± 41.8	151.4 ± 50.6	0.002*
HDL-C (mg/dl)	52.2 ± 9.7	50.1 ± 12.0	0.617
Apo A1 (mg/dL)	139.3 ± 19.9	140.1 ± 22.9	0.916
Apo B (mg/dL)	138.7 ± 30,2	106.3 ± 31.6	0.005*
Triglyceride (mg/dL)	127.9 ± 52.1	144.6 ± 73.5	0.484
CRP (mg/dL)	0.4 ± 0.7	0.3 ± 0.6	0.707
Glycemia (mg/dL)	116.4 ± 79.9	107.5 ± 48,2	0.667

Numbers are n (%), for categorical variables, or mean ± SD, for continuous variables; (*) p < 0.05; Apo A1: apolipoprotein A1; Apo B: apolipoprotein B; CRP-C: reactive protein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

However, when patients were stratified according to genetic testing positivity, those with any of the studied mutations did not show any correlation between LDL-C and other variables, while for those without a mutation, there was a moderate, statistically significant correlation between LDL-C and the clinical point score (R = 0.554, p = 0.01), as well as a borderline significant, moderate correlation between LDL-C and body fat (R = 0.441, p = 0.05).

Discussion

FH is a disorder of cholesterol metabolism and indeed one of the most common inherited disorders.[2,10] Rates of premature cardiovascular disease are much higher in patients with FH, but long-term drug therapy has the potential to lower cardiovascular event rates in patients with FH, leading to similar rates to those found in the general population.[11] Since effective primary prevention in the setting of FH requires its early diagnosis, the largest knowledge we have on this disease, the best we may recognize it and accomplish adequate patient management.

In this study, patients with genetically confirmed FH had, as expected, a higher clinical score for FH. In addition, they had more clinical evidence of severe hypercholesterolemia such as xanthelasma, possibly since the monogenic group have had severely elevated LDL-C level since birth, and thus, a greater cumulative "LDL-C burden".[12] Finally, LDL-C and Apo B levels were higher than in those patients with negative genetic testing, as previously demonstrated.[13,14] Apo B is the main protein constituent of lipoproteins such as VLDL and LDL, and concentrations of Apo B tend to mirror those of LDL-C.[15] Plasma levels of apolipoprotein B represent all atherogenic lipoproteins in the circulation; however, because every atherogenic particle contains a single apolipoprotein B molecule, Apo B levels also provide an accurate reflection of the number of atherogenic particles.[16]

Of note, LDL-C levels were correlated with the clinical point score and with body fat, both in the overall patient population and in patients without the genetic confirmation of FH. In those with genetically confirmed FH, there were no correlations between LDL-C and other clinical or biochemical variables in patients. This might suggest that the former might have less severe forms of FH related to other mutations, or severe hypercholesterolemia due to other etiologies, and in those cases the level of LDL-C would be also associated with modifiable or environmental factors. In contrast, in patients with FH, the severity of the derangements caused by the mutations would be the predominant factor determining LDL-C levels, what would turn other correlations with anthropometric or biochemical variables less significant.

This study is limited by the small sample size, which turns the results hypothesis-generating. Importantly, it may be possible that a proportion of the patients have a mutation in whomever as a yet unidentified gene. With standard molecular diagnostic techniques, a known mutation can be detected in 20–30% of patients with possible FH and 60–80% of patients with definite FH.[17,18] Since approximately 2/3 of patients have possible FH, no mutations are detected in about 60% of tested patients with this disorder[17] what has led to a search for additional FH-causing genes. However, some clinically diagnosed cases of FH may be polygenic, due to the inheritance of a greater than average number of common LDL-C raising alleles (each causing a slight effect) leading to an increase in LDL-C above the diagnostic cut off.[19]

Conclusions

The present results suggest that in patients with severe hypercholesterolemia and the FH phenotype, even in the absence of genetic confirmation of FH, patient management should have special attention directed towards modifiable factors associated with LDL-C, as body fat. A decrease in body fat might determine a reduction of LDL-C, what is known to decrease cardiovascular risk.[20]

Author contributions

Conception and design of the research: Lorenzo A, James CE, Pereira AC, Moreira ASB; Acquisition of data: Silva JDL, James CE, Pereira AC; Analysis and interpretation of the data: Lorenzo A; Statistical analysis: Silva JDL; Obtaining financing: Moreira ASB; Writing of the manuscript: Lorenzo A, Silva JDL; Critical revision of the manuscript for intellectual content: Lorenzo A, Moreira ASB.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number #26802514.4.0000.5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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The Presence and Extension of Myocardial Fibrosis in the Undetermined Form of Chagas' Disease: A Study Using Magnetic Resonance

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Abstract

Background: Previous data has shown that patients in the indeterminate form of Chagas disease may present myocardial fibrosis as shown on through magnetic resonance imaging (MRI). However, there is little information available regarding the degree of severity of myocardial fibrosis in these individuals. This variable has the potential to predict the evolution of Chagas' disease into its cardiac form.

Objectives: To describe the frequency and extent of myocardial fibrosis evaluated using an MRI in patients in the indeterminate form, and to compare it with other forms of the disease.

Methods: Patients were admitted one after another. Their clinical history was collected and they were submitted to laboratory exams and an MRI.

Results: Sixty-one patients with Chagas' disease, with an average age of 58 ± 9 years old, 17 patients in the indeterminate form, 16 in the cardiac form without left ventricular (LV) dysfunction and 28 in the cardiac form with LV dysfunction were studied. P <0.05 was considered to be statistically significant. Late enhancement was detected in 37 patients (64%). Myocardial fibrosis was identified in 6 individuals in indeterminate form (41%; 95% CI 23-66) in a proportion similar to that observed in cardiac form without LV dysfunction (44%); p = 1.0. Among the individuals with fibrosis, the total area of the affected myocardium was 4.1% (IIQ: 2.1 - 10.7) in the indeterminate form versus 2.3% (IIQ: 1-5) in the cardiac form without LV (p = 0.18). The left ventricular fraction ejection in subjects in the indeterminate form was similar to that of the individuals in the cardiac form without ventricular dysfunction (p = 0.09).

Conclusion: The presence of fibrosis in the indeterminate form of Chagas' disease has a frequency and extension similar to that of in the cardiac form without dysfunction, suggesting that the former is part of a subclinical disease spectrum, rather than lacking cardiac involvement. (Arq Bras Cardiol. 2018; 110(2):124-131)

Keywords: Chagas Disease; Chagas Cardiomyopathy; Fibrosis; Magnetic Resonance Imaging.

Introduction

Chagas' disease is a potentially debilitating endemic problem in Latin American countries and has led to an estimated loss of 750,000 years of productive life.[1-5] Three stages of Chagas' disease are recognized: acute, indeterminate and chronic.[4,6] After the acute phase, about two-thirds of infected patients remain in the indeterminate form, which is characterized by the absence of significant clinical, electrocardiographic or radiological manifestations. However, the disease does not manifest itself in these patients and one-third of them progress to some type of cardiac and/or digestive manifestation, and thus are reclassified as chronic.[7]

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Identifying the indeterminate patients that are prone to progress to the chronic form serve as a basis for the research of preventive strategies and a better understanding of the pathological processes that lead to this evolution. However, there are no predictive markers or models capable of estimating the risk of this change.

As such, several researchers consider myocardial fibrosis to be a possible substrate for the development and progression of ventricular dysfunction, arrhythmia, and death.[3,8-10] The etiopathogenic process that promotes fibrosis involves a multifactorial relationship between the aspects related to the etiologic agent and those related to the host[2,11-14]

The advent of cardiovascular magnetic resonance imaging (CMR), with the use of the late enhancement technique allows for the identification of myocardial fibrosis. Furthermore, it has a gold standard rating with a close anatomopathological correlation.[15] There is evidence that CMR is able to provide images with high spatial resolution and a high level accuracy in assessing ventricular function.[16] Previous data have shown that even patients with the indeterminate form may have myocardial fibrosis

when tested using CMR.[17] However, there is little data available on the degree of myocardial fibrosis presented by these individuals, which demonstrates the potential of this variable in the prediction of evolution to the cardiac form. The purpose of this paper is to describe the frequency and extent of myocardial fibrosis evaluated using CMR in patients in the indeterminate form. In order to contextualize this situation, these patients were compared to other individuals in the chronic cardiac form with and without left ventricular dysfunction.

Methods

Study population

Individuals with Chagas' disease were recruited between January of 2012 and December of 2013 at the Chagas' disease outpatient clinic of the Hospital São Rafael, a tertiary referral center in Salvador, Bahia, Brazil.

Inclusion criteria were: between 18 and 70 years old and a diagnosis of Chagas' disease confirmed by two positive serological tests (indirect hemagglutination and indirect immunofluorescence). The exclusion criteria were: an acute form of Chagas' disease; previous myocardial infarction, coronary artery disease, or the presence of two risk factors; primary valve disease; terminal renal disease on dialysis; active hepatitis or cirrhosis; hematological, neoplastic or bone diseases and contraindication to magnetic resonance imaging.

The study fulfilled its purpose from the Declaration of Helsinki and was approved by the Ethics Committee of the São Rafael Hospital. All of the individuals signed the Informed Consent Term prior to their participation.

The Forms of Chagas' Disease

The indeterminate form was defined by the presence of a *Trypanosoma cruzi* infection in the absence of clinical manifestations. Signs of cardiac involvement were characterized by normal electrocardiograms, chest X-rays and echocardiograms. The cardiac form without ventricular dysfunction was defined by individuals with cardiac involvement known as abnormal electrocardiograms (typically right bundle branch blocks and left anterosuperior hemiblocks) and without left ventricular dysfunction on the echocardiogram. The cardiac form with ventricular dysfunction was composed of individuals with a reduced left ventricular ejection fraction.

Clinical and laboratory data

All of the individuals underwent biochemical tests, a 12-lead electrocardiogram, a chest X-ray, 24-hour holter monitoring, a cardiac stress test, a Doppler echocardiogram and a CMR. Scores were calculated as follows: functional classes III and IV by the New York Heart Association (NYHA) (5 points), X-ray cardiomegaly (5 points), left ventricular dysfunction, global or segmental echocardiography (3 points), non-sustained ventricular tachycardia during the 24 hour holter monitoring (3 points), low QRS voltage on the electrocardiogram (2 points) and male (2 points). They were then classified into three risk groups according to the score obtained: low risk (0 to 6 points), intermediate risk (7 to 11 points) and high risk (12 to 20 points).[18]

Cardiac magnetic resonance imaging

A CMR was performed using the Sigma HDx1,5-T system (General Electric; Fairfield, CT, USA). To evaluate how the functioning of the left ventricular, synchronized images were acquired from the electrocardiogram in the expiratory apnea, including in the short axis, long axis and the four chamber planes, in different sequences. The acquisition parameters applied to the dynamic sequence were: a repetition time (RT) of 3.5 ms, an echo time (ET) of 1.5 ms, a flip angle of 60º, a bandwidth of 125 kHz, a field of view of 35 x 35 cm, a matrix of 256 x 148, a temporal resolution (RT) of 35 ms, a cut thickness of 8.0 mm without an interval between cuts. Images from the late enhancement technique were acquired with each heart beat 10 to 20 minutes after the administration of a gadolinium-based contrast agent (0.1 mmol/kg), using a 7.2 ms RT, a 3.1 ms ET, an angle of inclination of 20º, the first phase of cardiac cycle, 16/32 lines per follow-up, a matrix size of 256 x 192, a cut thickness of 8.0 mm, an interval between 2 mm cuts, a field of view of 32 to 38 cm, an inversion time of 150 to 300 ms, a bandwidth of 31,25 kHz, and 2 NEX (number of excitations). The late enhancement technique was used to investigate the presence of myocardial fibrosis, which was estimated by a qualitative (visual) method in accordance with the presence or absence of late enhancement, location and pattern presented; and quantitatively, using percentage values in relation to the total myocardial mass. All analyses were performed with the Siemens Argus program (Simens AG, Munich, Germany).

Statistical analysis

The categorical data were expressed as numbers (percentages, 95% confidence interval - 95% CI), and continuous data were expressed as mean ± standard deviation (SD) or median and interquartile range (IIQ). Normality was determined by the Kolmogorov-Smirnov test. The comparison of the continuous variables with normal distribution was performed using Student's unpaired t test and Anova (one-way analysis). The Bonferroni method was used for a post-hoc comparison between the groups. Fisher's exact test was used to compare proportions. The Kruskal-Wallis test was used to analyze non-normal continuous variables. Simple linear regression was used in the associations between fibrotic mass and the fraction of the left ventricular ejection. The analyses were performed using the SPSS program, version 20.0 (IBM), and p values below 0.05 (two-tailed test) were considered statistically significant.

As an a priori primary analysis, the frequency and extent of myocardial fibrosis in the indeterminate form was described, and cardiac forms were compared with and without dysfunction. As a post-hoc secondary analysis, the association of fibrosis with the ejection fraction and the Rassi score was tested. Additionally, clinical and laboratory parameters were compared between the indeterminate form and the cardiac form without dysfunction.

Results

Clinical characteristics

A total of 61 individuals with Chagas' disease, 56% female, with a mean age of 58 ± 9 years old were evaluated. Seventeen of them were in the indeterminate form, sixteen were in the cardiac form without left ventricular (LV) dysfunction and twenty eight were in the cardiac form with LV dysfunction. The majority of the subjects (74%) were in the NYHA functional class I or II, and 4 (6.6%) had concurrent gastrointestinal involvement. 82% were from urban areas, 50 individuals had previously lived in a mud house, and 44 reported contact with triatomine bugs. 64% of the relatives of patients with Chagas' disease reported a testimony. Eight patients used benzonidazole as an etiological treatment. The prevalence of hypertension, diabetes mellitus, dyslipidemia and smoking was similar among the three groups. The median Rassi score was 5 (IIQ: 0 - 11), and was distributed as follows: 36 individuals were classified as low risk (59%), 10 were classified as intermediate risk (16%) and 15 as high risk (25%). Other clinical and demographic characteristics are described in Table 1 and in Figure 1.

The presence and extent of miocardial fibrose

Late enhancement was found in 37 of the 58 subjects submitted to a CMR (64%). The percentage of the total area of myocardium affected by fibrosis was 9.4% (IIQ: 2.4 - 18.4), and was located most frequently in the inferolateral and apical LV segments. The location of the fibrosis in the subnedocardial and transmural areas were the most prevalent (72%); however, transmural fibrosis occured more frequently in those with ventricular dysfunction; p = 0.001. Myocardial fibrosis was identified in 6 of the 17 individuals in the indeterminate form (41%; 95% CI: 23-66), which is a proportion similar to that observed in the cardiac form without LV dysfunction (44%, 7 of 16 individuals); p = 1.0. Among the individuals with fibrosis, the total area of the affected myocardium was 4.1% (IIQ: 2.1 - 10.7) in the indeterminate form versus 2.3%

Table 1 – Demographic and clinical characteristics

Variables	Subjects (n = 61)	Indeterminate form (n = 17)	Cardiac form without ventricular dysfunction (n = 16)	Cardiac form with ventricular dysfunction (n = 28)
Demographic characteristics				
Age (years), mean ± standard deviation	58 ± 8	59 ± 11	59 ± 9	58 ± 7
Female, n (%)	36 (59)	12 (70)	12 (75)	12 (43)
Lived in a mud house, n (%)	50 (82)	15 (88)	15 (94)	20 (71)
Family members with positive serology, n (%)	39 (64)	11 (65)	14 (88)	14 (50)
Digestive form, n (%)	4 (6.6)	–	2 (12)	2 (7)
Body mass index (kg/m^2), mean ± standard deviation	25 ± 4	26 ± 4	27 ± 4	26 ± 3
Comorbidities, n (%)				
Arterial hypertension	44 (72)	14 (82)	12 (75)	18 (64)
Diabetes mellitus	9 (15)	4 (23)	–	5 (18)
Syncope	6 (7)	1 (6)	1 (6)	2 (7)
Smoking	16 (26)	3 (18)	3 (18)	10 (36)
Congestive heart failure NYHA III/IV	16 (26)	–	–	16 (57)*
Laboratory characteristics				
Creatinine (mg/dL)	0.88 (0.7 – 0.99)	0.84 (0.7 – 0.98)	0.78 (0.6 – 0.91)	0.94 (0.7 – 1.0)
Sodium (mmoL/dL)	140 ± 3	138 ± 2	139 ± 2	139 ± 2
Hemoglobin (g/dL)	13.9 ± 0.9	14.2 ± 1.3	13.4 ± 0.7	14.2 ± 1.0
Total Cholesterol (mg/dL)	193 ± 38	202 ± 40	194 ± 42	200 ± 45
Reactive C protein (mg/dL)	1.15 (0.63 – 4.02)	1.71 (0.35 – 6.54)	1.24 (0.51 – 4.74)	1.09 (0.73 – 3.62)
NT-ProBNP (pg/mL)	686 (66 – 816)	60.5 (34 – 108)	96.0 (73 – 181)	839.5** (189 – 2271)
Troponin I (ng/mL)	0.684 (0.012 – 0.04)	0.012 (0.012 – 0.012)	0.012 (0.012 – 0.028)	0.038 (0.019 – 0.06)
LVEF (%)	54 ± 15	64 ± 3	64 ± 4	43 ± 10*
METS	9 ± 2.5	12 ± 3	9 ± 2	8 ± 2

*NYHA: New York Heart Association; NT-ProBNP: N-terminal pro B-type natriuretic peptide; LVEF: left ventricular ejection fraction; METS: metabolic equivalent of task. Data expressed as mean ± standard deviation or percentage (%) for discrete variables and median and interquartile range for continuous variables with non-normal distribution. *p < 0.001, Fisher's exact text. **p < 0.001, Kruskal-Wallis one-way analysis of variance.*

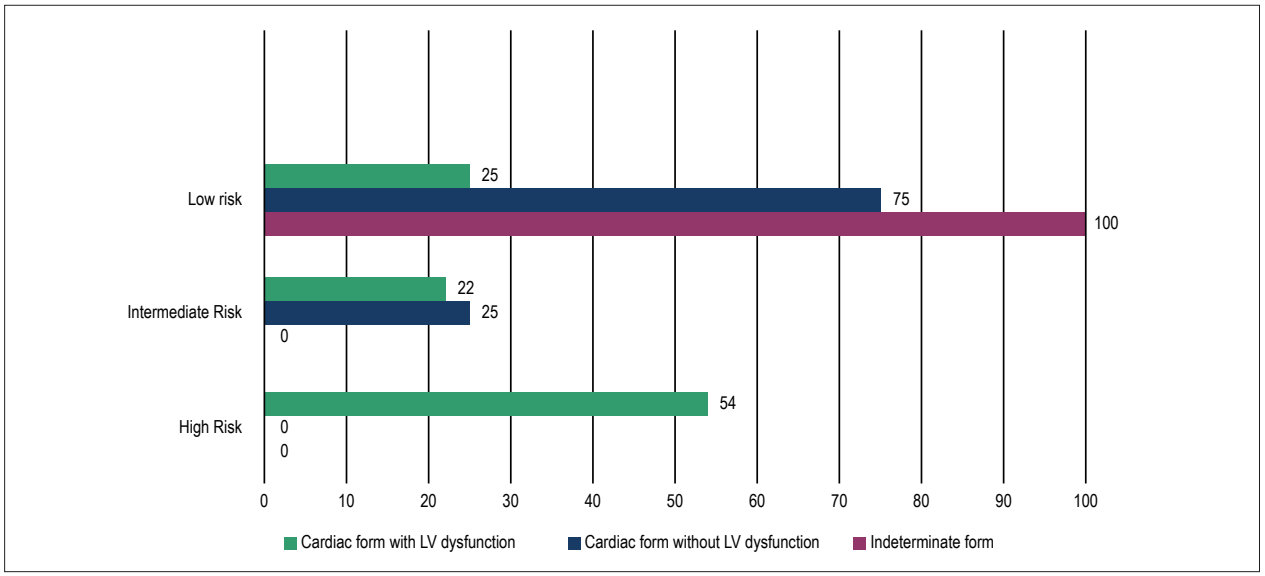

Figure 1 – *Rassi score in the different clinical forms of Chagas' disease. LV: left ventricular.*

(IIQ: 1-5) in cardiac form without LV (p = 0.18). In those with ventricular dysfunction, the percentage of fibrosis was higher than in the other groups, occurring in 23 of the 25 subjects (92%), with a compromised area of 15.2% (IIQ: 7.8-25); p < 0.001 (Figure 2).

The impact of myocardial fibrosis

The LV ejection fraction was significantly lower in individuals with late enhancement when compared to subjects without enhancement (69 ± 13 versus 48 ± 19%); p < 0.0001. A negative correlation was observed between the extent of fibrosis and ejection fraction (r = 0.565; p < 0.001). Through linear regression analysis, progressive reduction of the ejection fraction was observed at each percentage increase in the area affected by fibrosis. This analysis showed a regression coefficient (β) of -0.968, which corresponds to the estimated reduction in the ejection fraction of the LV at each 1% increase in the area of fibrosis (Figure 3).

There was a progressive increase in the amount of fibrosis in the different classes of the Rassi score, when subdivided into low, intermediate and high risk. The high-risk group had 13.8% (QI: 9 - 19) versus 4.9% (QI: 1 - 17) in the medium risk versus 0% (QI: 0 - 5) in the low risk group (p = 0.003). There was no difference in fibrotic mass between the low and intermediate risk classes (p = 0.19), nor was there a difference between intermediate and high risk (p = 1.0).

Severity of the disease in its indeterminate form versus in its cardiac form without left ventricular dysfunction

The left ventricular ejection fraction (LVEF) in individuals in the indeterminate form was 72 ± 8%, which is similar to the LVEF of patients in the cardiac form without ventricular dysfunction 67 ± 6%; p = 0.09. There were no NT-proBNP levels (125 pg/ml versus 159 pg/ml, p = 0.61), ultrasensitive CRP (4.6 mg/L versus 2.5 mg/L; p = 0, 40), TNF-alpha (0.9 pg/ml versus 1.2 pg/ml, p = 0.56), interleukins (p = 0.35), IFN-gamma (2.7 pg/ml vs. 3 3 pg/ml; p = 0.56) and MET (10 vs. 9.4, p = 0.66) achieved through exercise testing and the location of late enhancement (p = 0.44) when comparing patients in the indeterminate form with those in the cardiac form without dysfunction (Table 2).

All 17 individuals in the indeterminate form were classified as low risk according to the Rassi score. While 16 individuals were shown to be in the cardiac form without dysfunction, 12 (75%) were considered low risk and 4 were considered intermediate risk; p = 0.04.

Discussion

The present study highlighted the presence of myocardial fibrosis in patients in the indeterminate form of Chagas' disease. It was present in a frequency and extension similar to that of the group who had the disease in the cardiac form without ventricular dysfunction. Additionally, it was shown that ventricular function and clinical parameters are similar between these two forms.

CMR has been used for decades for the anatomical and functional evaluation of the heart. It is important due to the fact that it is non-invasive, does not use ionizing radiation, and has a high resolution, which allows for multiple studies concerning cardiac anatomy, function and tissue characterization with the late enhancement technique.[19-21]

Previous studies have validated the quantification of myocardial fibrosis using CMR in populations with Chagas' disease.[22,23] In 2005, Rochitte et al.[17] evaluated CMR with the use of the late enhancement technique in 51 patients with Chagas' heart disease, and found fibrosis in 68.6% of all of the individuals evaluated, and in 100% in those with ventricular tachycardia.[17] Regueiro et al.[23] found fibrosis in patients living outside the endemic area of the disease in a distribution of 7.4% of those in the indeterminate form, 15.8%

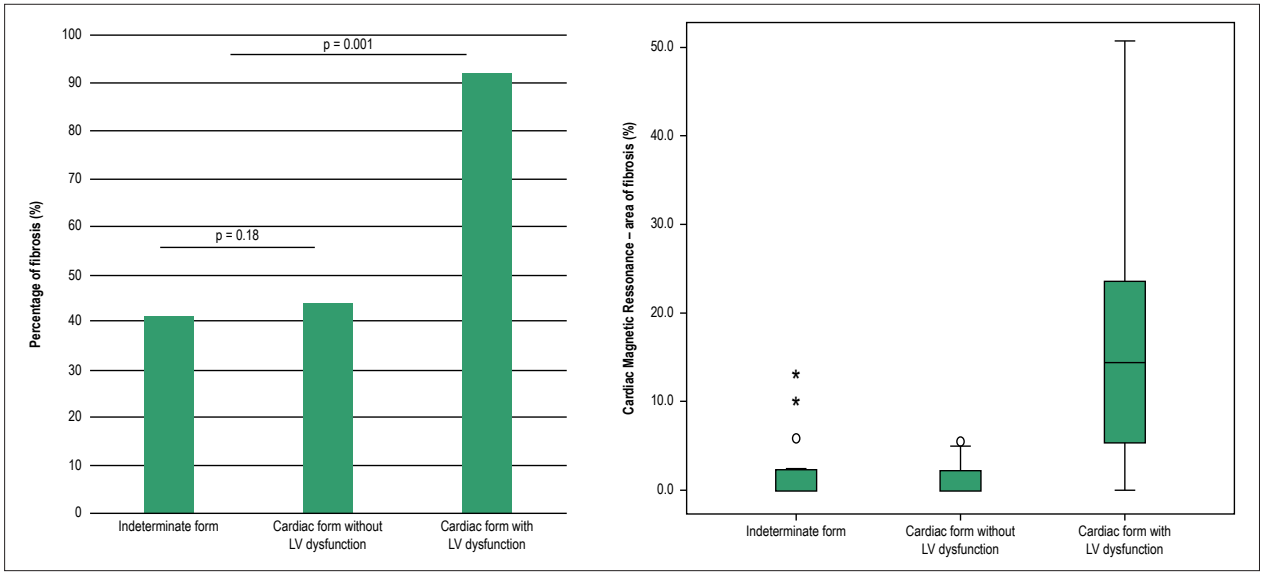

Figure 2 – *Myocardial fibrosis in the different clinical forms of Chagas' disease. LV: left ventricular.*

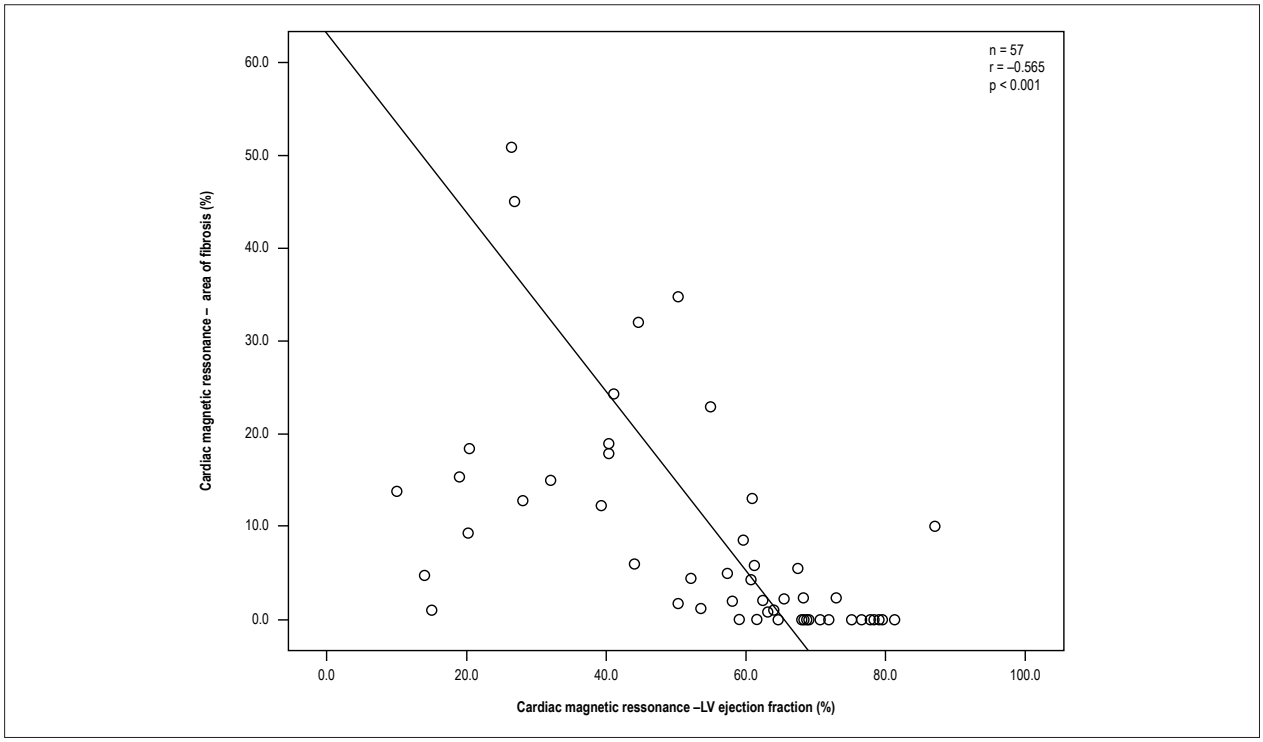

Figure 3 – *Linear regression analysis: influence of fibrosis on the left ventricular ejection fraction. LV: left ventricular.*

of those in the cardiac form without ventricular dysfunction, and 52.4% in those with ventricular dysfunction.[23] We found a percentage of fibrosis involvement similar to the previous study (64%), also showing progressive involvement in patients with LV dysfunction (92%).[17] However, in addition to previous research, our data demonstrate a prevalence of enhancement as well as the percentage of fibrosis-related area, which is similar between the indeterminate form and the non-dysfunctional form of the LV. We found no difference in the subendocardial and transmural location of fibrosis.

The description of the cardiac ultrastructural changes that occur in the indeterminate phase of Chagas' disease were initially reported in individuals with positive serology during necropsy after accidental death.[12] However, its designation as

Table 2 – Characteristics of the indeterminate form versus the cardiac form without left ventricular dysfunction

Variables	Indeterminate form (n = 17)	Cardiac form without ventricular dysfunction (n = 16)	p value
Rassi Score	2 (0 – 2)	6 (1 – 8)	0.30‡
Area of fibrosis from the CMR (%)	4.1 (2.1 – 10.7)	2.3 (1 – 5)	0.18‡
LV ejection fraction (%)	72 ± 8	67 ± 6	0.09†
Ventricular Tachycardia (%)	–	20	0.001*
METS	10 ± 3	9.4 ± 2	0.60†
Maximum VO_2	35 ± 10	33 ± 7	0.47†
NT-ProBNP (pg/mL)	125 (34 – 108)	171 (73 – 181)	0.61‡
Ultrasensitive PCR (mg/L)	1.7 (0.35 – 6.5)	1.2 (0.51 – 4.7)	0.40‡
Troponin I (ng/mL)	0.012 (0.0 – 0.012)	0.012 (0.012 – 0.028)	0.31‡
IL-2 (pg/mL)	0.21 (0.03 – 0.55)	0.27 (0.03 – 0.96)	0.14‡
IL-4 (pg/mL)	0.62 (0.00 – 1.6)	0.37 (0.2 – 2.2)	0.83‡
IL-6 (pg/mL)	2.26 (1.39 – 4.35)	3.98 (2.01 – 6.22)	0.50‡
IL-10 (pg/mL)	0.44 (0.19 – 1.06)	0.63 (0.50 – 1.61)	1.47‡
TNF-alfa (pg/mL)	0.48 (0.14 – 1.15)	0.72 (0.58 – 2.71)	1.16‡
IFN-gama (pg/mL)	2.07 (1.30 – 4.35)	2.15 (1.69 – 6.73)	0.51‡

*CMR: cardiac magnetic resonance; LV: left ventricular; METS: metabolic equivalent of task; Maximum VO_2: Maximum Oxygen volume; NT-ProBNP: N-terminal pro B-type natriuretic peptide. *Fisher's exact test; †Student's t test; ‡ Mann-Whitney's test. Data expressed as mean ± standard deviation or percentage (%) for discrete variables and median and interquartile range for continuous variables with non-normal distribution.*

an indeterminate form was impaired since it was impossible to analyze the electrocardiographic alterations. In 1997, Andrade et al.,[24] using a canine model, interpreted that the indeterminate form of the disease is characterized by a self-limited cycle of focal inflammatory alterations, with modulation and suppression of immune responses mediated by cells. Thus, they considered that the indeterminate form of Chagas' disease is characterized by a host-parasite equilibrium instead of a progressive damaging process.[24] As early as 1978, Andrade et al.[13] reported that chronic chagasic myocarditis lesions are not randomly distributed through the atrioventricular conduction system, but rather that there is a clear distribution of lesions in the conduction system.[13] We now know that a large percentage of patients in the indeterminate form show evidence of cardiac involvement in the detailed, non-invasive evaluation.[25] The data from the present study demonstrate that a CMR is not capable of differentiating the indeterminate form from the clinical form without LV dysfunction, since the percentage of fibrosis is similar between the two clinical forms. In this study, the percentage of fibrosis involvement in the indeterminate form (41.2%) was similar to the percentage in the cardiac form without LV dysfunction (43.8%).

Some limitations of the study should be recognized. No anatomical tests were performed to definitively rule out ischemic etiology as a cause of myocardial fibrosis. In order to minimize this possibility, an ergometric test was performed with all of the individuals, in addition to including the exclusion criteria of the presence of risk factors for atherosclerosis. Although it is recognized that to rule out coronary artery disease definitively, a coronary angiography would be necessary, the negative predictive value of the exercise test in these circumstances is very high. Coronary artery disease was excluded without performing a coronary angiography in order to avoid radiation and complications resulting from the procedure.

Conclusion

The presence of fibrosis in the indeterminate form of Chagas' disease has a frequency and extension similar to that of the cardiac form without dysfunction, suggesting that the former is part of a subclinical disease spectrum, rather than lacking cardiac involvement. Thus, indeterminate and cardiac forms without dysfunction resemble each other and differ significantly from cardiac form with dysfunction.

Author contributions

Conception and design of the research: Rabelo MMR, Macedo CT, Larocca T, Soares MBP, Correia LCL; Acquisition of data: Rabelo MMR, Macedo CT, Larocca T, Machado A, Pacheco T; Analysis and interpretation of the data and Statistical analysis: Rabelo MMR, Correia LCL; Obtaining financing: Rabelo MMR, Larocca T, Soares MBP; Writing of the manuscript: Rabelo MMR, Macedo CT, Soares MBP, Correia LCL; Critical revision of the manuscript for intellectual content: Rabelo MMR, Macedo CT, Souza BSF, Soares MBP, Ribeiro-dos-Santos R, Correia LCL; Interpretation of magnetic resonance data: Torreão J.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital São Rafael under the protocol number N° 41/10. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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An Alternative Method to Calculate Simplified Projected Aortic Valve Area at Normal Flow Rate

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Abstract

Background: Simplified projected aortic valve area (EOA_{proj}) is a valuable echocardiographic parameter in the evaluation of low flow low gradient aortic stenosis (LFLG AS). Its widespread use in clinical practice is hampered by the laborious process of flow rate (Q) calculation.

Objetive: This study proposes a less burdensome, alternative method of Q calculation to be incorporated in the original formula of EOA_{proj} and measures the agreement between the new proposed method of EOA_{proj} calculation and the original one.

Methods: Retrospective observational single-institution study that included all consecutive patients with classic LFLG AS that showed a Q variation with dobutamine infusion ≥ |15|% by both calculation methods.

Results: Twenty-two consecutive patients with classical LFLG AS who underwent dobutamine stress echocardiography were included. Nine patients showed a Q variation with dobutamine infusion calculated by both classical and alternative methods ≥ |15|% and were selected for further statistical analysis. Using the Bland-Altman method to assess agreement we found a systematic bias of 0,037 cm^2 (95% CI 0,004 – 0,066), meaning that on average the new method overestimates the EOA_{proj} in 0,037 cm^2 compared to the original method. The 95% limits of agreement are narrow (from -0,04 cm^2 to 0,12 cm^2), meaning that for 95% of individuals, EOA_{proj} calculated by the new method would be between 0,04 cm^2 less to 0,12 cm^2 more than the EOA_{proj} calculated by the original equation.

Conclusion: The bias and 95% limits of agreement of the new method are narrow and not clinically relevant, supporting the potential interchangeability of the two methods of EOA_{proj} calculation. As the new method requires less additional measurements, it would be easier to implement in clinical practice, promoting an increase in the use of EOA_{proj}. (Arq Bras Cardiol. 2018; 110(2):132-139)

Keywords: Aortic Valve Stenosis / diagnosis; Aortic Valve Stenosis / diagnostic imaging; Echocardiography, Stress; Heart Valves / physiopathology.

Introduction

Classical low-flow, low-gradient (LFLG) aortic stenosis (AS) is characterized by the combination of a calcified aortic valve with an effective orifice area (EOA) compatible with severe stenosis, a low transvalvular velocity or pressure gradient suggestive of moderate stenosis and a low left ventricular ejection fraction (LVEF).[1] Dobutamine stress echocardiography (DSE) may aid in the distinction between patients with true severe AS and those with pseudo-severe AS by promoting a potential increase in flow. Hence, traditional hemodynamic indices of stenosis severity could be evaluated at normal flow rates and easily interpreted.[2] The main limitation of this exam is the unpredictability of flow augmentation, leading to ambiguous changes of mean pressure gradient and EOA.[3] Projected aortic valve area at normal transvalvular flow rate (250 mL/min) – EOA_{proj} - is an echocardiographic parameter that was developed in order to overcome this limitation. It consists of the effective orifice aortic area that would have occurred at a standardized flow rate of 250 mL/min, enabling the comparison of AS severity between patients with different flow rate profiles with dobutamine infusion.[4] The determination of this new parameter requires the calculation of at least the basal and peak flow rate in each patient. The original formula of EOA_{proj} published by Blais *et al*. proposed the calculation of flow rate as the quotient between stroke volume and the ejection time (ET), which requires 3 different measurements: 1) left ventricular outflow tract (LVOT) diameter; 2) LVOT velocity-time integral and 3) ET measured at the aortic velocity spectrum.[4] Flow rate can also be determined by the product of LVOT area and LVOT mean velocity, which requires only 2 measurements: 1) LVOT diameter and 2) LVOT mean velocity.[5] This alternative method to calculate flow rate is less cumbersome and less susceptible to inter-observer and intra-observer variability as it requires less measurements.

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The aim of the present study is to measure the agreement between two methods of calculation of simplified EOA_{proj} using two different approaches of flow rate determination in patients with classical LFLG AS.

Methods

Retrospective observational single-institution study that included all consecutive patients with LFLG AS with depressed LVEF (definition in accordance with the 2014 AHA/ACC Guidelines for the Management of Valvular Heart Disease[1]) referred for DSE evaluation between September/2011 and November/2015.

Patients admitted to the study had to fulfill all the following criteria: 1) age ≥ 18 years old; 2) EOA ≤ 1.0 cm^2 or EOA indexed to body surface area ≤ 0.6 cm^2/m^2 and maximal transaortic velocity (Vmax) < 4 m/s or mean transaortic gradient (Gmean) < 40 mmHg and 3) LVEF < 50%. Patients with more than mild aortic regurgitation or more than mild mitral regurgitation or stenosis were excluded.

After completing DSE, patients were classified into groups in terms of severity of the stenosis in agreement with the 2014 AHA/ACC Guidelines for the Management of Valvular Heart Disease:

- Patients with true severe LFLG AS: EOA ≤ 1.0 cm^2 with Vmax ≥ 4 m/s at any flow rate
- Patients who did not fulfill the criteria for true severe LFLG AS having: a) EOA ≤ 1.0 cm^2 with Vmax < 4m/s (persistent area – gradient mismatch), b) EOA > 1.0 cm^2 with Vmax ≥ 4 m/s or c) EOA > 1.0 cm^2 with Vmax < 4 m/s (pseudo-severe AS)

Echocardiographic assessment

Echocardiographic examination was performed using commercially available equipment (Vivid – 7; General Electric Vingmed, Milwaukee, WI) with a 3.5-MHz transducer.

After the acquisition of the baseline study, a low dose dobutamine infusion protocol was begun at 5 ug/Kg body weight per minute, titrated upward in stages of 5 ug/Kg per minute every 5 minutes up to a maximal dose of 20 ug/Kg per minute. Systemic blood pressure and the 12-lead electrocardiogram were monitored throughout the test. Continuous wave Doppler of the aortic valve velocity spectrum and pulsed-wave Doppler of the LVOT velocity spectrum were recorded at baseline and in the last 2 minutes of each stage of the protocol. LVOT diameter was measured in the basal parasternal long axis view and was assumed to have remained constant during the test protocol.

Raw data was stored digitally and analysis was performed off-line by a single independent operator, using the EchoPac Clinical Workstation Software (General Electric, Vingmed, Milwaukee, WI). For each Doppler measurement, three cycles were averaged, avoiding post-extrasystolic beats. Transaortic gradients were calculated using the simplified Bernoulli equation ($\Delta P = 4v^2$, where ΔP is in mmHg and v is the aortic velocity in m/s). EOA of the aortic valve was calculated from the continuity equation - $EOA = CSA_{LVOT} \times (LVOT_{VTI} \div Ao_{VTI})$ -, where EOA is in cm^2, $LVOT_{VTI}$ is the subaortic velocity -time integral and Ao_{VTI} is the aortic velocity-time integral both in cm. CSA_{LVOT} is the cross sectional area (in cm^2) of the LVOT calculated from the LVOT diameter measured in the parasternal long axis view (d in cm) assuming a circular geometry - $CSA_{LVOT} = \pi \times (d/2)^2$. Left ventricular end diastolic and end systolic volumes (LVEDV and LVESV, respectively) and LVEF were assessed by standard 4 chamber and 2 chamber views using the biplane Simpson method. Stroke volume (SV) was calculated from the following equation: $= LVOT_{VTI} \times CSA_{LVOT}$, where SV is in mL/beat, $LVOT_{VTI}$ is in cm and CSA_{LVOT} is in cm^2. Flow rate (Q) was calculated using 2 different methods:

- a classical method using the formula $Q_{classic} = 1000 \times \frac{LVOT_{VTI} \times CSA_{LVOT}}{TE}$, where $Q_{classic}$ is in mL/sec, $LVOT_{VTI}$ is in cm, CSA_{LVOT} is in cm^2 and ET is the ejection time in ms measured in the continuous wave Doppler of the aortic valve velocity spectrum.[4]
- an alternative method using the formula $Q_{alternative} = CSA_{LVOT} \times Vmean_{LVOT} \times 100$, where $Q_{alternative}$ is in mL/sec, CSA_{LVOT} is in cm^2 and $Vmean_{LVOT}$ is the mean velocity of blood in the LVOT during the ejection period in m/sec and is measured in the pulsed-wave Doppler of the LVOT velocity spectrum.[5]

Patients with flow rate variation with dobutamine infusion ≥ |15|% in both classical and alternative methods were selected and simplified aortic valve area at 250 mL/s flow rate (EOA_{proj}) was calculated according to the formula published by Blais et al[4]: $EOA_{proj} = EOA_{basal} + \frac{\Delta EOA}{\Delta Q} \times (250 - Q_{basal})$, where EOA_{proj} is in cm^2, Q is the mean transvalvular flow rate, EOA_{basal} and Q_{basal} are the EOA and Q at rest and ΔEOA and ΔQ are the absolute variation in EOA and Q with dobutamine infusion.[4] As we used two different methods to calculate flow rate we obtained two sets of values of simplified EOA_{proj} in each eligible patient: 1) a classical simplified EOA_{proj} using the classical method of flow rate calculation and 2) an alternative simplified EOA_{proj} using the alternative method of flow rate calculation.

Statistical analysis

Categorical variables are described by frequencies and percentages. Continuous variables are presented as mean ± standard deviation.

A scatter plot and a linear regression model were constructed to assess the strength of linear relation between the classic and the alternative methods of calculation of EOA_{proj} and to quantify the proportion of variance that the two methods have in common. Finally, in order to evaluate the agreement between the two methods (i.e., how much the new method is likely to differ from the old), we built a Bland-Altman plot – a plot of the paired differences between the two methods against their mean. Normal distribution of the paired differences was verified by the use of Shapiro-Wilk normality test. The bias was computed as the mean of the differences of the two methods. A one sample t test was conducted against the null hypothesis of no bias to evaluate the statistical significance of the calculated bias. Ninety-five percent-limits of agreement were computed as the mean bias plus or minus 1.96 time its standard deviation.[6] Two-tailed p values < 0,05 were considered statistically significant.

IBM SPSS Statistics version 23 (IBM, Vienna, Austria) and GraphPad Prism version 7.0 (GraphPad Software, La Jolla California, USA) were used for statistical analysis.

Results

Baseline characteristics

Between September/2011 and November/2015, 22 patients [15 (68%) men, mean age 72 ± 9 years] with classical LFLG AS underwent a low dose dobutamine stress echocardiography in order to evaluate the true severity of the AS. No major adverse events were reported. Table 1 shows the baseline clinical and echocardiographic features of these patients as well as the hemodynamic evolution with dobutamine infusion. 8 (36%) patients reached the AHA/ACC criteria for true severe aortic stenosis, 11(50%) patients maintained the valve area – gradient discordance present at baseline and 3 (14%) patients showed a progression of hemodynamic indices suggestive of pseudo severe aortic stenosis. No patient ended up the stress exam with inversion of the area – gradient mismatch (ie, aortic valve area > 1,0 cm^2 and Vmax ≥ 4 m/s).

Flow rate at baseline and at peak dobutamine infusion was calculated using both the classic $\left(Q_{classic} = 1000 \times \frac{LVOT_{VTI} \times CSA_{LVOT}}{ET}\right)$ and the alternative equations ($Q_{alternative} = CSA_{LVOT} \times Vmean_{LVOT} \times 100$) in all patients. Only 9 (41%) patients achieved a flow rate variation with dobutamine infusion assessed by both methods ≥ |15|%, enabling the simultaneous determination of the simplified projected aortic valve area at normal flow rate by the classic and the alternative formulas. Table 2 shows the baseline and peak dobutamine echocardiographic characteristics of this subset group of patients.

A scatter plot showing the classic simplified projected aortic valve area values against the respective alternative simplified projected aortic valve area values was built (Figure 1). As suggested by the scatter plot, a strong linear association between the two methods of calculation was found – r (7) = 0,99, p < 0,001.

Simple regression was conducted to find the best line that predicts the simplified projected aortic valve area calculated by the alternative method from the simplified projected aortic valve area calculated by the classic method. The results were statistically significant, F (1,7) = 245,5, p < 0,0001. The identified equation to understand this relationship was: alternative EOA_{proj} = 1.00 (95% CI 0.85 – 1.15) x Classic EOA_{proj} + 0,036 (95% CI -0.111 – 0.182). The adjusted R^2 was 0.97, meaning that 97% of the variance of the alternative EOA_{proj} can be explained by classic EOA_{proj}.

A Bland-Altman analysis was performed to assess agreement between the two methods of EOA_{proj} calculation. In Figure 2 the Y axis shows the differences between the two paired EOA_{proj} measurements (alternative method – classic method) and the X axis represents the average of these measurements $\left(\frac{\text{Alternative method} + \text{Classic method}}{2}\right)$. Normal distribution of the differences between paired measurements was verified by use of the Shapiro-Wilk test for normal distribution (test statistics = 0,854, df = 9, p = 0,082). There is no trend in increases in the variability of the differences in relation to their mean. The calculated bias (the average of the paired differences) is 0.037 cm^2 (95% CI 0.004 – 0.066), meaning that on average EOA_{proj} calculated by the alternative method measures 0.037 cm^2 more than EOA_{proj} calculated by the classic method. This bias is statistically significant (t = 2.619, df = 8, p = 0.031). The calculated 95% limits of agreement between the two methods are -0,04 and 0,12, which means that for 95% of the individuals, the EOA_{proj} calculated by the alternative method would be between 0,04 cm^2 less and 0,12 cm^2 more than the EOA_{proj} calculated by the classic method.

Discussion

The EOA_{proj} is defined as the EOA of the aortic valve that would have occurred at a hypothetical standardized flow rate of 250 mL/s. This new echocardiographic index was developed in order to overcome the variable and unpredictable effect of dobutamine in flow rate.[4] In fact, patients with classic LFLG AS undergoing DSE have a wide variable response in terms of flow rate progression, which may be due to multiple factors including the variable presence of myocardial contractile reserve, the unpredictable chronotropic response to dobutamine and the potential development of left ventricle dyssynchrony with dobutamine infusion[3] Such variability in flow rate response may impose an insurmountable obstacle in the interpretation of ambiguous changes in mean pressure gradient and EOA. By normalizing the EOA at a hypothetical flow rate of 250 mL/s, the EOA_{proj} enables direct comparison of AS severity in patients with classic LFLG AS that present different flow rate profiles with dobutamine infusion. In addition to make the interpretation of DSE results easier, this new parameter has also been shown to be related to actual AS severity (calcification at surgery) and to have an important value in mortality prediction.[4,7]

In order to calculate the EOA_{proj}, EOA is plotted against the mean transvalvular flow rate at different stages of DSE. The slope of this curve – called compliance – is then used to predict EOA at 250 mL/min.[4] A simplified version of the original formula substitutes the curve slope for an easier to calculate quotient $\frac{\text{Peak EOA} - \text{Rest EOA}}{\text{Peak Q} - \text{Rest Q}}$. Thus, the simplified version of the EOA_{proj} formula can be expressed as $EOA_{proj} = EOA_{basal} + \frac{\text{Peak EOA} - \text{Rest EOA}}{\text{Peak Q} - \text{Rest Q}} \times (250 - Q_{rest})$.[8]

Both the original and simplified version of the EOA_{proj} formulae recommend the calculation of flow rate as the quotient between stroke volume and ET which requires 3 different measurements: 1) LVOT diameter ($LVOT_D$); 2) LVOT velocity-time integral ($LVOT_{VTI}$) and 3) ET measured at the aortic velocity spectrum. Both $LVOT_D$ and $LVOT_{VTI}$ are measures routinely done in DSE protocols performed for classic LFLG AS evaluation as they are needed to calculate EOA of the aortic valve by the continuity equation. However, the need for ET measured at the aortic velocity spectrum adds the requirement for an extra measurement in the usual protocol of DSE. Furthermore, this flow rate

Table 1 – Clinical and echocardiographic characteristics of the low-flow low-gradient aortic stenosis patients at baseline and at 20 ug/Kg/min Dobutamine infusion

Low Flow Low Gradient Aortic Stenosis (n = 22)		
Demographics and Physical Examination		
Age, yr	72 ± 8.8	
Male sex, n (%)	15 (68)	
Weight, Kg	71 ± 12.7	
Height, cm	163 ± 8.4	
Body surface area, m^2	1.76 ± 0.183	
Hemodynamic Indices		
	Basal	**Peak Dobutamine**
Heart rate, bpm	66 ± 8.9	80 ± 18,9
Systolic Blood Pressure, mmHg	115 ± 20.7	139 ± 31,3
Diastolic Blood Pressure, mmHg	62 ± 12.1	64 ± 18,9
Classic Q, mL/s	202 ± 63.3	236 ± 56,3
Alternative Q, mL/s	169 ± 51.2	223 ± 53,9
SV, mL	54 ± 16.0	62 ± 14,4
SVI, mL/m^2	30 ± 8.4	35 ± 8,7
LVEDV, mL	145 ± 56.9	136 ± 41,7
LVESV, mL	97 ± 42.9	79 ± 38,5
LVEF, %	33 ± 9.8	43 ± 15,3
Indices of Aortic Stenosis Severity		
	Basal	**Peak Dobutamine**
V_{max}, m/s	3.2 ± 0.50	3,9 ± 0,55
G_{mean}, mmHg	24 ± 7.3	37 ± 12,2
VTI Ratio	0.22 ± 0.06	0,25 ± 0,07
EOA, cm^2	0.43 ± 0.091	0,49 ± 0,116
EOAi, cm^2/m^2	0.44 (0.35 – 0.50)	0,46 (0,43 – 0,54)
Classification of Aortic Stenosis in Terms of Severity		
True Severe Low Flow Low Gradient AS, n (%)	8 (36)	
Pseudo-Severe Low Flow Low Gradient AS, n (%)	3 (14)	
Persistent Area-Gradient Mismatch Low Flow Low Gradient AS, n (%)	11 (50)	
Simplified Aortic Valve Area at flow rate 250 mL/min		
Classic EOA_{proj}, cm^2	0.93 ± 0.220 (n = 14)*	
Alternative EOA_{proj}, cm^2	0.98 ± 0.238 (n = 14)**	

*Data are presented as mean ± standard deviation or number (%) of patients, as appropriate. Classic Q: flow rate calculated by the classic formula; Alternative Q: flow rate calculated by the alternative formula; SV: stroke volume; SVI: stroke volume index; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; V_{max}: maximum velocity of aortic Doppler spectrum; G_{mean}: transaortic mean pressure gradient; VTI Ratio: velocity time integral ratio; EOA: effective orifice aortic valve area; EOAi: indexed effective orifice aortic valve area; Classic EOA_{proj}: simplified projected aortic valve area calculated using the classic flow rate formula; Alternative EOA_{proj}: simplified projected aortic valve area calculated using the alternative flow rate formula; AS: aortic stenosis. * Only 14 patients had a flow rate variation with dobutamine infusion estimated with the classical formula ≥ |15| %, enabling the calculation of the classic EOA_{proj}. ** Only 14 patients had a flow rate variation with dobutamine infusion estimated with the alternative formula ≥ |15| %, enabling the calculation of the alternative EOA_{proj}.*

formula involves measurements acquired in different places and, inevitably, in different time points, encompassing an intrinsic bias.

Flow rate can also be determined by the product of left ventricular outflow tract area and left ventricular outflow tract mean velocity, which requires only 2 measurements: 1) $LVOT_D$ and 2) mean velocity of blood at LVOT during the ejection period ($LVOT_{Vmean}$). $LVOT_{Vmean}$ is given automatically in most echocardiography software when assessing $LVOT_{VTI}$ (a fundamental step in EOA calculation by the continuity equation). This alternative formula is less cumbersome to calculate as it does not need an additional measurement in

Table 2 – Clinical and Echocardiographic Characteristics of the Low Flow Low Gradient Aortic Stenosis Patients with Flow Variation calculated by both methods ≥ |15| % with Dobutamine Infusion

Low Flow Low Gradient Aortic Stenosis with Classic and Alternative ΔQ ≥ |15|% (n = 9)		
Demographics and Physical Examination		
Age, yr	73 ± 7,1	
Male sex, n (%)	6 (67)	
Weight, Kg	67 ± 13,0	
Height, cm	162 ± 5,8	
Body surface area, m^2	1,70 ± 0,164	
Hemodynamic Indices		
	Basal	**Peak Dobutamine**
Heart rate, bpm	67 ± 10,6	81 ± 19,8
Systolic Blood Pressure, mmHg	113 ± 23,9	134 ± 35,2
Diastolic Blood Pressure, mmHg	60 ± 12,6	58 ± 14,1
Classic Q, mL/s	174 ± 45,3	155 ± 42,3
Alternative Q, mL/s	254 ± 55,5	242 ± 56,7
SV, mL	47 ± 13,9	65 ± 15,0
SVI, mL/m^2	28 ± 6,9	38 ± 8,4
LVEDV, mL	155 ± 74,9	129 ± 46,6
LVESV, mL	107 ± 47,2	72 ± 25,6
LVEF, %	30 ± 9,5	42 ± 13,7
Indices of Aortic Stenosis Severity		
	Basal	**Peak Dobutamine**
V_{max}, m/s	3,2 ± 0,47	4,0 ± 0,64
G_{mean}, mmHg	24 ± 5,7	39 ± 13,9
VTI Ratio	0,20 ± 0,056	0,27 ± 0,066
EOA, cm^2	0,68 ± 0,185	0,94 ± 0,238
EOAi, cm^2/m^2	0,40 ± 0,093	0,55 ± 0,126
Classification of Aortic Stenosis in Terms of Severity		
True Severe Low Flow Low Gradient AS, n (%)	4 (44)	
Pseudo-Severe Low Flow Low Gradient AS, n (%)	2 (22)	
Persistent Area-Gradient Mismatch Low Flow Low Gradient AS, n (%)	3 (33)	
Simplified Aortic Valve Area at flow rate 250 mL/min		
Classic EOA_{proj}, cm^2	0,94 ± 0,246	
Alternative EOA_{proj}, cm^2	0,98 ± 0,248	

Data are presented as mean ± standard deviation or number (%) of patients, as appropriate. ΔQ: variation of flow rate from the baseline with dobutamine infusion, presented as fractional change (%); Classic Q: flow rate calculated by the classic formula; Alternative Q: flow rate calculated by the alternative formula; SV: stroke volume; SVI: stroke volume index; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; V_{max}: maximum velocity of aortic Doppler spectrum; G_{mean}- transaortic mean pressure gradient; VTI Ratio: velocity time integral ratio; EOA: effective orifice aortic valve area; EOAi: indexed effective orifice aortic valve area; Classic EOA_{proj}: simplified projected aortic valve area calculated using the classic flow rate formula; Alternative EOA_{proj}: simplified projected aortic valve area calculated using the alternative flow rate formula; AS: aortic stenosis.

the aortic velocity spectrum. Also, as it only requires 2 different measurements, it is less prone to increased inter-observer and intra-observer variability.

This study aimed to assess how much the EOA_{proj} calculated using an alternative method to estimate flow rate differs from the EOA_{proj} calculated by the standard formula. The Bland-Altman method was used to assess agreement between the two methods. As previously published, Pearson correlation and linear regression analysis can be misleading in terms of assessing agreement between two measurement methods, as data which seem to be in poor agreement (for instance, a change in scale of measurement) can be highly correlated.[6,9] Bland-Altman method assesses how well the methods agree on average

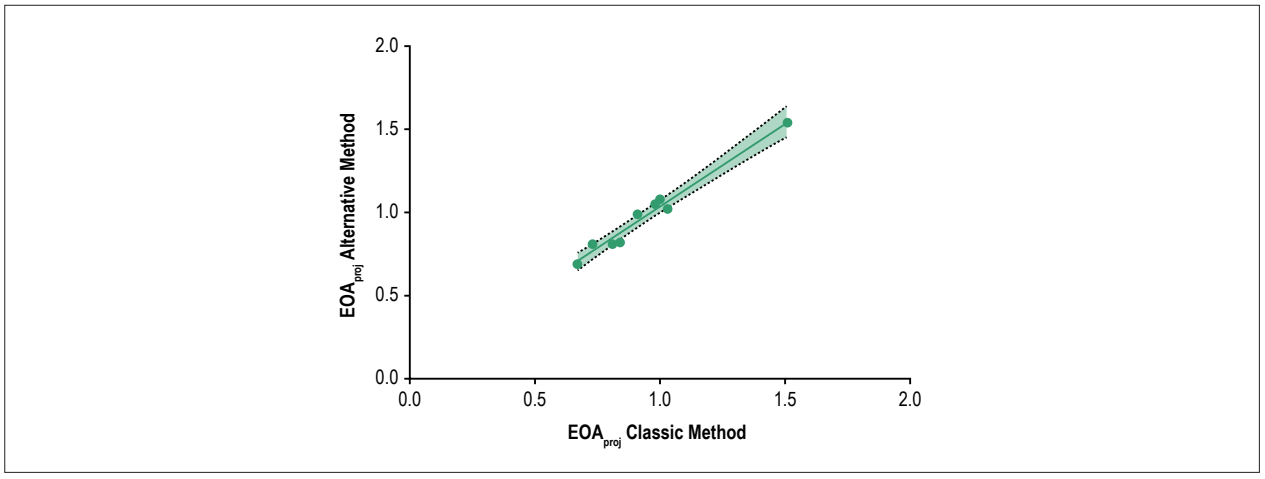

Figure 1 – *Scatter plot showing the classic simplified projected aortic valve area values against the alternative simplified projected aortic valve area values with a superimposed regression line (solid line) with 95% confidence bands (dashed lines).*

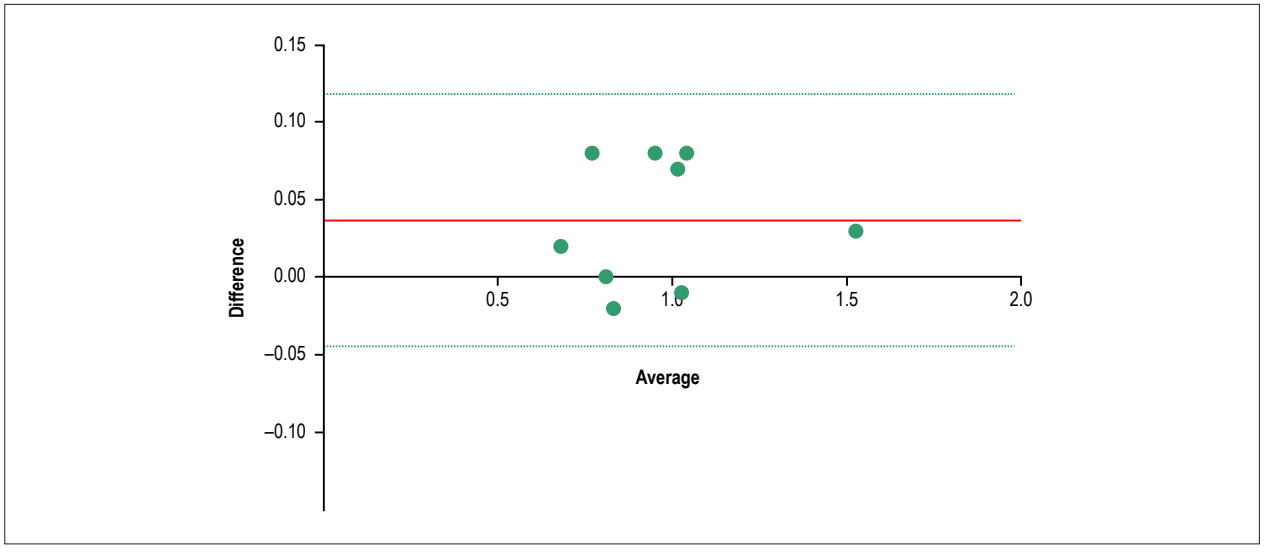

Figure 2 – *Bland-Altman plot, in which the difference of the two paired EOA_{proj} measurements is plotted against their mean. The solid line parallel to the x axis represents the bias and the dashed lines parallel to the x axis represent the limits of agreement.*

(by estimating the mean of the differences for individuals – the systematic bias) and how well the measurements agree for individuals (by examining the variability of the differences and the calculation of the limits of agreement which quantify the range of values that can be expected to cover agreement for most of the subjects).[10]

Using the Bland-Altman method, we found a systematic bias of 0.037 cm^2 (95% CI 0.004 – 0.066), meaning that on average the alternative method overestimates the EOA_{proj} in 0,037 cm^2 compared to the classic method. Despite being statistically significant, this bias is not clinically significant as it is less than 0.1 cm^2. Also, the 95% limits of agreement are quite narrow (from -0,04 cm^2 to 0,12 cm^2), meaning that for 95% of individuals, EOA_{proj} calculated by the alternative method would be between 0,04 cm^2 less to 0,12 cm^2 more than the EOA_{proj} calculated by the classic equation. Such narrow range is the largest likely differences between the two methods, and do not compromise the clinical agreement between the two methods. Therefore, it is reasonable to acknowledge the potential interchangeability of the two methods of EOA_{proj} calculation in clinical practice.

Conclusion

This study presented a new method to calculate the simplified EOA of the aortic valve at normal flow rate using a less cumbersome equation to estimate flow rate and tested the agreement of this new method with the previous reported by Blais et al.[4] The bias and 95% limits of agreement of the new method are narrow and not clinically relevant, supporting the potential interchangeable use of

both methods in clinical practice. As the new method requires less additional measurements, it would be easier to implement it in clinical practice, promoting an increase in the use of EOA_{proj} - a valuable echocardiographic parameter in the evaluation of LFLG AS.

Limitations

This is a small retrospective single-institution study that is inherently underpowered to assess small differences in echocardiographic variables between groups. A higher number of patients is needed to investigate potential discrepancies in the performance of both EOA_{proj} calculation methods in different subsets of LFLG AS patients. Therefore, the results presented here must be interpreted with caution.

Author contributions

Conception and design of the research: Ferreira JSSM, Moreira N, Ferreira R, Martins R; Acquisition of data: Ferreira JSSM, Moreira N, Mendes S; Analysis and interpretation of the data: Ferreira JSSM, Moreira N, Ferreira R, Martins R, Ferreira MJ; Statistical analysis: Ferreira JSSM, Ferreira R; Writing of the manuscript: Ferreira JSSM, Moreira N, Ferreira R, Mendes S, Martins R; Critical revision of the manuscript for intellectual content: Ferreira JSSM, Moreira N, Ferreira R, Mendes S, Martins R, Ferreira MJ, Pego M.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina da Universidade de Coimbra under the protocol number CE-016/2017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Global Longitudinal Strain Accuracy for Cardiotoxicity Prediction in a Cohort of Breast Cancer Patients During Anthracycline and/or Trastuzumab Treatment

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Abstract

Background: **The high cardiotoxicity morbidity and mortality rates associated with the antineoplastic therapy for breast cancer could be reduced with the early use of cardioprotective drugs. However, the low sensitivity of left ventricular ejection fraction limits its use in that preventive strategy. New parameters, such as global longitudinal strain, are being used in the early detection of contractile function changes.**

Objectives: **To assess the incidence of cardiotoxicity in patients treated for breast cancer, the independent factors associated with that event, and the ability of strain to identify it early.**

Methods: **Prospective observational study of consecutive outpatients diagnosed with breast cancer, with no previous antineoplastic treatment and no ventricular dysfunction, who underwent anthracycline and/or trastuzumab therapy. The patients were quarterly evaluated on a 6- to 12-month follow-up by an observer blind to therapy. Cox regression was used to evaluate the association of cardiotoxicity with clinical, therapeutic and echocardiographic variables. A ROC curve was built to identify the strain cutoff point on the third month that could predict the ejection fraction reduction on the sixth month. For all tests, the statistical significance level adopted was $p \leq 0.05$.**

Results: **Of 49 women (mean age, 49.7 ± 12.2 years), cardiotoxicity was identified in 5 (10%) on the third (n = 2) and sixth (n = 3) months of follow-up. Strain was independently associated with the event (p = 0.004; HR = 2.77; 95%CI: 1.39-5.54), with a cutoff point for absolute value of -16.6 (AUC = 0.95; 95%CI: 0.87-1.0) or a cutoff point for percentage reduction of 14% (AUC = 0.97; 95%CI: 0.9-1.0).**

Conclusion: **The 14% reduction in strain (absolute value of -16.6) allowed the early identification of patients who could develop anthracycline and/or trastuzumab-induced cardiotoxicity. (Arq Bras Cardiol. 2018; 110(2):140-150)**

Keywords: **Breast Neoplasms/drug therapy; Cardiotoxicity; Stroke Volume; Trastuzumab; Indicators of Morbidity and Mortality**

Introduction

Advances in the treatment of several tumors, such as the new antineoplastic drugs, have improved the survival of patients with cancer, resulting in more than 12 million survivors.[1] That, however, has allowed the identification of side effects, such as cardiotoxicity, responsible for an increase in mortality.[2,3]

In 2016, the European Society of Cardiology has published a position paper recommending the diagnosis of cardiotoxicity be made in the presence of an ejection fraction (EF) reduction >10% for values below normality (53%).[4] Prior to that publication, different definitions of cardiotoxicity were used, hindering the assessment of its real incidence.[2] The most commonly used definition has been elaborated by the committee of cardiac review and assessment of trastuzumab-related cardiotoxicity, and consists of a reduction of 5% or more in EF values lower than 55%, accompanied by signs and/or symptoms of heart failure (HF), or a reduction of 10% or more in EF values lower than 55%, without clinical findings of HF.[5-8]

Cardiotoxicity is a well-established side effect of several antineoplastic drugs, particularly anthracyclines and trastuzumab, used for breast cancer treatment.[9,10]

The identification of patients at high risk for developing cardiotoxicity would be the ideal strategy to reduce mortality.

Global longitudinal strain (GLS) is used in clinical practice aimed at the early detection of changes in myocardial contractile function.[11] However, neither GLS use nor its cutoff point to predict cardiotoxicity have been standardized.

The American Society of Echocardiography and the European Association of Cardiovascular Imaging have agreed that deformity changes precede ventricular dysfunction.

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A reduction > 15% in GLS, immediately after or during anthracycline treatment, was the most useful parameter to predict cardiotoxicity, while a reduction < 8% might exclude its diagnosis.[12] However, there is a grey zone between those values.

This study was aimed at assessing the incidence of breast cancer treatment-induced cardiotoxicity, identifying the independent risk factors associated with that event (drugs, dose, radiotherapy, clinical data and echocardiographic variables), and at identifying the best GLS cutoff point for the early detection of cardiotoxicity, prior to EF reduction.

Methods

This is a prospective and observational study of consecutive patients referred to the Oncology Outpatient Clinic of the Clementino Fraga Filho University-Affiliated Hospital (HUCFF), Rio de Janeiro, Brazil, with confirmed diagnosis of breast cancer and indication for potentially cardiotoxic antineoplastic treatment. Data were collected from January 22, 2015, to June 19, 2016, by filling in a form consisting of patient's clinical information, physical exam, echocardiographic data and proposed treatment.

The inclusion criteria were: age ≥ 18 years; diagnosis of breast cancer, with neither previous antineoplastic treatment nor radiotherapy; normal EF, according to the last recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[13] (> 54%, by use of the Simpson's method), on the first Doppler echocardiogram before treatment; and antineoplastic treatment planning with anthracyclines and/or trastuzumab.

The exclusion criteria were as follows: impossibility of accurately assessing GLS because of an inappropriate acoustic window; presence of cardiac arrhythmias and/or non-sinus rhythms; use of beta-blockers and/or angiotensin-converting-enzyme inhibitors and/or angiotensin receptor blockers; and moderate or severe heart valve disease.

The patients who met the inclusion criteria underwent Doppler echocardiography at baseline, before initiating the anthracycline, and then every 3 months, during a 6- to 12-month follow-up at the HUCFF. All tests were performed by one single professional, who was blind to the treatment instituted. Two distinct protocols of antineoplastic drugs were used:

1. FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2) in 3 cycles, every 21 days, followed by docetaxel 100 mg/m^2 in other 3 cycles, every 21 days;
2. Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 in 4 cycles, every 21 days, followed by paclitaxel 80 mg/m^2 weekly, for 12 cycles, for both adjuvant and neoadjuvant treatments.

The patients eligible for trastuzumab should undergo genetic assessment with human epidermal growth factor receptor 2 (HER2) test. Those who had a positive HER2 test result (+++/+++) or undetermined HER2 test result (++/+++), but positive FISH (*Fluorescence in Situ Hybridization*), were assigned to adjuvant treatment. Trastuzumab would be offered for 1 year, with 18 applications at 21-day intervals, with an initial dose of 8 mg/kg, followed by a maintenance dose of 6mg/m^2.

In 19 months (01/22/2015 to 06/19/2016), 58 patients were referred to the Oncology Service of the HUCFF to undergo Doppler echocardiography. Of those 58 patients, 9 were excluded because of inappropriate acoustic window (2 were on beta-blockers), leaving 49 patients as the study population.

Doppler echocardiography

Doppler echocardiography was performed with the patient at rest in the left lateral position, using the Vivid S6-GE device (GE, Vingmed Ultrassound Horten, Norway), LCD 17" monitor, with image acquisition with a 3S transducer and harmonic imaging. The measurements were reassessed by a second observer, also blind to the treatment instituted and specialized in the method. Interobserver agreement was assessed. All tests were performed with the same device. Sector and depth were adjusted to optimize the image. The measurements and image acquisition followed the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[13]

The following echocardiographic variables were assessed: EF, calculated by use of the Simpson's method, considering the normal value of EF > 54% for the female sex, according to the current recommendations;[13] diastolic function, evaluated by use of mitral flow with anterograde values of E wave and A wave, tissue Doppler of septal and lateral mitral annulus, measures of S' wave (systolic velocity of the mitral ring) and E/E' ratio; S wave of the right ventricle (cm/s); indexed left atrial volume (mL/m^2); tricuspid annular plane systolic excursion (TAPSE); and pulmonary artery systolic pressure (PASP).

In our study, cardiotoxicity was defined, in accordance with the cardiac review committee and expert recommendations on trastuzumab-related cardiotoxicity, as a reduction of at least 5% of EF values < 55% in symptomatic patients, or a reduction of at least 10% of EF values < 55% in asymptomatic patients.[8]

The GLS was acquired by use of Automated Functional Imaging (AFI) of three clips with images of the left ventricle on three apical views, so that all myocardial segments could be well visualized: 4-chamber, 2-chamber and 3-chamber views. The events of aortic valve opening and closure were marked. The images were acquired at a frame rate of 40-90 fps (> 70% of heart rate). Right ventricular (RV) strain was acquired by use of AFI. The acquisition of a clip of apical window projection adapted to RV assessment was necessary to include the entire RV free wall and its tip for further analysis. Three points were marked in the basal segments (inferior septum, tricuspid annulus) and apex. After that marking, the analysis was performed in the same way described for the left ventricle.

The images were analyzed in the same device and same working station (EchoPAC 13.0, GE Vingmed Ultrassound Horten, Norway).

Reproducibility

The measures of left ventricular (LV) GLS, RV strain and RV free wall strain underwent intra- and interobserver agreement analysis by use of intraclass correlation coefficients. Bland-Altman plots were created to show the results of the interobserver analyses.

Tests at different follow-up times were randomly drawn, defining a sample of approximately 10% of all calculations of the GLS analyzed during the study. Data were reassessed by the same observer, blind to the treatment instituted and specialized in the method, so that intraobserver agreement could be assessed.

The interobserver analysis was performed by another professional, also specialized in the method with experience in GLS assessment, the major variable of this study. The second observer used the same clip selected by the first observer, with predefined configurations, such as depth, gain, value of pulse repetition frequency (PRF); however, the new regions of interest for myocardial markers were freely chosen during the reanalysis. If the observer agreed on the region of interest marked, the next step would be the approval of the six segments according to the walls assessed. Upon approval with a command on the working station screen, the values of GLS and segment strains were calculated and demonstrated by use of bull's eye. Therefore, the calculations of the LV GLS, RV strain and RV free wall strain were repeated at the working station by the second observer, who was blind to the time the Doppler echocardiography was performed, the treatment and the patient's outcome.

Statistical analysis

Data were prospectively recorded in the program SPSS 15.0 for Windows, also used for statistical analysis.

The categorical variables were expressed as frequency, being compared by use of chi-square test. The continuous variables were expressed as mean and standard deviation or median and interquartile range, according to their distribution, and compared by use of paired Student *t* test or Mann Whitney U test. The baseline values and those at 3, 6, 9 and 12 months from Doppler echocardiography were compared by use of one-way analysis of variance (ANOVA).

Cox regression analysis was used to identify independent echocardiographic variables predictive of cardiotoxicity.

Receiver operating characteristic (ROC) curves were created to define the most accurate cutoff points for the continuous variables independently associated with the event assessed.

The intra- and interobserver variabilities were analyzed with intraclass correlation coefficients, and Bland-Altman plots were created to show the results of the interobserver analyses.

For all tests, the statistical significance level adopted was $p \leq 0.05$.

Results

Of the 58 female patients consecutively referred to the Oncology Outpatient Clinic of the HUCFF, 49 were included in this study. Nine patients were excluded because of their high body mass index (BMI), which generates an inappropriate acoustic window to the LV GLS acquisition and EF calculation with the Simpson's method.

The mean age of the population studied was 49.7 ± 12.2 years, and the follow-up duration, 381 ± 29,8 days. Table 1 shows the baseline characteristics of the patients included in this study and of those excluded from it.

Regarding the oncological data, the most common histological type of tumor was invasive ductal carcinoma, observed in 70% of the patients. In 51% of the patients, the tumor was located in the left breast, 40.8% of the patients underwent surgery before chemotherapy, and 53.1%, radiotherapy (all of them after chemotherapy).

The patients underwent serial Doppler echocardiography, the first test being performed prior to treatment, and the following tests, on the third, sixth, ninth and twelfth months, in accordance to the study protocol. The LV GLS and the EF (Simpson's method) were obtained at all tests of the 49 patients. The mean time between undergoing the first Doppler echocardiography and initiating the antineoplastic treatment was 9 days.

The population studied and that excluded from the study were compared, and a similarity between the groups was observed.

Intra- and interobserver analysis of global longitudinal strain

The intraobserver intraclass correlation coefficients for LV GLS, RV strain, and RV free wall strain were 0.97 (95%CI: 0.91-0.99), 0.98 (95%CI: 0.93-0.99) and 0.98 (95%CI: 0.95-0.99), respectively. The interobserver intraclass correlation coefficients were 0.97 (95%CI: 0.92-0.99), 0.97 (95%CI: 0.92-0.99) and 0.98 (95%CI: 0.93-0.99), respectively. The results showed excellent inter- and intraobserver agreements. The excellent result of the interobserver analysis of the LV GLS, RV strain, and RV free wall strain can also be observed in Figures 1A, 1B and 1C (Bland-Altman plots).

Characteristics of the population that developed cardiotoxicity

All patients in our study received anthracyclines, and 80% of them underwent radiotherapy after chemotherapy. During the follow-up, five patients (10%) developed cardiotoxicity, two on the third month and three on the sixth month. Despite the lack of a statistically significant association, the mean age of the patients with cardiotoxicity was higher than that of the 44 patients without it. In addition, 80% of those patients underwent radiotherapy, which is clinically relevant. All patients used anthracyclines. For two patients (40%) who developed cardiotoxicity, trastuzumab was associated to the antineoplastic regimen. The baseline characteristics of the patients who developed cardiotoxicity are shown in Table 2.

Description of the echocardiographic parameters

The means of the echocardiographic variables of the patients with and without cardiotoxicity are shown in Table 3. On the third month, the mean LV GLS, as well as its difference regarding the baseline value, were significantly higher in the group with cardiotoxicity. Although the EF value on the third month differed between the groups, its difference from the baseline value did not behave like that. On the sixth month, there was a significant drop in the EF and LV GLS, in addition to changes in the S wave of the left ventricle and E/E'.

Table 4 shows the five cases of cardiotoxicity.

Table 1 – General characteristics of the population included in the study and excluded from it.

Variable	population included n= 49	population excluded n = 9	p
Age (years) *‖	49.7 ± 12.2	51.0 ± 12.9	0.78
Weight (kg) *‖	67.6 ± 12.6	90.5 ± 12.5	< 0.05
Height (m) *‖	1.5 ± 0.06	1.5 ± 0.09	0.75
BSA (m^2) *‖	1.65 ± 0.2	1.9 ± 0.2	< 0.05
BMI (kg/m^2) †§	26.1 (23.6 - 30.4)	37.9 (31.6 - 40.9)	< 0.001
SBP (mm Hg) *‖	125.1 ± 17.4	132.2 ± 12.0	0.25
DBP (mm Hg) *§	74.7 ± 12.0	84.4 ± 5.3	0.02
HR (bpm) *‖	77.2 ± 10.1	83.4 ± 13.7	0.12
EF (Teicholz - %) *‖	69.0 ± 0.7	67.7 ± 9.3	0.59
Total Anthracycline Dose (Equivalence) (mg/m^2) †§	600 (534-760)	600 (507-590)	0.68
Total Traztuzumab Dose (mg/m^2) *‖	6823.3 ± 2395.6	7079 ± 2207.6	0.88
SAH ‡	16 (32.7)	4 (44.4)	0.37
Type II DM ‡	2 (4.1)	0	0.71
Beta-blocker ‡	0	1 (11.1)	0.15
ACEI / ARB ‡	0	1 (11.1)	0.15
ASA ‡	2 (4.1)	0	0.71
HCTZ ‡	14 (28.6)	3 (33.3)	0.52
Statin ‡	3 (6.1)	0	0.59
Right breast CA ‡	24 (49.0)	8 (88.9)	0.03
Left breast CA ‡	25 (51.0)	2 (22.2)	0.11
Invasive ductal carcinoma ‡	34 (69.4)	9 (100)	
Lobular carcinoma ‡	7 (14.3)	0	0.16
Other subtypes ‡	8 (16.3)	0	
Pre-chemo surgery ‡	20 (40.8)	3 (33.3)	0.49
Radiotherapy ‡	26 (53.1)	7 (77.8)	0.16
Doxorubicin ‡	20 (40.8)	2 (22.2)	0.25
Epirubicin ‡	29 (59.2)	7 (77.8)	0.25
Trastuzumab ‡	8 (16.3)	2 (22.2)	0.48

** Mean (standard deviation); † Median (25^{th} - 75^{th} Percentile); ‡ N (%); BSA: Body Surface Area; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; EF: Ejection Fraction; SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; ACEI: Angiotensin-Converting-Enzyme Inhibitor; ARB - Angiotensin Receptor Blocker; ASA: Acetylsalicylic Acid; HCTZ: Hydrochlorothiazide; CA: Cancer; Chemo: Chemotherapy; + Median (25^{th} – 75^{th} Percentile); bpm: beats per minute. Categorical variables compared by use of chi-square test‡, p value ≤ 0.05. Continuous variables compared by use of Mann Whitney U test § or Student t test ‖, p value ≤ 0.05.*

When assessing the percentage reduction in the LV GLS, from baseline to the third month, between patients with and without cardiotoxicity, a clear difference is observed between the two groups (Figure 2A). That same behavior was not observed when assessing the percentage reduction in the EF in the same period, confirming that EF is not as sensitive as GLS to diagnose cardiotoxicity (Figure 2B).

The RV strain and RV free wall strain were acquired by using the same software developed for the analysis of the left ventricle, and showed mild non-significant changes on the third and sixth months, with subsequent normalization. However, TAPSE and tissue Doppler of the tricuspid annulus, measures related to the right ventricle, did not change during the follow-up.

Predictors of cardiotoxicity

Aiming at assessing the association of each echocardiographic variable with cardiotoxicity (outcome), Cox regression analysis was performed (Table 5).

The variables with p ≤0.05 on Cox regression univariate analysis went to multivariate analysis of independent predictors of cardiotoxicity: EF (Simpson's method), LV GLS on the third month, left atrial volume, and diastolic function. Two models were created, separating the information of left atrial volume and diastolic function, because both variables express similar information, and can be interpreted in the concept of collinearity. Only LV GLS on the third month remained an independent predictor of cardiotoxicity,

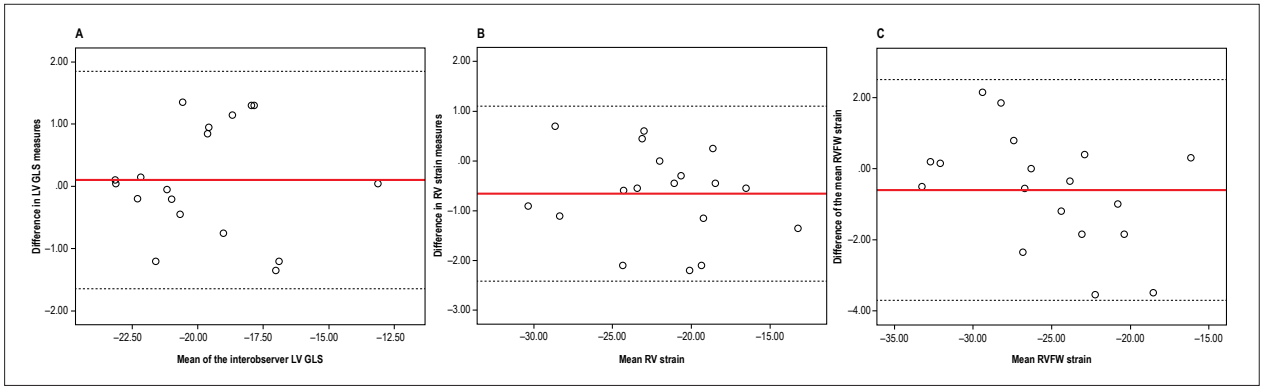

Figure 1 – *Bland-Altman plots showing interobserver analysis of left ventricular global longitudinal strain (LV GLS), right ventricular (RV) strain and right ventricular free wall (RVFW) strain in A, B and C, respectively.*

Table 2 – Baseline characteristics of the patients treated with anthracyclines and trastuzumab - Association with cardiotoxicity.

Variable	Cardiotoxicity		P
	Yes	No	
	n = 5	n = 44	
Age (years) *‖	56.4 ± 9.50	48.9 ± 12.30	0.60
Weight (kg) *‖	65.8 ± 10.80	67.9 ± 12.90	0.78
Height (m) *‖	1.58 ± 0.07	1.57 ± 0.08	0.80
BSA (m^2) *‖	1.63 ± 0.17	1.66 ± 1.17	0.80
BMI (kg/m^2) †§	27.3 (22.9-29.2)	26 (23.7-30.4)	0.94
SAH‡	2 (40%)	14 (31.8%)	0.53
White ethnicity ‡	4 (80%)	27 (61.4%)	0.39
Mixed ethnicity ‡	1 (20%)	17 (38.6%)	
Type II DM ‡	1 (20%)	1 (2.3%)	0.20
ASA ‡	1 (20%)	1 (2.3%)	0.20
Diuretic ‡	2 (40%)	12 (27.3%)	0.45
Statin ‡	0	3 (6.8%)	0. 72
SBP (mm Hg) ‡‖	128 ± 23.9	124.8 ± 16.9	0.30
DBP (mm Hg) ‡‖	72 ± 13.0	75 ± 12.0	0.88
HR (bpm) ‡‖	78.4 ± 8.3	77.1 ± 10.4	0.78
Invasive ductal carcinoma ‡	3 (60%)	31 (71%)	
Lobular carcinoma ‡	2 (40%)	5 (11.4%)	0.17
Other types ‡	0	8 (18.2%)	
FEC protocol ‡	4 (80%)	27 (61.4%)	0.64
AC protocol ‡	1 (20%)	17 (38.6%)	
Radiotherapy ‡	4 (80%)	22 (50%)	0.35
Total Trastuzumab Dose (mg/m^2) *‖	4257 ± 1899	6692 ± 2352	0.24
Total Anthracycline Dose (Equivalent dose mg/m^2) †‖	480 (402-720)	600 (525-795)	0.17

** Mean (standard deviation); † Median (25^{th} - 75^{th} Percentile); ‡ N (%); BSA: Body Surface Area; BMI: Body Mass Index; SAH - Systemic Arterial Hypertension; DM: Diabetes Mellitus; ASA: Acetylsalicylic Acid; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; FEC: 5-Fluorouracil + Epirubicin + Cyclophosphamide; AC: Doxorubicin + Cyclophosphamide. Categorical variables compared by use of chi-square test ‡, p value ≤ 0.05.* Continuous variables compared by use of Mann Whitney U test § or Student *t* test ‖, p value ≤ 0.05.

Table 3 – Echocardiographic characteristics of the patients treated with anthracyclines and trastuzumab - Association with cardiotoxicity.

ECHO	Variable*	Cardiotoxicity		P
		Sim	Não	
		n = 5	n = 44	
Baseline ECHO	EF (%)	64 ± 4.8	68.3 ± 7.7	0.120
	GLS (%)	-19.3 ± 1.2	-20.5 ± 2.0	0.100
	E/E'	8.9 ± 2.5	7.9 ± 1.6	0.450
	LV S (cm/s)	7.8 ± 1.1	8.3 ± 1.1	0.380
	RV S (cm/s)	12.6 ± 2.1	12.9 ± 2.0	0.760
ECHO 3 months	EF (%)	57.6 ± 12.3	67.2 ± 6.4	0.006
	EF Dif. 3 months (%)	6.4 ± 16.2	1.1 ± 7.2	0.190
	GLS (%)	-15.2 ± 2	-19.6 ± 2.1	0.005
	GLS Dif. 3 months (%)	4.1 ± 1.6	0.8 ± 1.6	0.008
	E/E'	7.1 ± 1.6	8.6 ± 1.9	0.230
	LV S (cm/s)	8 ± 0.8	8.5 ± 1.6	0.600
	RV S (cm/s)	12.6 ± 2.2	12.9 ± 2.3	0.800
ECHO 6 months	EF (%)	52 ± 5.1	67.4 ± 6.6	0.001
	EF Dif. 6 months (%)	12 ± 5.2	0.9 ± 9.8	0.004
	GLS (%)	-15.6 ± 1.1	-19.4 ± 2	< 0.001
	GLS Dif. 6 months (%)	3.7 ± 1.8	1 ± 1.6	0.026
	E/E'	9	8.2 ± 2.4	0.040
	LV S (cm/s)	6.3 ± 0.5	7.8 ± 1.4	< 0.001
	RV S (cm/s)	11.8 ± 1.6	13 ± 2	0.200

** Means ± SD; ECHO: Echocardiography; EF: Ejection Fraction (Simpson's); EF Dif.: Ejection Fraction Difference; GLS Dif.: Global Longitudinal Strain Difference; E/E': Ratio between E and E' wave values on Doppler echocardiography; LV S: S wave of the left ventricle; RV S: S wave of the right ventricle. The echocardiographic variables were compared by using paired Student t test, p value ≤ 0.05.*

Table 4 – Description of the cases with cardiotoxicity.

Cases	EF			LV GLS		
	Baseline	3 Months	6 Months	Baseline	3 Months (% ΔGLS)	6 Months
1	66%	52%	58%	-19.4%	-12.9% (33.50)	-17.0%
2	65%	69%	50%	-18.7%	-16.0% (14.40)	-14.3%
3	56%	69%	49%	-19.2%	-16.5% (14.10)	-15.5%
4	64%	58%	45%	-21.2%	-17.4% (17.90)	-15.0%
5	69%	40%	53%	-18.0%	-13.3% (26.10)	-16.4%

EF: Ejection Fraction (Simpson's method); GLS: Global Longitudinal Strain; % ΔGLS: Percentage Variation of Global Longitudinal Strain.

maintaining a statistically significant association in the multivariate models, even when the variables selected on univariate regression were tested two by two.

ROC curves to predict cardiotoxicity by use of LV GLS

To define the most accurate cutoff point of the absolute LV GLS value on the third month to predict cardiotoxicity on the sixth month, a ROC curve was built (Figure 3A). The LV GLS value of -16.6 showed sensitivity of 80% and specificity of 95% to predict cardiotoxicity on the sixth month. Similarly, a second ROC curve was built to define the most accurate cutoff point of the percentage reduction of the LV GLS capable of predicting cardiotoxicity (Figure 3B). The LV GLS value of -14% showed sensitivity of 80% and specificity of 99% for that diagnosis. The accuracy of the percentage drop of 14% of the GLS (strain of the third month in regard to that of baseline) was assessed by use of its sensitivity and specificity (100% and 93%, respectively).

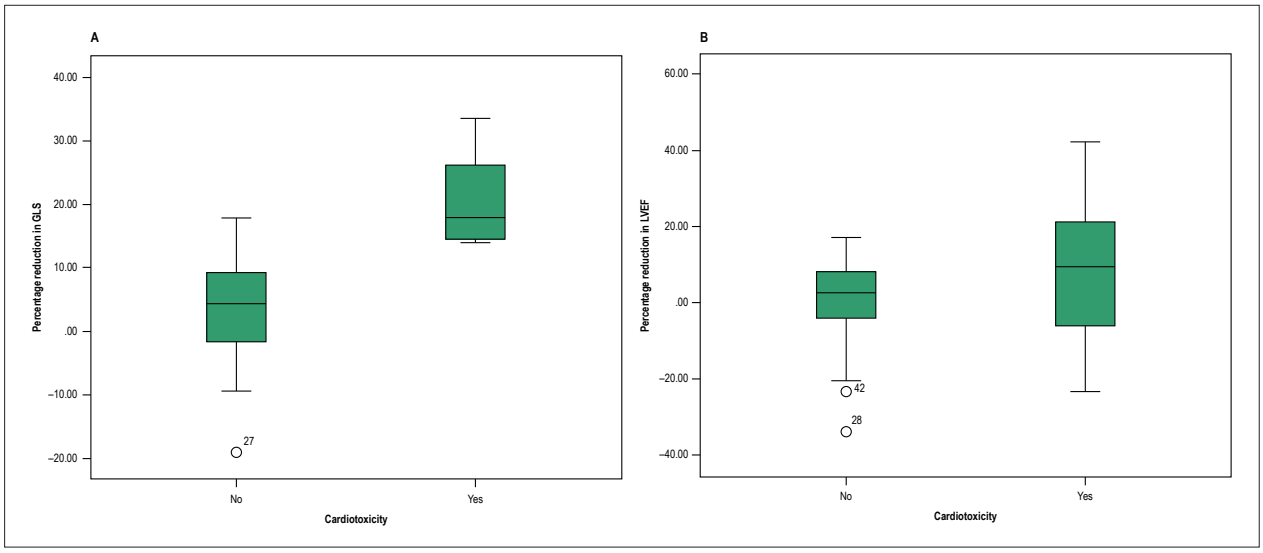

Figure 2 – *Boxplot illustrating the difference between the groups with and without cardiotoxicity. A, percentage reduction in left ventricular global longitudinal strain (GLS) variation; and B, percentage reduction in left ventricular ejection fraction (LVEF) variation.*

Table 5 – Cox Regression Models.

	B	SE	p	HR	95%CI
Cox regression model (Univariate)					
Diastolic function	0.551	0.221	0.013	1.735	1.126-2.675
Left Atrial Volume (ml/m^2)	- 0.354	0.154	0.022	0.702	0.519-0.950
LVEF (%)	- 0.117	0.046	0.011	0.889	0.813-0.973
GLS (%)	1.020	0.353	0.004	2.773	1.389-5.536
Cox regression model (Multivariate - A)					
Left Atrial Volume (ml/m^2)	- 0.218	0.249	0.382	0.804	0.494-1.311
LVEF (%)	0.108	0.084	0.198	1.115	0.945-1.314
GLS (%)	1.41	0.686	0.040	4.097	1.068-15.716
Cox regression model (Multivariate - B)					
LVEF (%)	0.143	0.103	0.163	1.154	0.944-1.412
GLS (%)	1.975	0.952	0.038	7.207	1.115-46.573
Diastolic function	- 0.153	0.345	0.658	0.858	0.436-1.688

B: Coefficient; SE: Standard Error; HR: Hazard Ratio; CI: Confidence Interval; LVEF: Left Ventricular Ejection Fraction; GLS: Global Longitudinal Strain.

Discussion

The results of the present study showed that the LV GLS was an excellent predictor of cardiotoxicity in our population, with high efficacy for its early diagnosis.

Profile of morbidity of the population studied

Our population was considered to have a low morbidity profile. The incidence of the risk factors that could be related to cardiotoxicity was very low, and no statistically significant association could be demonstrated. That profile differs from that of other studies, which had cases of smoking, previous use of chemotherapy, radiotherapy, in addition to a higher frequency of systemic arterial hypertension and diabetes mellitus.[14,15] The low morbidity profile can be associated with the lower incidence of cardiotoxicity observed in our population. Patients with the highest BMI were excluded from our study, because they could be considered at higher risk for cardiotoxicity, limiting the incidence rate of that event.

Definition of cardiotoxicity

The definition of cardiotoxicity is fundamental, because it is not uniform in different studies, hindering the assessment of the real incidence of the event. The cardiotoxicity incidence in a systematic review published in 2014 ranged from 13% to 32%.[15] Studies published by Sawaya et al.[16] and Baratta et al.[17] have found an incidence of 20%, using the same criterion of the trastuzumab committee. Our study found a cardiotoxicity

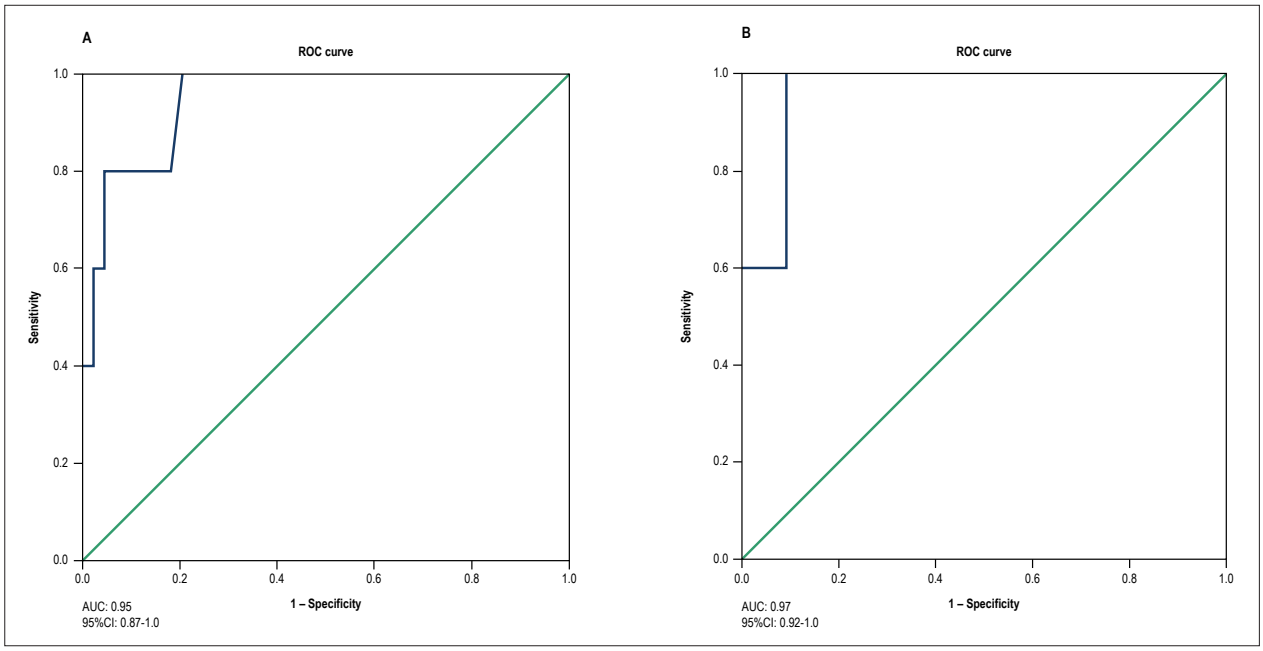

Figure 3 – *ROC curves to assess the cutoff point of the absolute value of left ventricular global longitudinal strain (GLS) (A), and the cutoff point of the percentage reduction in left ventricular GLS (B) as predictors of cardiotoxicity.*

incidence of 10%, lower than that reported by those studies. That could be explained by the low morbidity profile of our population, composed only by patients with breast cancer, with similar treatment protocols. In the study by Baratta et al.,[17] if the cardiotoxicity incidence would be calculated only among patients with breast cancer, a 12% rate would be found, similar to that of our population.

Characteristics of the population that developed cardiotoxicity

In our study, cardiotoxicity showed no statistically significant risk association with the clinical and anthropometric variables, histological type of tumor and treatment instituted. However, some variables evidenced clinically relevant information. The first was age, which was higher in the group that developed cardiotoxicity (mean of 56 years *versus* 49 years, in the group without cardiotoxicity), and could lead to a higher risk of events according to the literature. Another interesting variable, the total dose of anthracyclines and trastuzumab administered, which was lower in the group with cardiotoxicity, might be justified by the suspension or dose reduction of the antineoplastic drug by the oncology team in face of the drop in EF.

Choosing the best time for doppler echocardiography

There is no consensus between the European and American Societies of Cardiology about the time during the treatment in which the echocardiographies should be performed. In our population, two patients had cardiotoxicity on the third month. Analyzing retrospectively, if the Doppler echocardiography would be performed after each anthracycline cycle, the drop in LV GLS might have occurred before the reduction in EF on the third month. Therefore, Doppler echocardiography would ideally be performed after the end of each anthracycline cycle.

Marker of cardiotoxicity: 2D strain

Ejection fraction is not considered a good predictor of cardiotoxicity, because it does not detect early myocardial contractile function changes. Recent studies have demonstrated that strain changes precede EF changes in patients undergoing antineoplastic treatment.[14,16,18-21] However, no consensus has been reached regarding the specific cutoff point of that variable that should be used as a predictor of cardiotoxicity.

The results of our study confirm LV GLS as an excellent independent predictor of cardiotoxicity, which can be assessed by use of the data from Cox regression ($p = 0.004$, HR = 2.77; 95%CI: 1.39-5.54). None of the patients assessed showed the LV GLS drop after the EF drop. The LV GLS change occurred from the third month onward, while EF (Simpson's method) changed only on the sixth month.

There is no consensus in the literature regarding the LV GLS value that can predict cardiotoxicity. Some articles have mentioned that, using the Speckle Tracking technique, a 10% to 15% reduction could predict that outcome. The last European recommendation from 2016 states that a reduction > 15% could predict cardiotoxicity, while a reduction < 8% could exclude its diagnosis. However, there is a grey zone between those values.[12,22]

Because of data inconsistency, our study aimed at finding the best cutoff point of the absolute value and percentage reduction of LV GLS to predict cardiotoxicity. The five events that occurred in our study enabled the construction of ROC curves to assess the diagnosis of cardiotoxicity on the sixth month. The need to define the ideal cutoff point of the GLS drop percentage capable of preventing cardiotoxicity has also been approached by some authors in recent years. According to Sawaya et al.,[16] a 10% GLS drop on the third month of assessment could predict ventricular

dysfunction occurring on the sixth month, with sensitivity of 78%, specificity of 79% and negative predictive value of 93%. The sample calculation of that study was based on the hypothesis that a 14% GLS drop could predict cardiotoxicity, exactly the same value found in our study.

It is worth noting that all prognostic models, in addition to predictive accuracy, should have the variables easily obtained. Doppler echocardiography is widely available and easily accessible, involves no radiation, being performed at the bedside. Its use in the follow-up of patients with breast cancer is a criterion of quality in healthcare services, mainly when using GLS, capable of predicting cardiotoxicity in those patients. However, it should be performed by echocardiography professionals trained in the method, with excellent image acquisition, to minimize the intra- and interobserver variabilities, using the same device and software, creating an individualized set for image acquisition and subsequent assessment. In our study, those values were found using the GE software. The different brands of devices have different normality range values. An agreement regarding those values has not been achieved between the manufacturers. Most studies and guidelines use a percentage variation of strain to define the presence of cardiotoxicity. Using the patient's baseline measures as control, and guaranteeing that all measures are taken with the same equipment and technique, the variations seem more reliable.

Study limitations

The sequential echocardiographies were performed by the same examiner. Although the examiner was blind to the treatment instituted, an influence of the previous assessment on the subsequent tests could exist. However, the interobserver analysis showed an excellent correlation between data, and the second observer was blind not only to treatment, but also to the echocardiography times and previous results. Thus, although an assessment bias might have existed, it would not be strong enough to alter the results found.

The strain calculation requires an appropriate acoustic window. The patients excluded were those with the highest BMI, who would be at higher risk for cardiotoxicity according to the literature. In addition, in patients undergoing left breast surgery before the antineoplastic treatment, the presence of the expander or the surgical wound itself could interfere with the analysis. Limitations regarding the method also apply, and could be related to the test being performed by an untrained professional, or might be related to the devices available, taking into account that the strain values vary according to the brand of the device used.

Our study showed a low incidence of cardiotoxicity, which could limit the multivariate analysis. Currently, the literature is reviewing the assumption that a robust multivariate analysis should involve at least ten outcomes for each variable analyzed. There are three well-known simulation studies that assess that criterion for regression models, and they do not agree. Currently, in addition to the number of events per variable, the regression model depends on several other factors, such as the association of variables and outcomes, and some statistical studies report on the use of a smaller number of outcomes for each variable analyzed.[23,24]

Conclusions

The incidence of cardiotoxicity associated with the antineoplastic treatment for breast cancer was 10% in our institution.

Our population with a low cardiovascular morbidity profile showed no association between cardiotoxicity and the risk factors classically described, such as clinical and anthropometric variables and treatment.

A significant LV GLS drop was observed from the third month onward, characterizing that variable as an independent predictor of cardiotoxicity, with a cutoff point of an absolute LV GLS value of -16.6% or a percentage LV GLS variation of -14%.

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Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Gripp EA, Oliveira GE, Feijó LA, Garcia MI, Xavier SS, Sousa AS; Acquisition of data: Gripp EA, Oliveira GE; Analysis and interpretation of the data: Gripp EA, Feijó LA, Garcia MI, Xavier SS, Sousa AS; Statistical analysis: Feijó LA, Garcia MI, Xavier SS, Sousa AS.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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Uninterrupted Use of Oral Anticoagulants for the Ablation of Atrial Flutter: A Single Center Cohort of 154 Patients

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Abstract

Background: The uninterrupted use of oral anticoagulation (OAC) with vitamin K antagonists (VKAs) for electrophysiology procedures has been more and more recommended. The clinical practice in our service recommends the continuous use of these drugs for atrial flutter ablation. There is little evidence as to the uninterrupted use of non-vitamin K antagonist oral anticoagulants (NOACs) in this scenario.

Objective: To compare the rates of complications related with the uninterrupted use of different types of oral anticoagulants in patients referred to atrial flutter (AFL) ablation.

Methods: Historical, single-center cohort of ablation procedures by AFL conducted from November 2012 to April 2016. The primary outcome was the occurrence of hemorrhagic or embolic complication during the procedure. The secondary outcome was the occurrence of stroke or transient ischemic attack (TIA) in follow-up. The statistical significance level was 5%.

Results: There were 288 ablations per AFL; 154 were carried out with the uninterrupted use of OAC (57.8% with VKA and 42.2% with NOAC). Mean age was 57 ± 13 years. The rate of hemorrhagic complication during the procedure was 3% in each group (p = NS). The rate of stroke/TIA was, respectively, of 56/1,000 people-year in the VKA group against zero/1,000 people-year in the NOAC group (p = 0.02).

Conclusion: In our population there were no hemorrhagic complications regarding the procedure of OAC use uninterruptedly, including NOACs. There was higher occurrence of stroke/TIA in the follow-up of the group of patients undergoing VKAs; however, this difference may not only be a result of the type of OAC used. (Arq Bras Cardiol. 2018; 110(2):151-156)

Keywords: Anticoagulants; Vitamin K; Catheter Ablation; Atrial Flutter; Thromboembolism.

Introduction

The guidelines of the oral anticoagulant therapy[1] recommend the suspension of these medications and the performance of heparin bridging, at the conduction of a wide range of invasive Cardiology procedures. Recently, the new classes of non-vitamin K antagonist oral anticoagulants (NOACs: rivaroxaban, apixaban, dabigatran and edoxaban) has proven to be effective to prevent the thromboembolic events in patients with atrial fibrillation (AF) and atrial flutter (AFL).[2]

The catheter ablation for AFL is a highly successful procedure in the reversion for the sinus rhythm.[3,4] These cases require at least four weeks of anticoagulation before the procedure, as well as in electrical cardioversions, for the prevention of strokes or thromboembolic phenomena that can occur after the reversion of AFL to the sinus rhythm.[5] Studies show that the use of NOACs seems to be safe in the prevention of these thromboembolic phenomena, for the reversion to the sinus rhythm.[6,7]

After the ablation, the use of anticoagulant is recommended for all patients for at least one month after the reversion to the sinus rhythm.[5] The uninterrupted use of oral anticoagulant for AF procedures has proven to be safe[8,9], and our institution adopts such a recommendation also for patients with AFL. Therefore, in this scenario, there are few studies carried out in Brazil.

The main objective of this study was to demonstrate the safety of the uninterrupted use of anticoagulation during flutter ablation, comparing the patients using NOACs with the vitamin K antagonists (VKAs). More specifically, we assessed the rate of hemorrhagic complications, as well as the occurrence of thromboembolic events throughout follow-up.

Methods

Our study is a historical cohort that includes the procedures of ablation for AFL carried out in our Electrophysiology service (Instituto de Cardiologia Fundação Universitária de Cardiologia do Rio Grande do Sul). Of the 5,506 procedures conducted between November 2012 and April 2016, 288 (5.2%)

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corresponded to ablation for AFL. Data collection counted on the present description of the electrophysiological reports and with information obtained in an electronic and physical chart. The patients who discontinued the follow-up at the hospital outpatient clinic were selected for a telephone interview, and their consent was registered by the listener.

AFL was defined as a macro-reentrant atrial arrhythmia, electrocardiographically characterized by the presence of F-waves with constant morphology, and atrial frequency higher than 250 bpm. AFL typical was considered when the electrocardiogram (ECG) showed negative F-waves in derivations DII, DIII and VF, and positive in V1.[3]

The parameters of the left ventricular ejection fraction (LVEF) and left atrial (LA) diameter were collected by the most recent echocardiogram found in the records, that had been conducted before ablation, which includes both transesophageal (TEE) and transthoracic (TTE) examinations. The ejection fraction was calculated using the methods of Teichholz or Simpson, according to the presence of segmental dysfunction. The atrial diameters were assessed using the M mode.

The charts were revised aiming at recording the clinical information that was necessary for points in the score of CHA_2DS_2VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and female gender): sex, age, diagnosis of systemic arterial hypertension (SAH), diabetes mellitus (DM), congestive heart failure (CHF) or LVEF < 50%, peripheral vascular disease, myocardial infarction or aortic atherosclerosis and history of stroke or TIA. The referred diagnoses were defined according to previous publications.[10] Data of anticoagulation were registered before the ablation.

The patients who were receiving the same medication in the four weeks prior to the procedure were considered as undergoing uninterrupted use: VKAs (warfarin and phenprocoumon), with international normalized ratio (INR) between 2 and 3.5, and NOACs (dabigatran, rivaroxaban and apixaban). All patients received the dosage of NOAC on the day before the procedure, in the morning or in the afternoon, at the assistant physician's choice and according to the posology of the NOAC used (once or twice a day). None of the cases was performed with an interval higher than 24 hours after the administration of the daily use NOACs, or 12 hours after the ones with double dosage. The dose on the day of the ablation was instituted four hours after the removal of the introductory sheaths. The patients on VKA received the dose of the medication four hours after the removal of the introducers.

The patients were followed-up at the outpatient clinic, and the first appointment was conducted from one to three months after ablation, through a clinical visit and 12-lead ECG. During the follow-up of these patients, we also included the data referring to emergency care or hospitalizations that took place in our institution.

The patients who discontinued the follow-up at the outpatient clinic were selected for a telephone interview to clarify the following:

- If they continued to use the anticoagulant;
- If they presented an episode of stroke or TIA;
- If they had any late complications related with the procedure.

The Research Ethics Committee of our hospital approved the study protocol and we obtained a consent from all listeners for the performance of the interview. The study's protocol n. is UP 5252/16.

Outcomes

We defined the following as main outcomes: the occurrence of hemorrhagic complication during the procedure; some examples are cardiac tamponade, bleeding that requires transfusion, bleeding with reduction of ten percentage points in the hematocrit, local vascular complication requiring intervention (major hemorrhagic events), and clinically uncomplicated hematomas (minor hemorrhagic event); adverse heart events were considered as a compound of all mortality causes, stroke, TIA, during follow-up.

One specialist of each field validated each outcome.

Exclusion criteria

All patients with AFL submitted to a second procedure were excluded, as well as those with history of previous ablation at another service, those with left AFL and those who did not undergo the uninterrupted use of OAC in the peri-procedural period. The patients using low-molecular-weight heparin (full anticoagulant dose or unfractionated heparin in continuous intravenous infusion, even if anticoagulated) were not included in this study.

Statistical analysis

The data were stored and analyzed with the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean ± standard-deviation, and compared by the Student's *t* test for independent samples. The categorical variables were expressed in percentage and compared using the χ^2 test. The variables were considered normal according to the observation of the central tendency measurements, kurtosis and asymmetry in the frequency histograms. The incidence density was calculated using the people-time interval for the occurrence of thromboembolic phenomena in the post-ablation follow-up. This measure was carried out combining the number of people and the contribution of time during the study, and it was used as a denominator in the incidence rates. It was defined as the sum of individual units of time to which the people in the population studied were exposed, or at risk for the outcome of interest. The statistical significance level adopted was 5%.

Results

In the study period, there were 288 ablations per AFL. Of these, 154 were conducted with the uninterrupted use of oral anticoagulants, and these cases were included in the study. Figure 1 demonstrates the organization chart of inclusion of cases in the study. The mean age was 57.3 ± 13.1, and most were male (70%). The mean CHA_2DS_2-VASc was 2.1 ± 1.5 points, and 63% had a score higher than or equal to 2. Of the ablations, 98% were carried out with an 8 mm catheter – only 2% were conducted with an irrigated catheter.

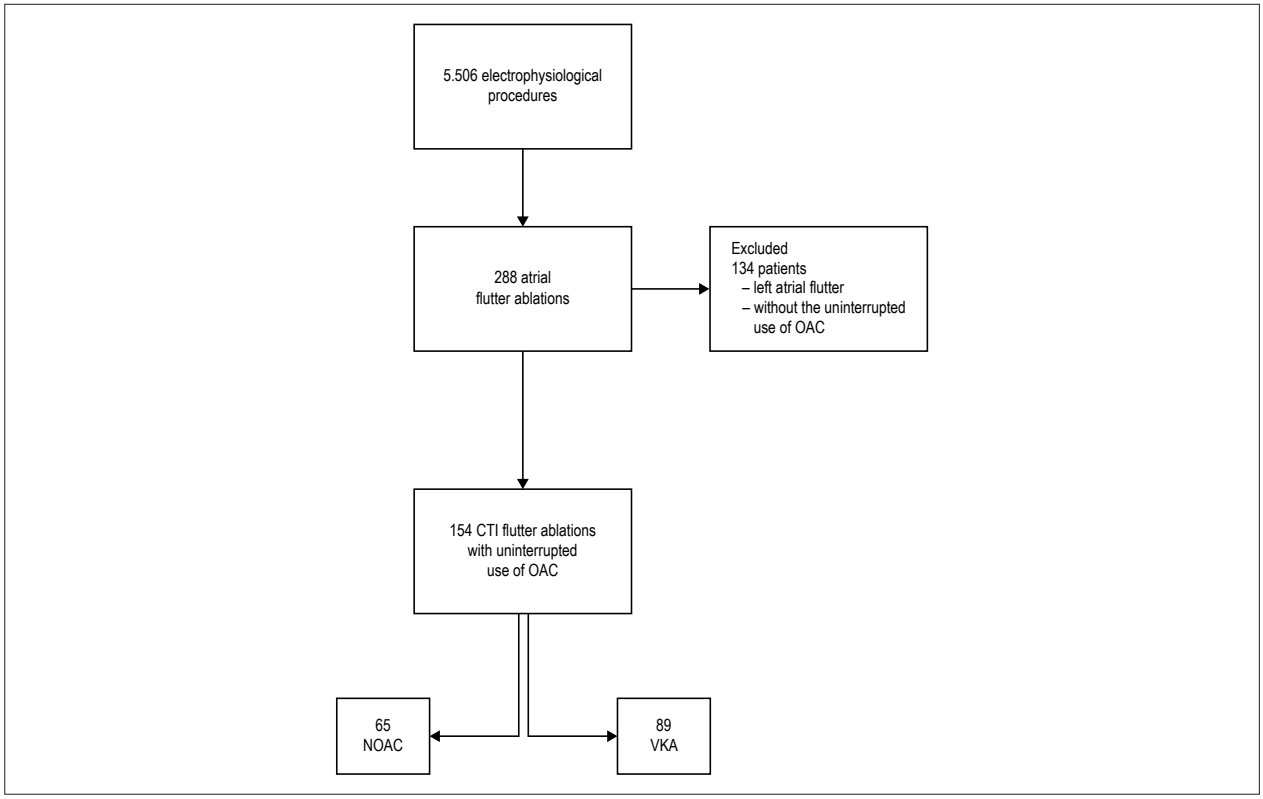

Figure 1 – *Study flowchart. CTI: cavotricuspid isthmus dependent flutter; OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulants; VKA: vitamin K anticoagulant antagonists.*

The VKAs were used uninterruptedly in 57.8% of the cases, and NOACs, in 42.2% of the participants. The mean INR was 2.54 ± 0.54 in the VKA group on the day of the ablation. The patients using NOAC were the majority at a sinus rhythm on the day of the ablation. These patients had smaller left atriums. Besides, they also used more antiarrhythmic drugs, less beta-blockers and statins, with lower prevalence of previous heart surgery when compared to patients using VKA. Table 1 shows the clinical characteristics of the patients stratified by type of anticoagulant used. Table 2 exemplifies the frequency of use of different types of NOACs and VKAs used in the study.

The rates of hemorrhagic complication related with the procedure was 3% in each group (p = 0.97). There were no cases of cardiac tamponade or major hemorrhagic complication in the patients of the study. The main complications related with the procedure were inguinal hematomas. The rate of stroke / TIA was 57/1,000 people-year in the VKA group against zero/1,000 people-year in the NOAC group (p = 0.02).

Discussion

Our study shows the safety of the use of oral anticoagulants (VKAs or NOACs) in the periprocedural period of the radiofrequency ablation of typical AFL. The use of periprocedural anticoagulation is based on the frequent finding of atrial thrombi or of spontaneous echo contrast in the transesophageal echocardiogram.[11] The studies about the oral anticoagulation in these patients, however, are scarce, and there are no clear recommendations in the guidelines about the handling of periprocedural anticoagulation for the ablation of AFL.[8,12-14]

A retrospective study with 254 patients, comparing periprocedural warfarin and dabigatran of ablation of AFL and AF, demonstrated similar results to that of our cohort, with low rates of thromboembolic and hemorrhagic complications. However, the authors do not show the number of patients with AFL included in the study.[12]

A second retrospective study with 60 patients who used dabigatran or rivaroxaban in the periprocedural period of AFL ablation demonstrated low incidence of hemorrhagic complications, with 4 minor bleedings (3 of the 23 patients using dabigatran 150 mg b.i.d, and 1 of the patients using rivaroxaban 20 mg), and no major bleeding.

A second retrospective study with 60 patients who used dabigatran or rivaroxaban in the periprocedural period of AFL ablation demonstrated low incidence of hemorrhagic complications, with 4 minor bleedings (3 of the 23 patients using dabigatran 150 mg b.i.d. and 1 of the 11 patients using rivaroxaban 20 mg), and no major bleeding. A patient using dabigatran 110 mg b.i.d. presented with ischemic stroke 27h after the procedure, in the uninterrupted use of anticoagulant, with preprocedural transesophageal echocardiogram that did not show atrial thrombi. This study, however, collected data only until the hospital discharge of the patients; therefore, the security data of the use of these medications may be underestimated.[15]

Table 1 – Difference between the populations that received vitamin-K antagonists and the ones who received non-vitamin K antagonists uninterruptedly for atrial flutter ablation

Factor	NOAC (n = 65)	VKA (n = 89)	p value
Previous history of AF	23 (35.4%)	28 (31.5%)	0.77
Age (years)	58.1 ± 11.7	56.8 ± 14.1	0.55
Gender (male)	45 (69.2%)	63 (70.8%)	0.97
Sinus basal rhythm	33 (50.8%)	28 (31.4%)	0.02
LVEF (%)	59.6 ± 12.3	58.0 ± 16.6	0.57
LA (mm)	44.3 ± 6.2	47.7 ± 7.7	0.01
$CHA_2DS_2VASc \geq 2$	64.6%	61.8%	0.852
– SAH	59.4%	73.0%	0.07
– DM	20.6%	20.2%	0.95
– Stroke	9.5%	3.4%	0.113
Beta-blockers	55.4%	79.8%	0.002
Calcium channel blockers	10.8%	13.5%	0.79
ACEi/ARB	44.6%	55.1%	0.26
Diuretics	29.2%	41.6%	0.16
Digoxin	12.9%	14.9%	0.90
Statins	27.7%	44.9%	0.04
ASA	15.4%	28.1%	0.09
Antiarrhythmic drugs	55.4%	33.7%	0.01
Previous heart surgery	7.7%	38.6%	< 0.001
– Valvar	0.0%	22.7%	0.0001
Ischemic cardiopathy	10.8%	19.3%	0.22
Congenit cardiopathy	9.2%	9.1%	0.79
Myocardiopathy	10.8%	19.3%	0.22
COPD	3.0%	7.9%	0.36

NOAC: non-vitamin K antagonist oral anticoagulants; VKA: vitamin K anticoagulant antagonists; AF: atrial fibrilation; LVEF: left ventricular ejection fraction; LA: left atrium; CHA2DS2VASc: risk for stroke (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and female gender); SAH: systemic arterial hypertension; DM: diabete mellitus; ACEi/ARB: angiotensin-converting enzyme inhibitors / angiotensin receptor blocker; ASA: acetylsalicylic acid; COPD: Chronic obstructive pulmonary disease. The p value expresses the difference of the Student's t test for the continuous variables and the χ^2 in the categorical variables. The statistical significance level adopted was 5%.

Table 2 – Type of non-vitamin K antagonist oral anticoagulants and vitamin K anticoagulant antagonists used uninterruptedly for the atrial flutter ablation

NOAC (n = 65)%	VKA (n = 89)%
Rivaroxaban (41) 63.0%	Warfarin (77) 86.5%
Dabigatran (14) 21.6%	Phenprocoumon (12) 13.5%
Apixaban (10) 15.4 %	

NOAC: non-vitamin K antagonist oral anticoagulants; VKA: vitamin K antagonist.

A third retrospective study of NOACs in this scenario compared patients using apixaban (n = 105), paired with others that used phenprocoumon (n = 210) until hospital discharge.[13] Only the patients submitted to ablation of left atrial arrhythmia were included, unlike our cohort, which only included cases of typical flutter. All patients were using oral anticoagulation for at least four weeks, and the use of anticoagulation was uninterrupted, with use of endovenous heparin during the procedure. There were no thromboembolic events; minor bleedings occurred in 10.5% of the patients using apixaban, and in 12.3% of those using phenprocoumon (p = 0.61). Our cohort demonstrated fewer hemorrhagic complications, however, no procedure carried out approached the left atrium.

Proving the variability in the handling of periprocedural anticoagulation of AFL ablation, a study conducted in Europe and in Canada showed that 6% of the centers do not use routine anticoagulation in typical AFL ablation, and that only 31% of the centers performed preprocedural anticoagulation for a minimum period of 4 weeks.[16] Regarding the use of NOACs, only 35% of the centers perform the procedure with the uninterrupted use of medication, and those who suspended the medication demonstrate great variation in the period of the suspension.

The increasing use of NOACs since 2010, as demonstrated by the study GARFIELD-AF,[17] points to the need of data collection regarding the use of these classes of drugs in the most varied scenarios. The scenario of AFL ablation, however, requires prospective studies that are able to unify the conducts of the electrophysiology centers. Our study points to the security of these drugs and paves the way for the clinical trials to be conducted.

One point to be emphasized in our study was the almost exclusive use of the 8 mm ablation catheter, which may not reflect the reality of other services. There is a sensation that, in the region of the cavotricuspid isthmus, whose thickness ranges between 0.5 and 5 mm,[18,19] the application of high energy (70 W) may lead to an increasing risk of perforation. However, the studies that assessed the use of 8 mm catheters, in comparison to irrigated ones, in the ablation of isthmus-dependent AFL, demonstrated there were no significant differences in the occurrence of vaporization lesions ("pop") or cardiac perforation.[20-22] The occurrence of carbonization at the end of the catheter, however, seems to be higher than in the irrigated catheter,[20] but this fact was not measured in our study.

Study limitations

As limitations of our study, we mentioned that part of data collection was conducted retrospectively, through the analysis of medical records, which could lead to bias in the confirmation of the outcomes. However, our center presents a routine of peri and post-procedural care, which contemplates the collected variables, which mitigates the potential bias. Also, the number of patients analyzed may not have been sufficient to detect a statistically significant difference between the groups regarding the lower incidence outcomes. Another important aspect is that, even though the incidence density for ischemic events was higher in our study in the VKA group, this does not mean that one strategy is superior to another in the post-ablation period. As demonstrated, the patients using VKA have different characteristics than those using NOAC. The comparison between two distinct groups of patients is a significant limitation of this study. Besides the bias caused by the retrospective design, the VKA group presents almost 23% of the etiology patients (against none in the NOAC group). The valvar patients clearly presented with higher thromboembolic risk. Also, since this is an observational design, strategies for the strict control of therapeutic-target achieving (TTA) time were not conducted, and studies carried out in our service demonstrated mean TTA of about 50% in our population.[23]

Conclusion

This historical cohort points to the safety in the conduction of radiofrequency ablation of typical AFL procedures with the uninterrupted use of oral anticoagulants, regardless of the class of this group of medication.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Leiria TLL; Acquisition of data: Medeiros AK, Almeida ED, Ley ALG, Santos CBL; Statistical analysis: Medeiros AK, Ley ALG; Writing of the manuscript: Leiria TLL, Almeida ED, Sant'Anna RT, Pires LM, Lima GG; Critical revision of the manuscript for intellectual content: Sant'Anna RT, Kruse ML, Pires LM, Lima GG.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Cardiologia / Fundação Universitária de Cardiologia under the protocol number UP 5252/16. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Correlation between Very Short and Short-Term Blood Pressure Variability in Diabetic-Hypertensive and Healthy Subjects

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Abstract

Background: Blood pressure (BP) variability can be evaluated by 24-hour ambulatory BP monitoring (24h-ABPM), but its concordance with results from finger BP measurement (FBPM) has not been established yet.

Objective: The aim of this study was to compare parameters of short-term (24h-ABPM) with very short-term BP variability (FBPM) in healthy (C) and diabetic-hypertensive (DH) subjects.

Methods: Cross-sectional study with 51 DH subjects and 12 C subjects who underwent 24h-ABPM [extracting time-rate, standard deviation (SD), coefficient of variation (CV)] and short-term beat-to-beat recording at rest and after standing-up maneuvers [FBPM, extracting BP and heart rate (HR) variability parameters in the frequency domain, autoregressive spectral analysis]. Spearman correlation coefficient was used to correlate BP and HR variability parameters obtained from both FBPM and 24h-ABPM (divided into daytime, nighttime, and total). Statistical significance was set at $p < 0.05$.

Results: There was a circadian variation of BP levels in C and DH groups; systolic BP and time-rate were higher in DH subjects in all periods evaluated. In C subjects, high positive correlations were shown between time-rate index (24h-ABPM) and LF component of short-term variability (FBPM, total, $R = 0.591$, $p = 0.043$); standard deviation (24h-ABPM) with LF component BPV (FBPM, total, $R = 0.608$, $p = 0.036$), coefficient of variation (24h-ABPM) with total BPV (FBPM, daytime, -0.585, $p = 0.046$) and alpha index (FBPM, daytime, -0.592, $p = 0.043$), time rate (24h-ABPM) and delta LF/HF (FBPM, total, $R = 0.636$, $p = 0.026$; daytime $R = 0,857$, $p < 0.001$). Records obtained from DH showed weak positive correlations.

Conclusions: Indices obtained from 24h-ABPM (total, daytime) reflect BP and HR variability evaluated by FBPM in healthy individuals. This does not apply for DH subjects. (Arq Bras Cardiol. 2018; 110(2):157-165)

Keywords: Hypertension; Diabetes Mellitus, Type 2; Autonomic Nervous System; Blood Pressure Monitoring, Ambulatory.

Introduction

Blood pressure (BP) variability results from the interplay between external environmental stimuli, vascular system, and biological autonomic regulation of circulation.[1] Abnormalities in BP variability, evaluated by continuous intra-arterial ambulatory BP monitoring, are associated with poor outcomes in normotensive and hypertensive subjects.[2-4] Noninvasive methods such as finger BP measurement (FBPM) are good alternatives to invasive BP monitoring, as they are accurate non-invasive estimates of beat-to-beat radial BP, providing data that can estimate very short-term BP variability.[5,6] In addition, beat-to-beat records allow the extraction of information regarding heart rate (HR) variability that is directly related to cardiac autonomic control impairment[7,8] and associated with poor outcomes in both general[9] and diabetic populations.[10] However, due to practical and economic reasons, this method cannot be routinely used in the evaluation of outpatients.

The development of noninvasive 24-hour ambulatory BP monitoring (24h-ABPM), with multiple readings throughout day and night, has made short-term BP variability estimate through several indices possible.[11] However, there are major differences between BP variability obtained from beat-to-beat records and that obtained by 24h-ABPM. Besides the duration of the series—very short- (FBPM) or short-term (24h-ABPM)—, BP series obtained by FBPM allows studying beat-to-beat variability, while 24h-ABPM series are sampled every 10-15 minutes within 24 hours.[6] While non-invasive beat-to-beat methods allow detecting fast oscillations resulting from inter-beat variations, it is inefficient to access very slow waves in short series; 24h-ABPM, in turn, detects slow variations only.[12,13] As both methods provide information about BP signals originating from the same cardiovascular system, a correlation between oscillatory components of overlapping bands obtained from FBPM and 24h-ABPM is expected;

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however, studies on the association between BP variability evaluated by 24h-ABPM indices and target organ damage have shown contradictory results.[4,14]

Our report was aimed to compare three different parameters of short-term BP variability in 24h-ABPM, with very short-term BP variability measured by indices obtained from the FBPM in healthy subjects and in a population at high cardiovascular risk comprised of diabetic hypertensive subjects.

Methods

Study design and population

This cross-sectional study was conducted at the outpatient clinic of the Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil), a tertiary teaching hospital, and Instituto de Cardiologia do Rio Grande do Sul, Fundação Universitária de Cardiologia, from January 2009 to December 2012. The study was approved by the Ethics Committee of both Institutions (nº 0469.0.001.000-08 and 4313/09, respectively), which is accredited by the Office of Human Research Protections as an Institutional Review Board, in agreement with the principles outlined in the Declaration of Helsinki. After protocol approval, all subjects signed a written informed consent for participation. Adult patients of both genders, aged 18-65 years, and with hypertension and type 2 diabetes mellitus were invited to participate (DH group). Control group (C) consisted of healthy subjects, that is, without diagnosis or medication for hypertension and diabetes.

Clinical evaluation

Patients underwent demographic and clinical baseline data collection. Diabetes mellitus was defined by two fasting plasma glucose ≥ 126 mg/dl or use of antidiabetic agents or personal history of diabetes. Blood pressure was measured with an office aneroid sphygmomanometer and the mean values were estimated after an two measures on average. The cuff size was selected according to arm circumference. Hypertension was defined by mean blood pressure ≥ 140/90 mmHg or use of antihypertensive medication. After baseline data collection, subjects were randomly assigned to evaluations, being first submitted to 24h-ABPM or to FBPM. The interval between the two examinations was of no more than 15 days.

Short-term blood pressure variability evaluation (24h-ABPM)

All individuals were submitted to a 24h-ABPM in a usual working day, using a monitor (Spacelabs 90207, Spacelabs, Redmond, WA). Measurements were obtained every 15 minutes from 7 a.m. to 11 p.m., and every 20 minutes from 11 p.m. to 7 a.m. to complete 24 hours of the period studied. Cuff size was selected according to subjects' arm circumference.[14]

Based on the results of 24h-ABPM, the mean 24-hour systolic (SBP) and diastolic (DBP) blood pressures were calculated for each patient. Three different parameters of SBP variability were calculated: 1) time-rate index (rate of change in SBP over time in mmHg/min, defined as the first derivative values of SBP by time); 2) coefficient of variation of systolic BP within 24 hours (SD/mean pressure x 100%); and 3) mean of standard deviation of 24-hour systolic BP. The time-rate index allows the calculation of angular coefficients' sum and aims to measure how fast or slow and in which direction SBP values change. The measure was calculated using the following formula, where r is the rate of BP variability over time (considering the differences between BP measurements at each time interval) and N is the number of recordings:[15]

$$R = |\bar{r}| = \frac{\sum_{i=1}^{N-1} |ri|}{N-1}$$

In addition, considering circadian variations of BP and possible differences between daytime and nighttime 24h-ABPM parameters, data were divided into daytime and nighttime according to patients' reports and were also analyzed separately, considering both periods. Circadian behavior differences were calculated by subtracting nighttime from daytime values for each parameter.

Very short-term blood pressure variability evaluation (FBPM)

Blood pressure was recorded continuously, on a beat-to-beat basis, using the FINAPRES system (Ohmeda 2300, Monitoring Systems, Englewood, CO, USA).[16] In this method, the pressure wave can be continuously monitored by a sensor placed on the patient's non-dominant middle finger, detecting small oscillations only. The experimental protocol had measurements at two different stages: ten minutes at rest in a sitting position and ten minutes after standing-up maneuver (sympathetic activation).

The BP signal was digitized by the CODAS system (Computer Operated Data Acquisition Software; DATAQ, Instruments, AKRON, OH, USA), sampling at 1 kHz and analyzed for each condition. Pulse interval (PI) tachogram and systolic arterial (SA) systogram series were constructed through the algorithm of Windaq/DATAQ, which identifies systolic peaks from BP waves. Systogram and tachogram series were analyzed by spectral analysis (frequency domain analysis) using an autoregressive model, applied to stationary intervals, which were selected in each segment condition. The stationarity of each time series was tested as previously reported.[17] Short-term BP and HR variabilities were evaluated based on systogram and tachogram analyses, respectively.

In humans, the frequency domain analysis considers three distinct bands: high frequency (HF), which includes the interval between 0.15 and 0.4 Hz; low frequency (LF) between 0.04 and 0.15 Hz; and very low frequency (VLF), lower than 0.04 Hz.[18,19] The same analysis was applied to tachogram series. Among parameters obtained by frequency domain analysis, LF and HF components are distinguished by physiological significance. They are mainly related to sympathetic and parasympathetic cardiac modulations, respectively; the relation between them—LF/HF index—is related to sympathetic-vagal balance;[20] and the absolute powers of LF and VLF components are predominantly related to vascular sympathetic modulation and to renin-angiotensin system modulation on SBP, respectively.[1] The alpha index was obtained from the square root of the ratio between the LF component of tachogram and systogram when coherence, assessed by cross-spectral analysis, exceeded 0.5 in these

bands[21] and expressed spontaneous baroreflex sensitivity. All series were analyzed by a trained researcher who was also blinded to conditions and subjects.

Delta indices were calculated for HR variability (HRV), LF/HF index and LF component of BPV, using variable values before (rest) and after standing-up maneuver (sympathetic activation, SA) for normalization, as follows:

$$\text{Delta} = \frac{\text{SA} - \text{REST}}{\text{REST}}$$

These indices had been previously proposed in order to quantify autonomic responses to standing-up maneuver.[22,23]

Biochemical measurements

Venous blood samples for biochemical measurements were drawn after 12-hour fasting. Plasma glucose was determined by the glucose oxidase method, serum creatinine by Jaffé's reaction, and glycated hemoglobin (HbA1c) by ion-exchange HPLC (Merck-Hitachi L-9100 HbA_{1c} analyzer; Merck, Darmstadt, Germany). Serum cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Darmstadt, Germany; Boehringer Mannheim, Buenos Aires, Argentina), and HDL cholesterol by a homogeneous direct method (autoanalyzer, ADVIA 1650). Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula.[24]

Statistical analyses

Data are expressed as mean ± standard deviation (SD) or medians and interquartile intervals, according to normality plots with tests and percentages. Pearson's chi-square, unpaired Student's t-test, Mann-Whitney rank sum test, two-way repeated measures ANOVA or Friedman repeated measures analysis of variance on rank, *post hoc* Student-Newman-Keuls were used when variables were compared between groups, as indicated. The correlation between the different indices obtained by 24h-ABPM and by FBPM were analyzed by the Spearman's correlation coefficient. Correlations were considered for discussion only if they were statistically significant and represented large-effect sizes, as defined by a correlation coefficient of 0.50 or higher.[25] All statistical analyses were performed using the SPSS statistical software package version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

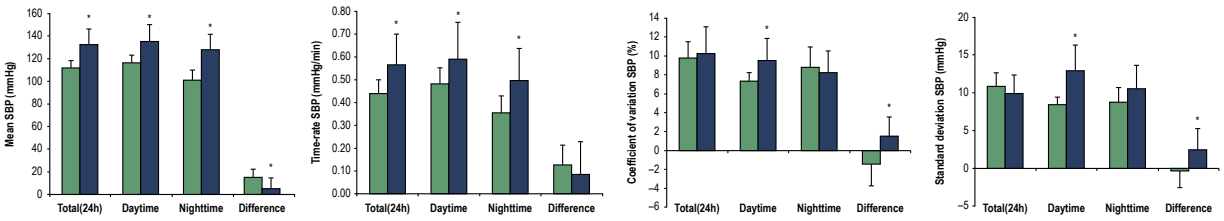
Twelve healthy subjects (C) and 73 diabetic-hypertensive patients (DH) were selected; all C and 51 DH had complete data from 24h-ABPM and FBPM. Controls were 51.7 ± 8.1 years old and 50% were men; DH were 57.3 ± 8.1 years-old, 12% were men, 54.9% had their office BP well-controlled (< 130/80 mmHg) and 35.8% had good metabolic control (HbA1c < 7.0%). Clinical characteristics are shown in Table 1.

Short-term BP variability (24h-ABPM) results are displayed in Figure 1. There were differences among the indices obtained from total, daytime, and nighttime periods for both C and DH groups, confirming the expected circadian variations and justifying the division into periods. Comparisons between C and DH groups are represented by the bar graph, which shows that higher SBP and time-rate obtained from SBP in DH group for all periods evaluated. The mean of the standard deviation and the coefficient of variation of 24-hour SBP were different between C and DH in daytime only. Circadian behavior differences, calculated by subtracting nighttime from daytime values, show a lower reduction of mean SBP at night in DH patients as compared to controls. The differences obtained for

Table 1 – Clinical characteristics of controls (C) and diabetic-hypertensive (DH) subjects.

Variables	Controls (n = 12)	Diabetic-hypertensive (n = 51)	p
Age (years)	51.6 ± 4.4	57.3 ± 8.1	0.011
Male gender	6 (50.0)	11 (20.8)	0.065
BMI (Kg/m^2)	23.5 ± 2.3	30.5 ± 4.2	< 0.001
Office SBP (mmHg)	116.0 ± 8.2	139.2 ± 17.2	< 0.001
Office DBP (mmHg)	77.0 ± 5.0	80.9 ± 11.9	0.086
Duration of diabetes (years)	-	6.9 (3.0-10.0)	
Fasting plasma glucose (mg/dL)	-	156.5 ± 55.1	
HbA1c (%)	-	8.2 ± 2.0	
Total cholesterol (mg/dl)	-	181. 2 ± 32.6	
HDL cholesterol (mg/dl)	-	42.6 ± 13.2	
Triglycerides (mg/dl)	-	180.5 (132.8 – 248.5)	
Creatinine (mg/dl)	-	0.82 ± 0.2	
Microalbuminuria (> 17 µg/min)	-	14 (27.4)	

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein; FBPM: Short-Term Blood Pressure. Continuous variables are expressed as mean ± standard deviation or median and interquartile range (p25-p75) and percentiles. Categorical variables are expressed as number (%). Comparisons were tested by Pearson's χ2 test and Student's t test.



Variable	C			DH		
	Total (24h)	Daytime	Nighttime	Total (24h)	Daytime	Nighttime
Mean SBP (mmHg)	111.8 ± 6.6	116.2 ± 6.8†	101.2 ± 8.4†#	132.4 ± 13.8	135.2 ± 15.2†	128.2 ± 13.7†#
Time-rate, SBP (mmHg/min)	0.44 ± 0.06	0.48 ± 0.07†	0.36 ± 0.08†#	0.56 ± 0.13	0.59 ± 0.16	0.50 ± 0.14†#
Coefficient of variation, SBP (%)	9.8 ± 1.7	7.3 ± 0.9†	8.8 ± 2.1#	10.3 ± 2.8	9.5 ± 2.3†	8.3 ± 2.3†#
Standard deviation of mean SBP (mmHg)	10.9 ± 1.8	8.4 ± 1.0†	8.8 ± 1.9†	10.0 ± 2.4	12.9 ± 3.4†	10.6 ± 2.3†#

Figure 1 – *Short-term BP variability (24h-ABPM). Data are shown as mean ± SD. SBP, systolic blood pressure. Analysis using 24-hour records (total) and divided into daytime and nighttime periods. Graph shows a comparison between controls (C, green bars) and diabetic-hypertensive (DH, blue bars) groups, also including circadian behaviour differences, calculated by subtracting nighttime from daytime values (Difference, last bars of each graphic). * p < 0.05 vs. C, Student's t-test. Table reports all values, compared by Friedman repeated measures analysis of variance on rank, post hoc Student-Newman-Keuls. † p < 0.05 vs. total period; # p < 0.05 vs. daytime period.*

Table 2 – Very short-term blood pressure variability and heart rate variability (FBPM) at rest and after standing-up maneuver.

Variable	C (n = 12)		DH (n = 51)		P		
	At rest	Standing up	At rest	Standing up	Group	Condition	Interaction
Mean BP (mmHg)	114.6 ± 23.6	112.6 ± 18.2	129.4 ± 17.7	123.8 ± 21.6	0.019	0.494	0.147
Very short-term BPV ($mmHg^2$)	21.57 ± 12.20	37.17 ± 16.12*	25.27 ± 20.08	25.23 ± 23.04	0.504	0.058	0.047
LF component of BPV ($mmHg^2$)	1.80 ± 1.13	13.84 ± 11.93	4.59 ± 6.02	9.26 ± 10.61	0.879	< 0.001	0.060
HF component of BPV ($mmHg^2$)	1.40 ± 1.57	3.73 ± 3.02*	3.44 ± 3.46#	2.25 ± 1.64*	0.538	0.323	< 0.001
Mean HR (bpm)	66.2 ± 9.3	77.8 ± 8.7*	70.8 ± 11.9	77.2 ± 13.9*	0.419	< 0.001	0.016
HRV (s^2)	1.47 ± 1.71	1.07 ± 0.78	0.73 ± 0.79	0.45 ± 0.42	0.005	0.010	0.658
LF component of HRV (nu)	40.77 ± 16.84	61.48 ± 16.90	31.08 ± 21.07#	40.69 ± 23.62	0.014	< 0.001	0.339
HF component of HRV (nu)	50.65 ± 14.79	30.07 ± 15.33	49.91 ± 22.35	36.19 ± 20.48	0.842	< 0.001	0.464
LF/HF index	0.99 ± 0.76	3.33 ± 3.16	1.09 ± 1.54	2.69 ± 4.13	0.902	0.001	0.744
Alpha index (ms/mmHg)	15.04 ± 9.75	6.43 ± 5.24*	8.24 ± 7.70#	4.72 ± 3.89*	< 0.001	< 0.001	0.003

*Data are shown as mean ± SD. HR: heart rate, HRV: heart rate variability, BP: blood pressure, BPV: BP variability, LF: low frequency component, HF: high frequency component. *p < 0.05 vs. rest condition; #p < 0.05 vs. C; FBPM: Short-Term Blood Pressure. Two-way repeated measures ANOVA. Post hoc Student-Newman-Keuls.*

the coefficient of variation and mean of standard deviation of 24-hour systolic BP were positive in DH, negative in C, and different between groups.

Very short-term BP variability and HR variability (FBPM) results obtained by spectral analysis are displayed in Table 2. As expected, BP was higher in DH *vs.* C at rest and after standing-up maneuver. Heart rate variability, LF component of HRV, and alpha index were lower in DH *vs.* C. The standing-up maneuver, applied to induce sympathetic activation, resulted in differences for all HR variability components, showing the expected response to this maneuver in both groups. However, BP variability did not change after the maneuver in DH subjects, and the alpha index (spontaneous baroreflex sensitivity) was lower at rest and after the maneuver in this group when compared to controls.

Autonomic response to standing-up maneuver assessed by delta indices (Figure 2) had a lower response for LF/HF ratio in DH group as compared to C group. Changes in delta HRV and delta_LF/HF variability (BPV) were not different.

Correlations between very short- and short-term BP variabilities are shown in Tables 3 (C group) and 4 (DH group). In C group, some correlations were found at rest, and some after the standing-up maneuver. At rest, standard deviation of 24-hour systolic BP (24h-ABPM) was positively correlated with the LF component of BP variability (FBPM) in 24-hour evaluation; the coefficient of variation (24h-ABPM) was negatively correlated with total BP variability and alpha index (FBPM) during daytime. After standing-up maneuver, time-rate (24h-ABPM) was positively correlated with the LF component of BP variability (FBPM, 24 hours, and daytime).

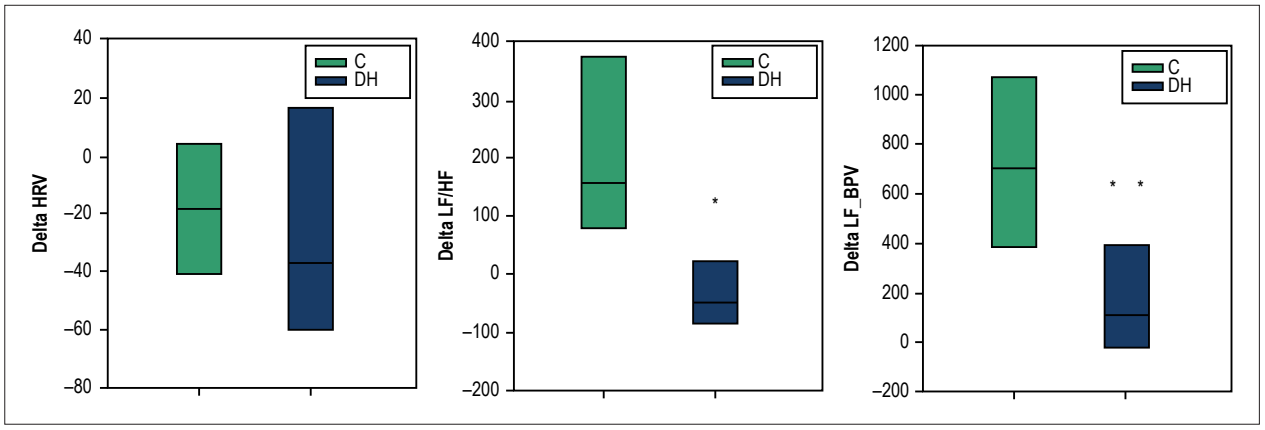


Figure 2 – *Autonomic response to standing-up maneuver as evaluated by delta indices: delta HRV (heart rate variability), delta LF/HF (low frequency/high frequency) and delta of LF of blood pressure variability (LF_BPV), calculated from HR variability, LF/HF index and LF component of BPV, respectively. Box plots (median, 25 and 75% interquartile intervals) showing comparison between controls (C, blue bars) and diabetic-hypertensive (DH, green bars) groups. * p < 0.001 and ** p = 0.009 vs. C, Mann-Whitney rank sum test.*

Table 3 – Correlation between very short- (FBPM) and short-term (24h-ABPM) BP variability parameters – Control group.

	24-hour			Daytime			Nighttime		
	Time-rate	Coefficient of variation	Standard deviation	Time-rate	Coefficient of variation	Standard deviation	Time-rate	Coefficient of variation	Standard deviation
AT REST									
Total BPV R	0.236	-0.042	-0.007	-0.247	-0.585	-0.315	0.555	0.210	0.301
(P)	0.461	0.897	0.983	0.439	0.046	0.319	0.061	0.513	0.341
LF component BPV R	0.373	0.538	0.608	0.370	0.445	0.559	0.021	0.343	0.438
(P)	0.233	0.071	0.036	0.236	0.147	0.059	0.948	0.276	0.155
Alpha index R	-0.127	-0.357	-0.322	-0.483	-0.592	-0.524	0.290	-0.056	0.063
(P)	0.695	0.255	0.308	0.111	0.043	0.080	0.361	0.863	0.846
AFTER SYMPATHETIC ACTIVATION (Standing-up maneuver)									
Total BPV R	0.418	0.350	0.427	0.138	-0.172	0.084	0.180	0.392	0.424
(P)	0.176	0.265	0.167	0.670	0.594	0.795	0.575	0.208	0.170
LF component BPV R	0.591	0.322	0.385	0.649	0.329	0.413	-0.074	0.315	0.263
(P)	0.043	0.308	0.217	0.022	0.296	0.183	0.819	0.319	0.409
Alpha index R	-0.116	-0.392	-0.322	-0.346	-0.312	-0.322	0.191	-0.503	-0.270
(P)	0.720	0.208	0.308	0.271	0.324	0.308	0.552	0.095	0.397
DELTA INDEXES (AT REST/ AFTER SYMPATHETIC ACTIVATION)									
Delta_HRV R	-0.056	-0.070	-0.105	0.353	0.081	-0.042	-0.541	-0.168	-0.340
(P)	0.862	0.829	0.746	0.261	0.803	0.897	0.070	0.602	0.280
Delta_LF/HF R	0.636	0.000	0.217	0.857	0.385	0.392	-0.233	-0.126	0.088
(P)	0.026	1.000	0.499	0.000	0.216	0.208	0.466	0.697	0.787
Delta LF_BPV R	0.299	-0.091	-0.077	0.282	0.011	-0.035	-0.170	-0.035	-0.217
(P)	0.346	0.779	0.812	0.374	0.974	0.914	0.598	0.914	0.498

BPV: blood pressure variability, LF: low frequency, LF_BPV: LF component of BPV; FBPM: Short-Term Blood Pressure. Statistic correlation expressed as correlation coefficient (R) and significance (P), obtained by Spearman's test.

Table 4 – Correlation between very short- (FBPM) and short-term (24h-ABPM) BP variability parameters – DH group.

	24-hour			Daytime			Nighttime		
	Time-rate	Coefficient of variation	Standard deviation	Time-rate	Coefficient of variation	Standard deviation	Time-rate	Coefficient of variation	Standard deviation
AT REST									
Total BPV R	0.03	0.280	0.240	0.210	0.261	0.286	-0.036	0.026	0.103
(P)	0.486	0.046	0.090	0.152	0.064	0.042	0.807	0.857	0.471
LF component BPV R	0.330	0.356	0.347	0.332	0.185	0.259	0.234	0.278	0.337
(P)	0.022	0.010	0.013	0.021	0.194	0.066	0.110	0.048	0.016
Alpha index R	-0.371	-0.250	-0.264	-0.420	-0.171	-0.222	-0.158	-0.151	-0.220
(P)	0.009	0.076	0.062	0.003	0.229	0.117	0.283	0.289	0.122
AFTER SYMPATHETIC ACTIVATION (Standing-up maneuver)									
Total BPV R	0.192	0.403	0.413	0.269	0.447	0.486	0.033	0.029	0.176
(P)	0.191	0.003	0.003	0.065	0.001	0.000	0.826	0.841	0.218
LF component BPV R	0.140	0.274	0.283	0.156	0.166	0.245	0.042	0.090	0.134
(P)	0.341	0.052	0.044	0.290	0.244	0.083	0.777	0.532	0.349
Alpha index R	-0.359	-0.206	-0.263	-0.405	-0.098	-0.192	-0.172	-0.306	-0.336
(P)	0.012	0.146	0.063	0.004	0.493	0.177	0.243	0.029	0.016
DELTA INDEXES (AT REST/AFTER SYMPATHETIC ACTIVATION)									
Delta_HRV R	0.054	0.018	-0.011	-0.003	-0.045	-0.058	0.055	0.106	0.059
(P)	0.714	0.901	0.938	0.985	0.754	0.688	0.711	0.460	0.679
Delta_LF/HF R	-0.015	-0.152	-0.099	-0.037	-0.215	-0.190	0.088	0.097	0.083
(P)	0.922	0.291	0.492	0.807	0.134	0.186	0.557	0.501	0.568
Delta LF_BPV R	-0.162	-0.105	-0.077	-0.210	-0.093	-0.070	-0.069	-0.070	-0.097
(P)	0.271	0.464	0.590	0.152	0.515	0.623	0.643	0.623	0.500

BPV: blood pressure variability, LF: low frequency, LF_BPV: LF component of BPV; DH: Diabetic-Hypertensive. Statistic correlation expressed as correlation coefficient (R) and significance (P), obtained by Spearman's test

Time-rate (24h-ABPM) was correlated with delta_LF/HF (FBPM, 24 hours, and daytime). In DH group, although some correlations were statistically significant, none of them represented large-effect sizes (correlation coefficient of 0.50 or higher). Moderate-effect sizes (correlation coefficient near 0.50) were shown for total BP variability (24h-ABPM), coefficient of variation, and standard deviation (FBPM, 24 hours, and daytime). There was no correlation between short-term (24h-ABPM) and very short-term variability (FBPM) parameters, considering delta indices for DH subjects.

Discussion

BP and HR variabilities were assessed in healthy and diabetic-hypertensive individuals by two well-known methods—24h-ABPM and FBPM—, seeking potential concordance between results of each method, which was indeed observed. Correlations between indices of BP variability (time rate with LF component BPV, standard deviation with LF component BPV, and coefficient of variation with total BPV and alpha index) and indices of HR variability (time rate with delta_LF/HF) were high and significant in controls. On the other hand, few moderate correlations were observed in diabetic-hypertensive patients only after sympathetic activation.

As expected, there were differences between 24h-ABPM indices obtained in total, daytime, and nighttime periods because of the well-known circadian variations of BP levels[26,27] which occurred in both healthy and diabetic-hypertensive subjects. This leads us to conclude that data were adequately collected. Moreover, periods division showed differences between groups only when data collection included the day period, in accordance with previous reports.[28,29]

Additionally, indices obtained from FBPM had lower HRV, LF component of HRV, and alpha index (at rest and after standing-up maneuver) in DH *vs.* C group. This finding suggests the presence of autonomic neuropathy in the diabetic population, as expected and previously demonstrated by evaluating similar indices.[30,31]

In controls, correlations between very short- and short-term BP variability were present with FBPM data at rest and after the standing-up maneuver, but only when daytime data were included. This probably occurs because both methods are evaluating BP signals in similar situations, as 24h-ABPM provides data obtained mostly during routine activities in standing-up position (mean duration of nighttime period ~6.9h). The most significant correlations were those between time-rate index (24h-ABPM) and LF component of BP variability and delta_LF/HF (FBPM); also between the coefficient of variation (24h-ABPM) and between total BPV and the alpha index in all periods that included daytime data. The time-rate index obtained by 24h-ABPM (24-hour or daytime period) in healthy individuals is expected to reflect what the reference standard (FBPM) would show, considering LF component of BP variability and delta_LF/HF.

The weak correlations observed between 24h-ABPM and FBPM indices in the diabetic-hypertensive group depict a very different pattern, which is certainly related to their disease. Moreover, there was no correlation between short-term variability parameters and delta indices. These correlations are weak even though four times more patients were evaluated, which would show significant correlations if they in fact existed. We cannot exclude that one or both methods employed may provide false results for this specific population once FBPM, for example, depends on attaining good BP signals, and quality of such information was not good because of vascular disorders common to this population.[32] Therefore, we do not recommend 24h-ABPM to estimate very short-term BP variability parameters based on short-term variability indices for diabetic-hypertensive individuals.

Currently, the evaluation of BP variability across the several indices that can be obtained from 24h-ABPM or home blood pressure monitoring is not recommended by guidelines,[14,33] for predicting cardiovascular risk, or as additional goal for antihypertensive therapy, because literature has no consensus on these issues.[4,14,34,35] It is possible that evidence available is not strong enough to support this use because the tools used are not so reliable. We suggest that equations derived from the 24h-ABPM measurement for non-diabetic subjects would be useful for risk prediction, but not for diabetic-hypertensive patients. It is unknown, though, whether this pattern occurs in hypertensive-only populations. The use of BP variability reduction as a new target to explore in further intervention trials related to hypertension should only be considered after this information is validated.

Considering the high prevalence of autonomic neuropathy in diabetes,[36,37] and characteristic changes of this complication detected in the diabetic-hypertensive group (circadian behavior differences, lower spontaneous baroreflex sensitivity, HR variability and lower responses to stand-up in the LF/HF ratio vs. controls), we attributed to this complication some of the differences observed in other indices between groups. The standing-up maneuver is usually applied to induce sympathetic activation in very short-term BP variability evaluation, and in fact it induced the expected cardiac autonomic response for many indices in controls, but not for most of them in diabetic-hypertensive individuals.

Taking clinical characteristics of diabetic-hypertensive subjects into account and bearing in mind that the sample studied was obtained from a tertiary center, many patients were not adequately monitored (BP and metabolic control), indicating a high-risk group. Perhaps in this high-risk population, variability found in 24h-ABPM or other home BP evaluation methods may not successfully qualify higher cardiovascular risk beyond absolute systolic or diastolic BP, as previously described.[34,38] Also, the age differences found could, at least partially, overestimate the differences between groups, and therefore configure a limitation of this study.

Conclusions

In summary, short-term BP variability measured by time-rate index, standard deviation or coefficient of variation in 24h-ABPM are correlated with LF component BPV and delta_LF/HF obtained from FBPM in nondiabetic individuals. Such findings should be evaluated in further cohort studies adequately designed for this purpose, also seeking relations with hard outcomes. This correlation was not well established in diabetic-hypertensive subjects. Some indices obtained from FBPM for diabetic subjects are promising tools for the diagnosis of diabetic autonomic neuropathy. Considering a standard reference for the diagnosis of autonomic neuropathy, these indices and cutoff values should be evaluated in further studies adequately designed for this purpose.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Casali KR, Schaan B, Montano N, Massierer D, Neto FMF, Teló G, Ledur PS, Reinheimer M, Sbruzzi G, Gus M; Acquisition of data: Casali KR, Schaan B, Montano N, Massierer D, Teló G, Ledur PS, Reinheimer M, Sbruzzi G, Gus M; Statistical analysis: Casali KR, Teló G, Gus M; Obtaining financing: Schaan B, Gus M; Writing of the manuscript: Casali KR; Critical revision of the manuscript for intellectual content: Schaan B, Montano N, Massierer D, Neto FMF, Teló G, Ledur PS, Reinheimer M, Sbruzzi G, Gus M.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (RS) and Instituto de Cardiologia do Rio Grande do Sul / Fundação Universitária de Cardiologia under the protocol number 0469.0.001.000-08 and 4313/09. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Autonomic and Vascular Control in Prehypertensive Subjects with a Family History of Arterial Hypertension

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Abstract

Background: Individuals with a family history of systemic arterial hypertension (FHSAH) and / or prehypertension have a higher risk of developing this pathology.

Objective: To evaluate the autonomic and vascular functions of prehypertensive patients with FHSAH.

Methods: Twenty-five young volunteers with FHSAH, 14 normotensive and 11 prehypertensive subjects were submitted to vascular function evaluation by forearm vascular conductance(VC) during resting and reactive hyperemia (Hokanson®) and cardiac and peripheral autonomic modulation, quantified, respectively, by spectral analysis of heart rate (ECG) and systolic blood pressure (SBP) (FinometerPRO®). The transfer function analysis was used to measure the gain and response time of baroreflex. The statistical significance adopted was $p \leq 0.05$.

Results: Pre-hypertensive individuals, in relation to normotensive individuals, have higher VC both at rest (3.48 ± 1.26 vs. 2.67 ± 0.72 units, $p = 0.05$) and peak reactive hyperemia (25, 02 ± 8.18 vs. 18.66 ± 6.07 units, $p = 0.04$). The indices of cardiac autonomic modulation were similar between the groups. However, in the peripheral autonomic modulation, greater variability was observed in prehypertensive patients compared to normotensive individuals (9.4 [4.9-12.7] vs. 18.3 [14.8-26.7] $mmHg^2$; $p < 0.01$) and higher spectral components of very low (6.9 [2.0-11.1] vs. 13.5 [10.7-22.4] $mmHg^2$, $p = 0.01$) and low frequencies (1.7 [1.0-3.0] vs. 3.0 [2.0-4.0] $mmHg^2$, $p = 0.04$) of SBP. Additionally, we observed a lower gain of baroreflex control in prehypertensive patients compared to normotensive patients (12.16 ± 4.18 vs. 18.23 ± 7.11 ms/mmHg, $p = 0.03$), but similar delay time (-1.55 ± 0.66 vs. -1.58 ± 0.72 s, $p = 0.90$).

Conclusion: Prehypertensive patients with FHSAH have autonomic dysfunction and increased vascular conductance when compared to normotensive patients with the same risk factor. (Arq Bras Cardiol. 2018; 110(2):166-174)

Keywords: Hypertension / genetic; Autonomic Nervous System; Risk Factors; Endothelium, Vascular / physiopathology.

Introduction

Primary prevention has been recommended for individuals at increased risk for developing systemic arterial hypertension (SAH). Among them, individuals with a family history of SAH (FHSAH)[1,2] and / or prehypertension[3] stand out.

The reason for the increased susceptibility of hypertensive offspring to developing hypertension is not completely elucidated. However, studies indicate that autonomic abnormalities, such as increased sympathetic modulation,[4] reduction of heart rate variability[4] and reduction of baroreflex sensitivity[5] are among the changes that may contribute to the onset of hypertension in normotensive children of hypertensive individuals. In addition, vascular abnormalities have also been considered as potential candidates for the onset of hypertension in this population.[6,7]

In prehypertensive patients, similar to those with FHSAH, dysfunctions[8,9] and autonomic and vascular[10] have also been pointed out as the main etiological factors of pressure elevation.

Although prehypertension has a strong genetic predisposition,[11,12] the pathophysiological mechanisms responsible for pressure elevation in individuals with both risk factors, namely prehypertension and FHSAH, are not yet known. Therefore, this study aimed to evaluate the autonomic and vascular functions of prehypertensive individuals with FHSAH.

Methods

Sample

From the sample calculation performed based on the difference in sympathetic cardiac modulation of 0.31 ms^2 between the means of the normotensive and prehypertensive

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groups,[13] standard deviation of 0.21 ms², alpha errors of 5% and beta of 20%, 7 individuals in each group would be needed. The sample consisted of 25 volunteers, subdivided according to blood pressure levels in the normotensive groups (SBP < 121 mmHg and / or DBP < 80 mmHg; n = 14) and prehypertensive (SBP between 121 and 139 mmHg and/or DBP between 80 and 89 mmHg, n = 11).[14] All volunteers had FHSAH defined as father, mother, or both with a diagnosis of SAH, which was evaluated by means of a questionnaire.

Inclusion criteria adopted were age between 18 and 40 years, SBP lower than 140 mmHg, DBP lower than 90 mmHg and not involved in systematized physical exercises for at least six months prior to the research. In addition, only volunteers who had blood test results within 30 days prior to the start of the study in their medical records were included. Individuals with cardiometabolic diseases, smoking or drug treatment that could interfere with the cardiovascular system were not included.

This study was approved in the Committee of Ethics in Human Research of the HU / UFJF under the opinion nº 720/370. All volunteers signed the Free and Informed Consent Form.

Measures and procedures

Anthropometry

For body mass and height measurements, we used, respectively, a scale with a precision of 0.1 kg and a stadiometer with a precision of 0.5 cm coupled to it (Líder®). The body mass index was calculated by dividing the body mass by the squared height (kg / m²).[15] Waist circumference was measured using an inextensible metric tape (Cescorf®), with an accuracy of 0.1 cm. All of these variables were measured according to the criteria established by the American College of Sports Medicine.[16]

Blood pressure, heart rate and respiratory rate

With the volunteer at rest and in supine position, blood pressure (BP), heart rate and respiratory rate were monitored simultaneously for 15 minutes. Beat-to-beat BP was monitored by digital infrared photoplethysmography (FinometerPRO®) on the volunteer's dominant arm. Cardiac and respiratory rates were recorded continuously (Biopac®) using electrocardiogram in lead II and thoracic piezoelectric tape, respectively.

All acquired signals were reconstructed, digitized and recorded in a microcomputer with a sampling frequency of 1 kHz and 16-bit resolution for further analysis.

Forearm muscle blood flow and vascular conductance during rest and reactive hyperemia

Forearm muscle blood flow was evaluated using venous occlusion plethysmography (Hokanson® Plethysmograph). The volunteer was placed in dorsal decubitus position and the non-dominant forearm was raised above the level of the heart to ensure adequate venous drainage.

A silicon tube filled with mercury, connected to the low-pressure transducer and the plethysmograph, was placed around the volunteer's forearm, five centimeters away from the humeral-radial joint. One cuff was placed around the wrist and another at the top of the volunteer's arm. The wrist cuff was inflated at supra-systolic pressure level (200 mmHg) one minute before the measurements started and was kept inflated throughout the procedure. At 15-second intervals, the cuff placed on the arm was inflated at supra venous pressure (60 mmHg) for seven to eight seconds, then was deflated rapidly and maintained for the same period. This procedure totaled four cycles per minute.

The increase in tension in the silicone tube reflected the increase in forearm volume and, consequently, in an indirect way, increased forearm muscle blood flow, reported in ml/min/100 ml. The signal of the forearm muscle blood flow wave was acquired in real time in a computer through the *Non Invasive Vascular Program 3*.

The evaluation of peripheral vascular conductance was performed by dividing the peripheral vascular blood flow by the mean BP (mmHg), multiplied by 100 and expressed in "units".[17]

After measuring the forearm blood flow at rest for three minutes, the occlusion cuff positioned on the arm was inflated to 200 mmHg for five minutes. One minute before its deflation, the cuff placed on the wrist was also inflated to 200 mmHg remaining thus until the measurement was completed. After five minutes of occlusion, the arm cuff was rapidly deflated to induce reactive hyperemia and blood flow was recorded for the next three minutes, maintaining the cycle protocol, inflating to 60 mmHg for 10 seconds followed by 10 seconds of deflation.[18] It was considered peak flow, the value of the first wave flow after the onset of reactive hyperemia.

During the evaluation of the blood flow of the forearm at rest and the protocol of reactive hyperemia, BP was measured beat-to-beat (FinometerPRO®). Additionally, during the rest period, cardiac output, left ventricular contractility (dP/dT maximum) and total peripheral resistance were also measured by the same equipment. In order to calculate the cardiac index, the cardiac output was corrected by the body surface area.[19]

Cardiac and peripheral autonomic modulation

The variabilities of the iRR, SBP and respiratory activity were evaluated in the frequency domain by autorregressive spectral analysis.

In stationary segments of 250 to 300 points, the time series of the iRR, respiration and SBP were decomposed into their frequency components by the autoregressive method using the Levinson-Durbin feature and the Akaike criterion for the choice of model order.[20] This procedure allowed the automatic quantification of the central frequency and power of each relevant component of the spectrum. The spectral components of the frequency band between 0 and 0.04 Hz were considered very low frequency (VLF), the frequency band between 0.04 and 0.15 Hz was considered low frequency (LF) and the frequency band between 0.15 and 0.40 Hz, synchronized with respiration, considered

high frequency (HF). Due to the short registration period, the VLF component of iRR variability does not present well-established physiological explanation.[21] While the VLF of SBP variability seems to be related to myogenic vascular function.[22] The LF component of iRR variability reflects, predominantly, cardiac sympathetic modulation and the HF component, synchronized with respiration, cardiac parasympathetic modulation.[21] In the variability of SBP, the LF component quantifies the vasomotor sympathetic modulation, whereas the HF reflects the mechanical effect of respiration in the heart and vessels and does not represent an autonomic index.[23]

The spectral power of each component of the variability of iRR and SBP was calculated in absolute terms and in normalized units.[21] The ratio between the LF and HF components of the iRR was calculated to quantify the cardiac sympathovagal balance.

Arterial baroreflex control

The gain and the time delay of response of the baroreflex control of the heart rate were measured by the analysis of the transfer function analysis using the bivariate autoregressive identification procedure.[24] This procedure allowed the quantification of coherence, phase shift and gain among the time series of the iRR (output signal) and the SBP (input signal) as described by Freitas et al.[24]

In this study, the gain was calculated whenever the coherence between the signals was greater than 0.5 and the phase shift negative in the LF band, which indicates that the changes in the SBP preceded the changes in the iRR. In addition, it should be noted that the coherence, phase shift, gain and time delay of baroreflex control of heart rate were quantified at the central frequency corresponding to the maximum coherence within the LF band.

Experimental protocol

The evaluations were performed at the University Hospital of the Federal University of Juiz de Fora (HU-CAS), always in the morning. The volunteers were instructed not to ingest alcohol and / or caffeine and not to undertake vigorous physical activities within 24 hours prior to the evaluations as well as not eating fatty foods on the day of data collection.

The volunteers responded to the anamnesis that included the clinical data of the patients and their parents and were submitted to anthropometric evaluation. After the volunteers remained in the supine position for 10 minutes, simultaneous recording of heart rate, respiratory rate and BP was started for 15 minutes at rest. Then, the muscular blood flow of the forearm was measured during three minutes of rest and three minutes of reactive hyperemia.

Statistical analysis

Data were presented as mean ± standard deviation of the mean or as median and interquartile range. To verify the normality of the distribution of all variables analyzed, the Shapiro-Wilk test was used. In addition, the assumption of homogeneity of variance was also verified by the Lèvene test. The distribution of the sexes between the groups was presented in absolute and percentage values. Fisher's exact test was used to verify the possible difference between the proportions of the sexes and of volunteers with both hypertensive parents in the groups.

The possible differences related to the demographic, clinical and autonomic characteristics of the groups were verified through the unpaired *Student t* test for the data that presented normal distribution and Mann-Whitney U for the variables that violated this assumption. Two-way analysis of variance for repeated measures was used to test for possible differences between groups in vascular conductance during resting and reactive hyperemia. The main and interaction effects were analyzed with Bonferroni confidence interval adjustment.

All statistical analyzes were performed using SPSS® software version 20. The statistical significance was $p \leq 0.05$.

Results

Of the 25 volunteers analyzed, one normotensive volunteer did not meet the acceptability criteria for the analysis of the cardiac and peripheral autonomic modulation, and one normotensive volunteer and two prehypertensive patients did not attend to the analysis of arterial baroreflex function.

Table 1 shows the demographic and clinical characteristics of the groups evaluated. In addition to laboratory tests for glycemia, total cholesterol and triglycerides (Table 1), 13 normotensive volunteers and nine prehypertensive subjects measured serum creatinine levels (0.85 ± 0.21 and 0.94 ± 0.21 mg/dL, respectively), $p = 0.350$), and nine normotensive and seven prehypertensive patients measured serum uric acid levels (4.09 ± 1.55 and 4.84 ± 1.12 mg/dl, respectively, $p = 296$). No differences were observed between groups in any of the laboratory variables analyzed. Analysis of vascular function, measured by forearm vascular conductance during resting and reactive hyperemia, is shown in Figure 1. Vascular conductance increased during hyperemia in both the normotensive ($p < 0.01$) and prehypertensive ($p < 0.01$). In addition, although the prehypertensive group presented greater forearm vascular conductance both at rest ($p = 0.05$) and at the peak of reactive hyperemia ($p = 0.04$), this difference between groups tends to be more pronounced during the reactive hyperemia maneuver (interaction effect: $p = 0.05$).

Indices of cardiac autonomic modulation were similar between the groups (Table 2). However, in the peripheral autonomic modulation, greater variability (VarianceSBP) and higher VLFSBP and LFSBP spectral components were observed in prehypertensive patients compared to normotensive patients (Table 2). Additionally, we observed a lower gain of baroreflex control in prehypertensive patients (LFSBP-iRR gain), but similar LFSBP-iRR delay time between groups (Figure 2).

Table 3 shows the central frequency, phase shift and coherence of the LF component of the SBP-iRR relationship, as well as the central frequency and coherence of the LF and HF components of the relationship between respiratory activity and the iRR.

Table 1 – Demographic and clinical characteristics of the sample

Variable	Normotensive (n = 14)	Prehypertensive (n = 11)	p
Male gender n (%)	5 (35,7)	6 (54,5)	0,43[a]
Children of both hypertensive parents n (%)	4 (28,6)	5 (45,5)	0,43[a]
Age (years)	30 ± 6	29 ± 4	0,57[b]
BMI (kg/m²)	24 ± 4	25 ± 3	0,28[b]
Waist circumference (cm)	79 ± 11	82 ± 9	0,51[b]
Glycemia (mg/dl)	83 [80-93]	89 [83-93]	0,23[c]
Total Cholesterol (mg/dl)	177,9 ± 39,6	187,3 ± 29,7	0,53[b]
Triglycerides (mg/dl)	91,5 [57,9-131]	103,5 [63-148]	0,60[c]
SBP (mmHg)	116 [105-119]	128 [124-132]	< 0.01[c]
DBP (mmHg)	67 [60-71]	75 [71-75]	< 0.01[c]
Cardiac index (L/min/m²)	3,3 ± 0,3	3,7 ± 0,6	0,05[b]
Total peripheral resistance (mmHg/L)	15,0 [13,8-16,0]	13,8 [12,4-15,7]	0,15[c]
Cardiac contractility index (mmHg/s)	1113 ± 195	1340 ± 167	< 0,01[b]
Heart rate (bpm)	67 [63-69]	63 [62-76]	0,70[c]
Respiratory rate (ipm)	17 ± 2	17 ± 4	1,00[b]

Data presented as mean ± standard deviation of mean or median [interquartile range]; absolute value and percentage for males; [a]: Fisher's exact test; [b]: Unpaired Student t test; [c]: Mann-Whitney U-test; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

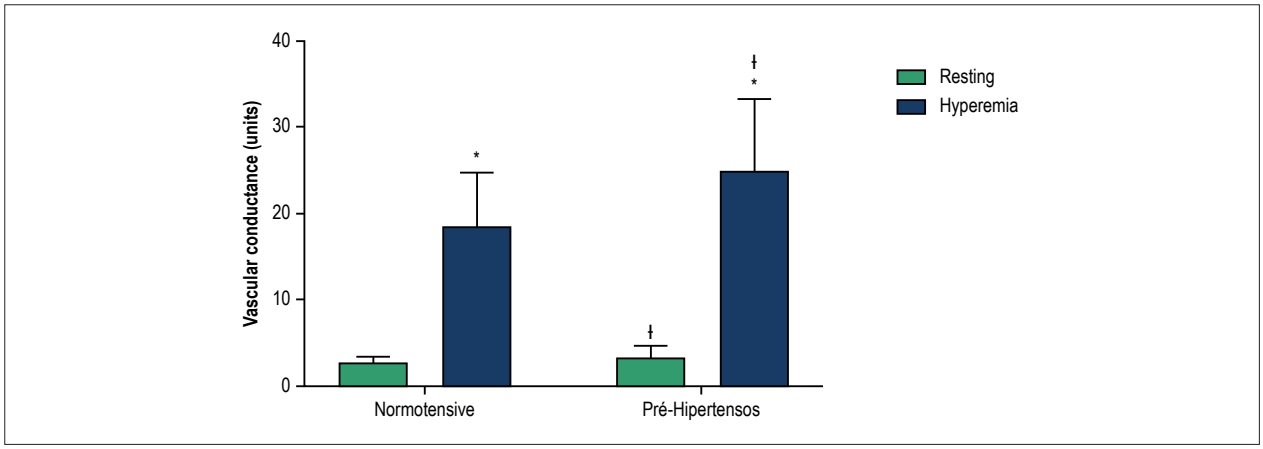

Figure 1 – *Vascular function. Data represented as mean ± standard deviation; ANOVA of two factors for repeated measures: *: significant differences in relation to rest; †: significant differences in relation to the normotensive group.*

Discussion

The main finding of this study is that peripheral autonomic dysfunction precedes the possible vascular dysfunction in prehypertensive individuals with FHSAH.

As expected, the prehypertensive group had higher SBP and DBP. Since blood pressure values are determined by cardiac output and peripheral vascular resistance, in this study, increased cardiac output by increasing systolic volume, possibly modulated by increased cardiac contractility, appears to be related to blood pressure elevation, since both heart rate and peripheral vascular resistance were similar between the groups. Similar results were obtained by Davis et al.,[12] who also observed elevation of cardiac index and cardiac contractility, but similar peripheral resistance, in young prehypertensive individuals when compared to normotensive ones. Thus, although the typical hemodynamic finding of hypertension is elevation of peripheral resistance, elevation of cardiac output appears to be responsible for pressure elevation in the early stages of disease development.[25]

In addition, studies have shown impairment in the vascular function of prehypertensive patients such as reduction of endothelium-dependent vasodilation, assessed by the infusion of acetylcholine,[10] reduction of the plasma concentration of vasodilatory substances, such as nitric oxide[26] and elevation of vasoconstrictors such as endothelin-1.[10,26] However, in this study,

Table 2 – Cardiac and peripheral autonomic modulation

Variable	Normotensive (n = 13)	Prehypertensive (n = 11)	p
Cardiac Modulation			
$Variance_{iRR}$ (ms^2)	2050 [985-3264]	1718 [1067-3806]	0,50[b]
VLF_{iRR} (ms^2)	905 ± 699	1178 ± 625	0,33[a]
LF_{iRR} (ms^2)	565 [277-1067]	413 [263-1360]	0,98[b]
HF_{iRR} (ms^2)	481 [212-897]	340 [195-606]	0,54[b]
LF_{iRR} (un)	51 ± 19	57 ± 17	0,46[a]
HFi_{RR} (un)	49 ± 19	43 ± 17	0,46[a]
LF/HF	0,90 [0,58-1,87]	1,52 [0,98-1,91]	0,50[b]
Peripheral modulation			
$Variance_{SBP}$ ($mmHg^2$)	9,4 [4,9-12,7]	18,3 [14,8-26,7]	< 0,01[b]
VLF_{SBP} ($mmHg^2$)	6,9 [2,0-11,1]	13,5 [10,7-22,4]	0,01[b]
LF_{SBP} ($mmHg^2$)	1,7 [1,0-3,0]	3,0 [2,0-4,0]	0,04[b]
HF_{SBP} ($mmHg^2$)	2,0 [1,0-2,0]	1,0[1,0-2,5]	0,77[b]
Breathing			
LF (un)	0 [0-6]	0 [0-12]	0,92[b]
HF (un)	100 [94-100]	100 [88-100]	0,92[b]

Data presented as mean ± standard deviation of mean or median [interquartile range];[a] unpaired Student t test; [b] - Mann-Whitney U-test; iRR: RR interval; SBP: systolic blood pressure; VLF : very low frequency; LF: low frequency; HF: high frequency; un: standard units.

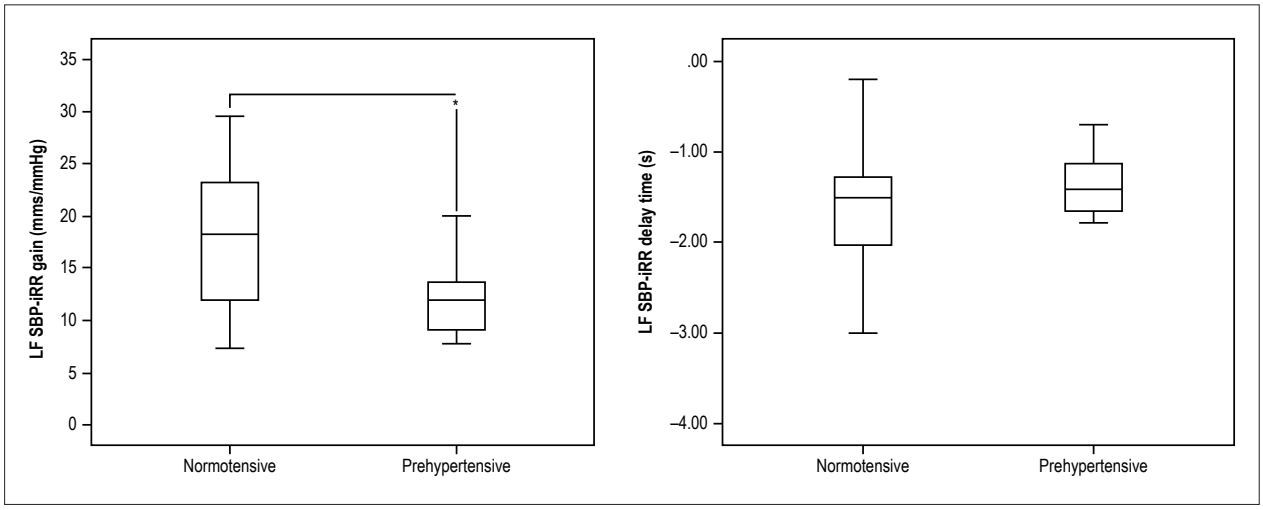

Figure 2 – *LF SBP-iRR gain and LF SBP-iRR delay time; Data represented in Box plot (minimum value, first quartile, median, third quartile and maximum value); iRR: RR interval; SBP: systolic blood pressure; LF: low frequency; Unpaired Student t test: *: significant difference in relation to the normotensive group (p = 0.03).*

we observed greater forearm vascular conductance in both the rest and the peak of reactive hyperemia in the prehypertensive patients when compared to the normotensive ones. Other studies, also using the venous occlusion plethysmography technique, obtained controversial results regarding the vascular function of prehypertensive patients. For example, Schwartz et al.[27] evaluated the resting forearm vascular conductance of normotensive and prehypertensive young men and did not observe differences between groups. Beck et al.[28] evaluated youngsters of both sexes and observed lower vascular conductance in prehypertensive patients in relation to the normotensive ones.

Already during the maneuver of reactive hyperemia, Beck et al.[26] and Beck et al.,[28] in contrast to the results of this study, observed a lower peak flow in prehypertensive patients using, respectively, venous occlusion plethysmography and high-resolution ultrasound. The differences between the results of this study and the others may be related to the

Table 3 – Arterial baroreflex function

Variable	Normotensive (n = 13)	Prehypertensive (n = 9)	p
SBP-iRR			
LF Central frequency (Hz)	0,10 ± 0,02	0,10 ± 0,01	0,58[a]
LF Phase shift (rad)	-0,96 ± 0,33	- 0,94 ± 0,31	0,90[a]
LF Coherence	0,85 ± 0,08	0,79 ±0,14	0,15[a]
Resp-iRR			
LF Central frequency (Hz)	0,14 [0,10-0,15]	0,10 [0,07-0,12]	0,08[b]
LF Coherence	0,47 ± 0,19	0,42 ± 0,16	0,56[a]
Central frequency HF (Hz)	0,29 [0,28-0,30]	0,32 [0,27-0,33]	0,42[b]
HF Coherence	0,96 [0,91-0,98]	0,93 [0,92-0,95]	0,22[b]

Data presented as mean ± standard deviation of mean or median [interquartile range];[a] unpaired Student t test; [b]: Mann-Whitney U-test; iRR-RR interval; SBP: systolic blood pressure; LF: low frequency; HF: high frequency.

characteristics of the population studied, such as the presence of FHSAH in both groups, since individuals with this risk factor have demonstrated vascular dysfunction in several studies.[6,7] In addition to FHSAH, pre-hypertensive volunteers in this study had higher cardiac and contractility rates, which may have triggered a local vasodilatory homeostatic response in an attempt to alleviate pressure elevation,[12] although this mechanism failed systematically in view of the fact that no difference was observed between groups in peripheral vascular resistance. No studies were found that investigated the association between cardiac and contractility indices and vascular conductance in prehypertensive patients. In hypertensive patients with hyperkinetic circulation, characterized by elevation of cardiac index and mean arterial pressure, Stevo et al.[29] observed greater forearm muscle blood flow compared to normotensive individuals. However, in this study the calculation of vascular conductance was not performed. Thus, future studies should investigate the association between these variables in pre-hypertensive individuals with a family history of arterial hypertension.

According to Davis et al.,[12] BP elevation in prehypertension results from hereditary disorders that present a set of genetic determinants and pathogenic traits that act on hemodynamic and autonomic events in series and trigger the SAH. In this scenario, autonomic alterations appear to be the first changes observed in prehypertensive patients.[12] However, although changes in the spectral indices of cardiac autonomic modulation in prehypertensive patients have been demonstrated in other studies,[8,30] in this one, they were not observed. Lin et al.,[13] who also observed LF and HF components in normalized units, as well as the LF/HF ratio of heart rate variability, similar among normotensive and prehypertensive youngsters, reported results similar to ours. A possible explanation for these contradictory results is the population studied. In this study, we evaluated normotensive and pre-hypertensive individuals with FHSAH, while the other studies did not control the distribution of this risk factor in the analyzed groups. Thus, since alterations in cardiac autonomic modulation have been demonstrated in normotensive individuals with hypertensive father and / or mother,[4,5] further studies are needed to elucidate these alterations in individuals who have both risk factors, prehypertension and FHSAH.

Regarding the autonomic peripheral modulation, in this study we verified dysfunctions in this system in the prehypertensive individuals. We observed a higher LF component of SBP variability in prehypertensive patients compared to normotensive patients, which shows a greater performance of vascular tone sympathetic modulation as well as myogenic vascular function in this population.[23] Similar results were reported by Hering et al.[31] and Seravalle et al.[9] who evaluated individuals with normal-high pressure and also observed greater peripheral sympathetic modulation, assessed by the microneurography technique, in these individuals when compared to normotensive individuals.

The variability of SBP, as well as elevation of pressure levels, has been recognized as an important risk factor for target organ damage.[32] In this study, pre-hypertensive individuals presented greater variance of SBP in relation to normotensive individuals, corroborating the results of Duprez et al.[33] However, these authors did not report the FHSAH of study participants.

BP fluctuations are triggered by multiple systems including the renin-angiotensin system, baroreflex, myogenic vascular response, and release of nitric oxide.[23] Thus, the elevations of the LF and VLF components observed in this study may be related to the increase in SBP variability through changes in myogenic vascular function.[23] The HF component, which appears to be related to endothelial nitric oxide[23], was similar between the groups and did not appear to be involved in increased pressure variability.

In addition, this study demonstrated a reduction in the baroreflex control of heart rate in prehypertensive individuals when compared to normotensive individuals, a factor that may also be related to the increased pressure variability and peripheral sympathetic modulation observed.[34] The results of this study corroborate the findings of previous studies[9,11,13] that also observed reduction of baroreflex sensitivity in prehypertensive patients. However, this is the first to demonstrate autonomic changes in prehypertensive patients with FHSAH in relation to normotensive individuals with the same risk factor.

In addition to sensitivity, the response time of the baroreflex can also determine the efficiency of this reflex.[35] In this study, we verified the baroreflex response time preserved in prehypertensive patients. This characteristic of the baroreflex is mainly affected by changes in cardiac parasympathetic nervous modulation,[36] a change that was not observed in the prehypertensive patients evaluated in this study. Therefore, it is possible that the response time of the baroreflex could be affected later in the course of pressure rise and development of hypertension and that in the prehypertension phase only the reduction of the gain contributes to the reduction of the efficiency of this reflex. In addition, the fact that the volunteers in this study have FHSAH may be related to the observed results. No studies were found to investigate this time delay of the baroreflex effector response in prehypertensive individuals, as well as in children with hypertensive parents, which made difficult to compare our results.

This study demonstrated that prehypertensive youngsters with FHSAH present autonomic dysfunction and vascular function similar to normotensive with the same risk factor. Thus, the results of this study emphasize the importance of preventive intervention with measures aimed at attenuating this dysfunction and, consequently, acting on the prevention of hypertension in this population. In this sense, physical exercise has been considered effective since it acts in a beneficial way in multiple physiological systems.[37] In addition, the benefits of regular aerobic physical exercise in the attenuation of autonomic dysfunction have already been demonstrated both in prehypertensive patients[37] and in the descendants of hypertensive parents,[38] which leads us to believe that individuals with both risk factors may also benefit from the effects of this practice.

Limitations

The diagnosis of SAH of the parents of the volunteers of this study was self-reported. Although self-report has been used in many studies,[38,39] future research should include detailed medical evaluation of the parents. The presence of renal diseases was not an exclusion criterion in this study, since all the necessary tests to exclude safely this characteristic were not performed. In spite of this, all the volunteers declared that they did not have a diagnosis of renal diseases and those who did the creatinine and uric acid tests presented normal values for these variables. Additionally, the women in this study were not evaluated during the same period of the menstrual cycle, a fact that may also be a limitation of this work. However, Jarvis et al.[40] and Carter et al.[41] observed no influence of the ovarian cycle phase on sympathetic modulation, heart rate and BP during rest in young women. Despite the limitations pointed out, the great strength of this study is the fact that we evaluated young adults, without medication and with similar glycemic and lipid profile.

Conclusion

We conclude that prehypertensive patients with FHSAH have autonomic dysfunction, characterized by increased peripheral sympathetic modulation and reduced baroreflex control of heart rate, and increased vascular conductance when compared to normotensive patients with the same risk factor.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Amaral JF, Borsato DMA, Freitas IMG, Toschi-Dias E, Martinez DG, Laterza MC; Acquisition of data: Amaral JF, Borsato DMA, Laterza MC; Analysis and interpretation of the data: Amaral JF, Borsato DMA, Freitas IMG, Toschi-Dias E, Laterza MC; Statistical analysis and Writing of the manuscript: Amaral JF, Laterza MC.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Universidade Federal de Juiz de Fora under the protocol number 720/370. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Current Practices in Myocardial Perfusion Scintigraphy in Brazil and Adherence to the IAEA Recommendations: Results of a Cross-Sectional Study

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Abstract

Background: **Data on the current situation of nuclear medicine practices in cardiology in Brazil are scarce. The International Atomic Energy Agency (IAEA) has recommended eight "good practices" to minimize patients' ionizing radiation exposure during myocardial perfusion scintigraphy (MPS).**

Objectives: **To assess the adoption of the eight good practices in MPS in Brazil.**

Methods: **Cross-sectional study with data obtained by use of a questionnaire. All hypothesis tests performed considered a significance level of 5%.**

Results: **We observed that 100% of the nuclear medicine services (NMS) assessed do not use thallium-201 as the preferred protocol. Regarding the use of technetium-99m, 57% of the NMS administer activities above the threshold recommended by the IAEA (36 mCi) or achieve an effective dose greater than 15 millisievert (mSv). The abbreviated stress-only myocardial perfusion imaging is not employed by 94% of the NMS; thus, only 19% count on strategies to reduce the radioactive doses. Approximately 52% of the NMS reported always performing dose adjustment for patient's weight, while 35% administer poorly calculated doses in the one-day protocol.**

Conclusion: **A considerable number of NMS in Brazil have not adopted at least six practices recommended by the IAEA. Despite the difficulties found in nuclear practice in some Brazilian regions, almost all obstacles observed can be overcome with no cost increase, emphasizing the importance of developing strategies for adopting "good practices" when performing MPS. (Arq Bras Cardiol. 2018; 110(2):175-180)**

Keywords: **Nuclear Medicine / methods; Myocardial Perfusion Imaging; Myocardial Ischemia / diagnostic imaging.**

Introduction

Myocardial perfusion scintigraphy (MPS) is a non-invasive, safe technique that uses physical or pharmacological stress to detect the presence of ischemia, assessing its early changes. The complication rate of MPS does not exceed that of exercise testing, whose mortality is estimated at 0.01%.[1]

Patients with ischemia evidenced on MPS are at higher risk for adverse outcomes as compared to those with a normal test. That stratification is fundamental, because invasive approaches are only beneficial to patients at increased risk. According to the European guidelines on revascularization, the best-established techniques for diagnosing ischemia are MPS and stress echocardiography.[2] Appropriate use of invasive procedures is fundamental, because they have a high cost. The IMPACT Study has shown that most of the cost to manage coronary disease derives from invasive procedures.[3]

Myocardial perfusion scintigraphy is the nuclear medicine procedure most used in Brazil, accounting for 54% of all scintigraphies performed within the Brazilian Unified Health System (SUS).[4] Although widely used, the practices are heterogeneous and can be refined, especially because they employ ionizing radiation, which, by principle of radioprotection, should be used in a justified and optimized way. Santos et al.,[5] assessing the use of scintigraphy in SUS, have observed a 12% rate of inappropriate use. Those authors have reported that, with appropriate use, there will be an 18.6% reduction in budget costs, in addition to a reduction in unnecessary radiation exposure.[5] Oliveira et al.,[6] however, assessing the MPS use at another institution, have found a rate of inappropriate tests of only 5.2%.[6]

Considering the heterogeneous use and radiation exposure, the International Atomic Energy Agency (IAEA) recommends eight "good practices" to minimize radiation exposure during MPS.[7] The INCAPS Study has assessed the adoption

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of those practices at 308 nuclear medicine services (NMS) in 65 countries, and only 142 NMS (45%) have shown a satisfactory rate. So far, there are no data on the use of those recommendations in Brazil, which is this study's objective.

Methods

This is a cross-sectional study with online self-administered questionnaire, which was sent to the email address of the technical managers of the NMS in operation in Brazil (403 NMS on the first trimester of 2016, according to data obtained at the site of the Brazilian Committee of Nuclear Energy (CNEN). The inclusion criterion in the study was that the NMS must be authorized by the CNEN to operate. The NMS performing fewer than 20 MPS per month, as well as duplicated responses, were excluded from this study, which resulted in 63 respondents (16% of total).

The questionnaire was elaborated based on the North American and European guidelines, with questions selected from the following IAEA publications: *Quality Management Audits in Nuclear Medicine Practices* (QUANUM)[8] and *Nuclear Medicine Database* (NUMDAB).[9] The questionnaire consisted of 49 questions, divided into the following 7 domains: demographic data of the NMS (5 items); technical team (10 items); patient care (4 items); radiopharmacy (8 items); equipment (7 items); test protocol (20 items); and postprocessing and image interpretation (2 items).

The multidisciplinary team of the NMS was considered to be complete when having at least one professional of each category: nuclear physician, medical physicist, pharmacist, biomedical physician scientist, nurse and technician.

Quality index (QI) was adopted to measure objectively the quality of the MPS, and comprises the sum of the practices that can be adopted in an NMS. The QI ranges from 0 to 8, a QI $\geq$ 6 being considered the desirable level for an NMS to have as suggested by the IAEA.[7]

Statistical analysis

The variables were tested for normality by use of the Kolmogorov-Smirnov method, revealing a non-normal distribution. Thus, descriptive analysis was performed by use of medians and interquartile range, and the Kruskal-Wallis and the Mann-Whitney U tests for independent samples were used. The Statistical Package for the Social Sciences, version 21, was used for the statistical analysis. All hypothesis tests performed considered a significance level of 5%, that is, the null hypothesis was rejected when p value < 0.05.

Results

The responding 63 NMS reflect the practice of 972 professionals, who account for an estimate of 13,200 MPS per month.

Figure 1 shows the histogram of the QI distribution at 63 NMS in Brazil, where the median QI found was 5. The lowest QI was 3, the lowest quartile equivalent to 25% of the QI scores was 4, and the highest quartile was 5. A QI $\geq$ 6, which is the desirable index, was only observed in 13 NMS (20.6% of the sample).

Table 1 discriminates the QI values according to the major characteristics of the NMS, aiming at identifying those associated with the highest QI values. Two variables showed significant association with an elevated QI: 1) the NMS location inside academic institutions as compared to non-academic ones ($p = 0.046$); and 2) presence in the NMS of a complete multidisciplinary team as compared to absence thereof ($p = 0.030$).

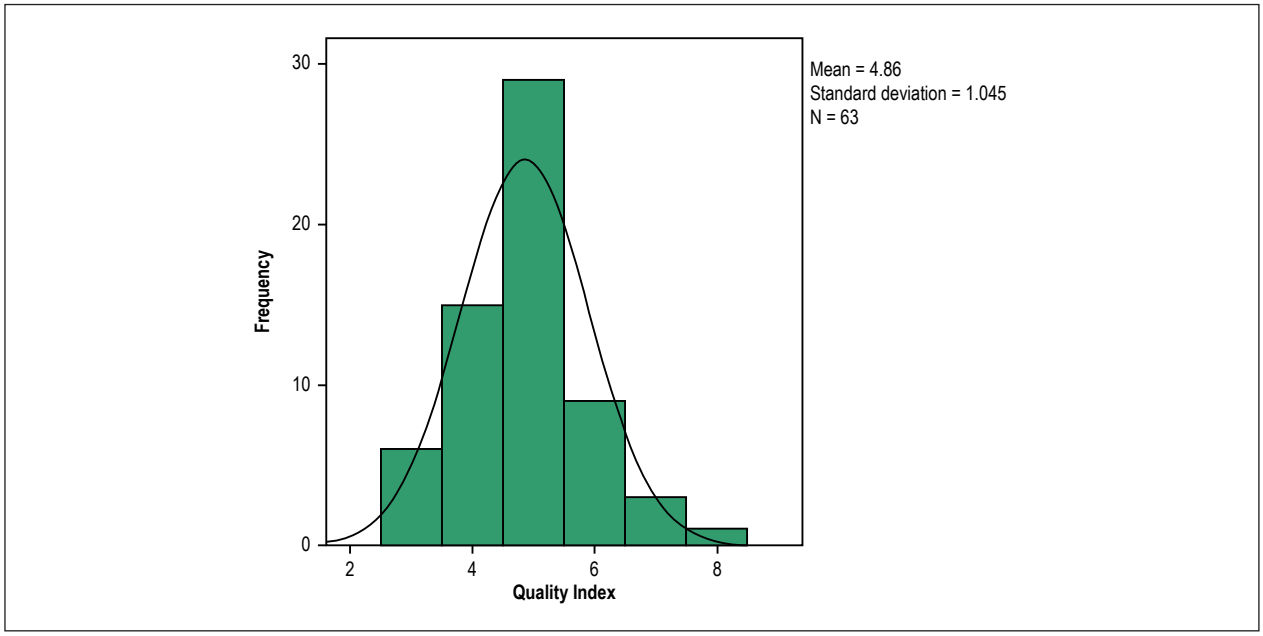

Figure 1 – *Distribution of the quality index (0 to 8) of good practices of 63 nuclear cardiology services in Brazil, 2016.*

Table 1 – Quality index according to the demographic, professional and regional characteristics of nuclear medicine services (NMS)

	N	Mean	Median	Standard deviation	p value
Brazilian region					
Southeast	34	5	5	1.044	
South	17	4.76	5	1.200	0.750*
West-Central	2	5.00	5	0.000	
Northeast	8	4.50	4	0.926	
North	2	4.50	4	0.707	
Type of NMS					
Private	55	4.91	5	1.076	**0.329**[ł]
Public	8	4.50	5	0.756	
University-affiliated					
Yes	7	5.57	5	0.78	**0.046**[ł]
No	56	4.77	5	1.04	
> 3 nuclear physicians					
Yes	45	4.76	5	0.85	**0.204**[ł]
No	16	5.19	5	1.47	
Complete multidisciplinary team					
Yes	12	5.33	5	0.98	**0.030**[ł]
No	51	4.75	5	1.03	
Exclusive NMS					
Yes	19	4.86	5		**0.956**[ł]
No	44		5		

** Independent-Samples Kruskal-Wallis test; [ł] Independent-Samples Mann-Whitney U test*

When assessing the amount of MPS performed monthly and its relation to the desirable QI (Table 2), we observed that institutions with QI ≥ 6 performed a statistically higher number of MPS than those that did not adopt at least six good practices (p = 0.043).

When assessing the presence of each good practice in the 63 NMS (Table 3), the most frequently adopted by all were as follows: 1) do not use the thallium-stress protocol; 2) do not use the dual-isotope protocol; and consequently 3) do not use increased Tl-201 activities. Conversely, the least frequently adopted good practice was the use of the abbreviated stress-only myocardial perfusion imaging, in only 6% of the NMS.

Discussion

The IAEA has been dedicated to promoting good practices in nuclear cardiology, undertaking the largest research about cardiological tests so far, by use of a cross-sectional study of global comprehensiveness called INCAPS, which evidenced that the adoption of good practices in NMS is highly heterogeneous in the continents. The NMS in Asia and Latin America showed the worst performance, with less than one quarter of the NMS achieving the desirable QI (≥ 6 good practices).[7] Information on the situation of the NMS in Brazil is scarce. After that research, the Brazilian Society of Nuclear Medicine, concerned with qualified practice, was one of the first entities to endorse the adoption of good practices in its guidelines, aimed at the continuous search for a reduction in radiation exposure (optimization).[10]

Thallium-201 scintigraphy has unfavorable physical characteristics, such as low counting rate and long physical half-life, which are associated with a higher dose of radiation absorbed, being considered a second option to Tc-99m-sestamibi. The use of Tl-201 is strictly recommended for myocardial viability studies, but with the new devices with highly effective detectors, there is a renewed interest in ultrafast dual-isotope protocols that enable the use of low doses and conveniently allow performing the complete test in less than 30 minutes.[11] In our study, we observed that 100% of the NMS assessed used neither Tl-201 nor dual-isotope as the preferred protocol, which is a good practice also associated with the financial aspect, considering the lower cost of Tc-99m-sestamibi and its easy use, which involves a medication kit. Thus, currently the traditional protocols of one or two days still predominate.

Conversely, the least frequently adopted good practice by the NMS in our study was the abbreviated stress-only myocardial perfusion imaging.[12] Chang et al.[13] have demonstrated that it is safe to use a single stress phase, without rest, in normal tests from the perfusional and contractile function viewpoint, which facilitated the dynamics of the NMS

Table 2 – Comparison of the mean numbers of myocardial perfusion scintigraphy (MPS) performed at the 63 nuclear medicine services

	N	Mean	Median	Standard deviation	p value
Number of MPS per month					
≥ 6 Good practices	13	298	280	230	0.043*
< 6 Good practices	50	186	120	304	

** Mann-Whitney U test*

Table 3 – Frequency (%) of the adoption of each good practice at the nuclear medicine services assessed in Brazil, 2016

Good practices	Brazil	
A	63	(100)
B	63	(100)
C	27	(42.86)
D	63	(100)
E	4	(6.35)
F	12	(19.05)
G	33	(52.38)
H	41	(65.08)

A: Avoid thallium-stress protocol; B: Avoid dual-isotope protocol; C: Avoid high Tc-99m activities; D: Avoid high Tl-201 activities; E: Perform only "Stress-Only"; F: Use strategies focused on dose reduction; G: Patient's weight-based activities; H: Avoid inappropriate activities that can generate the shine-through artifact.

and reduced by 61% the use of radiopharmaceuticals and radiation exposure. Gowd et al.[14] have listed the limitations to its wide adoption, such as non-familiarity with the assessment of a single phase, the need for processing images immediately after their acquisition, and the issues regarding reimbursement of expenses, considering that a significant part of the test is paid with the resting phase. Oliveira et al.[15] have been the first to approach the use of that protocol in Brazil, but the experience is still incipient.

An accurate test requires the use of proper radiation doses, avoiding the "shine-through" phenomenon.[16] One third of the NMS assessed still administer doses that can allow the interference of residual radiation with later images in the one-day protocol.[17] In that protocol, respecting the minimum three-hour interval between the phases, a dose three times higher than that of the first phase is required to avoid that artifact, which can lead to a reduction in the ischemic burden or even to false-negative results.[16] Recent studies have shown that protocols with ultra-low doses of sestamibi (5 mCi) during stress can be even more appropriate to prevent that artifact.[17]

The IAEA has suggested the Tc-99m threshold of 36 mCi as the maximum activity to be administered in a single injection;[7] however, half of the NMS assessed use activities over that threshold. Such thresholds are usually exceeded when the patient has a high body weight, the best strategy for that patient being to undergo MPS in the two-day protocol, eliminating, thus, the need for tripling the dose, providing lower radiation exposure and higher image quality.[10] The adjustment of the dose for the patient's weight is part of the CNEN norms and should be adopted as a rule.[18] Nevertheless, almost half of the NMS assessed have not adopted routinely this practice, missing an opportunity for improvement. That adjustment is aimed at using appropriate radiation doses to each patient's weight and attenuation rate, preventing overexposure or insufficient exposure, which leads to a low quality test.[19]

In addition, strategies for dose reduction have been considered. There is high-technology hardware, such as CZT cameras,[20,21] which provide high image resolution, and hybrid devices, such as SPECT-CT, which can eliminate the attenuation of soft tissues,[22] but they are not widely available. A strategy that can be used without additional costs for those without attenuation correction is the prone position during the acquisition of the stress phase of MPS. Placing the patient in the prone position reduces diaphragmatic attenuation and its interference with the images.[23,24] Many NMS have reported using that technique, but that can only be considered a strategy of dose reduction if the single stress phase is a practice adopted by the entire NMS. In prone MPS, the stress phase shows normal perfusion aspect and preserved contractility, but the patient should undergo the second phase anyhow. There was no dose reduction during that process.

In general, the QI was significantly higher in the academic institutions. In 2010, the MPS performed inside university-affiliated hospitals showed more appropriate and precise indications.[25] The NMS that promote research are constantly searching for knowledge, being updated by recent studies and new international recommendations very fast, being always one step ahead.

Another important and innovative finding was the significantly higher QI of the institutions that count on a complete multiprofessional team, comprised by nuclear

physician, medical physicist, pharmacist, biomedical physician scientist, nurse and technician (at least one of each). Thus, the NMS with professionals of different areas provide better patient care by adding multiple domains of knowledge.

The present study has some limitations, the most evident being the self-administered questionnaire, which attributes to the respondent the research's degree of reliability. Despite being a random sample, most respondents lived in the southern and southeastern regions of Brazil.

Conclusion

Our study assessed the adoption of good practices in nuclear cardiology tests at NMS in Brazil. Although the response rate to the questionnaire was only 16% of the total NMS on operation, not representing a probabilistic sample, this is the largest data collection about nuclear medicine practices in cardiology in Brazil so far. We observed that the adoption rate of good practices, measured by use of the QI, is heterogeneous, showing an opportunity for improvement. One fifth of the participants has achieved excellence, which was more frequent in university-affiliated SNM and in those with a complete multidisciplinary team.

We found that the adoption of good practices in the nuclear medicine tests in cardiology by the NMS assessed in Brazil is equivalent to that of other countries in Latin America, Asia and even North America, being, however, lower than that observed in other continents.

There is the opportunity for improvement without cost increase, which requires the adoption of encouraging educational interventions to strengthen cardiology in Brazil.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Rodrigues CVB, Oliveira A, Wiefels CC, Leão MS, Mesquita CT; Acquisition of data: Rodrigues CVB; Rodrigues CVB, Oliveira A, Wiefels CC, Leão MS, Mesquita CT; Statistical analysis: Rodrigues CVB, Oliveira A, Mesquita CT; Obtaining financing: Rodrigues CVB; Writing of the manuscript: Rodrigues CVB, Mesquita CT.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina da Universidade Federal Fluminense under the protocol number 36682714.5.0000.5243. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Heart Transplantation for Peripartum Cardiomyopathy: A Single-Center Experience

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Abstract

Background: Peripartum cardiomyopathy is an idiopathic disorder defined by the occurrence of acute heart failure during late pregnancy or post-partum period in the absence of any other definable cause. Its clinical course is variable and severe cases might require heart transplantation.

Objective: To investigate long-term outcomes after heart transplantation (HT) for peripartum cardiomyopathy (PPCM).

Methods: Out of a single-center series of 1938 HT, 14 HT were performed for PPCM. We evaluated clinical characteristics, transplant-related complications, and long-term outcomes, in comparison with 28 sex-matched controls. Primary endpoint was death from any cause; secondary endpoints were transplant-related complications (rejection, infection, cardiac allograft vasculopathy). A value of $p < 0.05$ was considered of statistical significance.

Results: PPCM patients and matched controls were comparable for most variables (all p values > 0.05), except for a higher use of inotropes at the time of HT in PPCM group ($p = 0.03$). During a median follow-up of 7.7 years, 16 patients died, 3 (21.5%) in PPCM group and 13 (46.5%) in control group. Mortality was significantly lower in PPCM group ($p = 0.03$). No significant difference was found in terms of transplant-related complications ($p > 0.05$).

Conclusions: Long-term outcomes following HT for PPCM are favorable. Heart transplantation is a valuable option for PPCM patients who did not recover significantly under medical treatment. (Arq Bras Cardiol. 2018; 110(2):181-187)

Keywords: Heart Failure; Cardiomyopathies / mortality; Peripartum Period; Heart Transplantation; Graft Rejection. / mortality.

Introduction

Peripartum cardiomyopathy (PPCM) is defined by the occurrence of acute heart failure (HF) during late pregnancy or post-partum period in the absence of any other definable cause or prior heart disease. Diagnostic criteria have recently been revised by the ESC Working Group on PPCM.[1] Disease incidence shows ethnic variations, with a greater prevalence among African women.[2] A deleterious combination of "anti angiogenic signaling excess" and "oxidative stress-prolactin axis" toward the end of pregnancy is suggested as key element in the pathophysiology of the disease.[3] Beside conventional treatment of HF,[4] targeted therapies including pharmacological prolactin blockade are being investigated.[5] Although half of patients will fully recover left ventricular systolic function, the clinical course of PPCM is highly variable.[6,7] Data from the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) recently assessed a 6% rate of death, heart transplantation, and left ventricular assist device (LVAD) implantation at 1 year in PPCM patients and more than 20% rate of persistent left ventricular (LV) dysfunction.[6] Baseline LVEF < 30%, baseline LV end-diastolic diameter (LVEDD) > 60mm, black ethnicity and post-partum diagnosis were correlated with poor prognosis.[6] Up to 10% of PPCM patients will require heart transplantation according to literature data.[6,8-10] Post-transplant prognosis for PPCM patients is at present still contradictory.[11-14] A higher incidence of rejection has been reported, particularly during the first year following transplantation, along with a lower graft survival.[13,14] Heart transplantation (HT) is however considered as a valuable option for PPCM patients presenting with HF unresponsive to maximal conventional treatment. The aim of this study is to compare all-cause mortality and transplant-related complications after HT for PPCM.

Methods

This is a retrospective single-center non-interventional study. Primary endpoint was all-cause mortality following heart transplantation (HT). Secondary endpoint was outcomes after HT including transplant-related complications (rejection, infection, cardiac allograft vasculopathy). All patients had single-center management with a consistent approach at both surgical and medical levels.

Patient population

A total of 1938 patients from whom 368 females were transplanted for severe HF in our institution. Fourteen patients met diagnosis criteria of PPCM. All our PPCM cases were ascertained with the most recent definition of the disease.[1] An extensive work-up was performed retrospectively for each

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patient to exclude other causes of HF. Twenty-eight age-matched female patients who underwent HT during the same period for other causes served as controls. Each PPCM patient was matched to two female control patients depending on their age at the time of transplantation (± 5 years) and on the era of transplantation (± 6 months). Survival was assessed until last follow-up. Demographics, pre- and post-transplant data were retrospectively collected from our institution's computerized medical charts. Information on follow-up was obtained retrospectively by direct patient interview for those who were still alive at the time of data collection. As this was an observational study, our institutional ethics board was not involved.

Post-transplant course

All patients had a similar post-transplant follow-up protocol. Endomyocardial biopsies were routinely performed during the first two years following HT, then, less frequently (every 6 months for years 2 to 5, then every year beyond 5th year), unless clinical indication. Coronary angiography was first performed at one-year post transplant then every two years if normal. We considered arbitrarily graft rejection as present or non-present, regardless of its type (antibody-mediated or cell-mediated rejection) and severity. The diagnosis of cell mediated rejection was based on Stanford grading system until 1990,[15] then, on the International Society for Heart and Lung Transplantation nomenclature (ISHLT;[16]). The ISHLT Guidelines on Antibodies-mediated rejection (AMR) were used for the definition of AMR rejections.[17,18] We considered rejection as "characterized" in the following situations: All cell-mediated rejections of grade > or = to 1A/1R; All proven antibodies mediated rejection regardless of grade; All symptomatic rejections i.e. with hemodynamic compromise or LV dysfunction.[19] All characterized rejections triggered therapeutic interventions.

Cardiac Allograft Vasculopathy (CAV) was considered in the setting of any angiographic evidence of coronary artery stenosis regardless of the need of specific treatment.[20] Infections were defined as any episode requiring hospitalization or intravenous treatment, including cytomegalovirus (CMV) infections.

Immunosuppressive therapy and rejection treatments varied over time. Induction therapy involved intravenous methylprednisolone, and rabbit anti-thymocyte globulin from 1986 to 2000; and antithymocyte globulin or Basiliximab since 2000. Long-term prophylactic immunosuppressive therapy was based on calcineurin inhibitors (mostly cyclosporine), azathioprine and long-term oral corticosteroids from 1986 to 2000; and calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mofetil and oral corticosteroids since 2000. Everolimus was not routinely used upon the study population. Of note, none of the patients in PPCM group received Bromocriptine.

Statistical considerations and analysis

Data are presented as the mean ± standard deviation, unless otherwise specified. Comparisons between groups for continuous variables were performed using the Student t-test or the Mann Whitney U test as appropriate. The chi-square or the Fisher exact tests were used for categorical variables as appropriate. The duration of follow up was computed using reverse the Kaplan Meier method. Survival was defined as being alive at the cut-off date for our study without the need of a retransplantation. Kaplan-Meier survival curves were constructed for the two groups and compared using the log rank test. A value of $p < 0.05$ was considered of statistical significance. All analyses were conducted with the use of SPSS 18.0 software (Chicago, Illinois).

Results

Pre-transplant characteristics

Pre-transplant characteristics are summarized in Tables 1 and 2. Patients in control group were transplanted for: idiopathic dilated (n = 10, 36%), ischemic (n = 8, 28.5%), congenital (n = 1, 3.5%), restrictive (n = 2, 7.1%), valvular (n = 2, 7.1%), and anthracyclines-induced (n = 3, 10.7%) cardiomyopathies or myocarditis (n = 2, 7.1%). There were significantly more patients requiring inotropes in PPCM group (n= 9, 64% in PPCM patients vs. n = 8, 28% in controls, p = 0.03). Patients requiring hemodynamic support were indiscriminately those recently diagnosed with PPCM and readily presenting with cardiogenic shock (n = 4/9), but also those with long time known PPCM and gradually progressing to end-stage heart failure (n = 5/9). Conversely, in control group, patients requiring inotropic support were more often those who were recently (< 1year) diagnosed with HF.

We found no significant difference considering African descent; the time spent on the transplant waiting list; right ventricular dysfunction; and HF severity at the time of diagnosis. No significant difference in HF treatment was noticed particularly in terms of ACE inhibitors or beta-blockers administration, and cardiac resynchronization therapy (CRT) / internal cardioverter defibrillator (ICD) implantation rates.

Regarding mechanical circulatory support (MCS) indication, no significant difference was observed. In PPCM group, one patient underwent intra-aortic balloon counterpulsation (IABP), two peripheral Extra-Corporeal Membrane Oxygenation (ECMO), one long-term Ventricular Assist Devices, and one CardioWest Total Artificial Heart implantation. In control group, two patients underwent IABP, seven peripheral or central ECMO, and two long term VADs.

Graft Characteristics and Immunosuppressive treatments

Graft characteristics were similar in the two groups. Mean ischemic time duration was 159 ± 12 minutes in PPCM group vs. 178 ± 13 minutes in control group. Mean age donor was 45 years for PPCM recipients and 46 years for controls. We observed no significant difference in terms of sex mismatch. As the patients were matched for transplantation period, there was no difference in immunosuppressive regimen.

Table 1 – General characteristics of PPCM patients

PPCM patients	Time from diagnosis to HT	Time on waiting list	Age at the time of HT	LVEF (%)	Inotropes	IABP	ECMO (P + C)	VAD	Cross-match
1	19 yrs	1 mth	49	30	Y	N	N	N	N
2	2 yrs	18 mths	30	15	N	N	N	N	N
3	8 yrs	< 1 mth	36	25	Y	N	N	N	N
4	10 mths	1 mth	39	25	N	N	N	N	N
5	5 mths	< 1 mth	35	10	Y	N	N	Y	N
6	3 mths	< 1 mth	35	23	N	N	N	N	N
7	13 yrs	< 1 mth	44	20	Y	N	N	N	N
8	1 mth	< 1 mth	33	14	Y	N	N	N	NA
9	4 mths	1 mth	29	15	Y	Y	Y	N	N
10	4 yrs	9 mths	34	32	Y	N	Y	Y	N
11	15 yrs	2 mths	47	25	N	N	N	N	N
12	1 yr	< 1 mth	27	10	N	N	N	N	NA
13	9 mths	< 1 mth	37	25	Y	N	N	N	NA
14	1 yr	2 mths	39	35	Y	N	N	N	N

LVEF: Left Ventricle Ejection Fraction; IABP: intra-aortic balloon counterpulsation; ECMO (P+C): Extra Corporeal Membrane Oxygenation (Peripheral + Central); VAD: Ventricular Assist Device; Y: Yes; N: No; NA: Not applicable; yr: year; m: month.

Table 2 – Pre-transplant characteristics in PPCM group and control subjects

Variable	PPCM group (n = 14)	Control group (n = 28)	p
Age at the time of HT, years	36.7 ± 6.5	38.4 ± 8.5	p = 0.4
Previous pregnancies	100% (n = 14)	50% (n = 14)	p = 0.3
Smoker	21% (n = 3)	42.8% (n = 12)	p = 0.1
Hypertension	7% (n = 1)	7% (n = 2)	p = 0.7
Beta-blockers	50% (n = 7)	42.8% (n = 12)	p = 0.5
ACE inhibitors	50% (n = 7)	75% (n = 21)	p = 0.6
Time on waiting list, months	2.4 ± 5	3.8 ± 5	p = 0.1
LVEF (%)	22 ± 8	24 ± 14	p = 0.9
Inotropes	64% (n = 9)	28.57% (n = 8)	p = 0.03
IABP	7% (n = 1)	7% (n = 2)	p = 0.7
ECMO	14% (n = 2)	25% (n = 7)	p = 0.5
VAD	14% (n = 2)	7% (n = 2)	p = 0.4

PPCM: peripartum cardiomyopathy; LVEF: Left Ventricle Ejection Fraction; RV: Right Ventricle; IABP: intra-aortic balloon counter pulsation; ECMO (P+C): Extra Corporeal Membrane Oxygenation (Peripheral + Central); VAD: Ventricular Assist Device. (Comparisons between groups for continuous variables were performed using the Student t-test or the Mann Whitney U test as appropriate).

Patients outcomes

During a median follow-up of 7.7 years, 16 patients died, 3 (21.5%) in PPCM group and 13 (46.5%) in control group. Mortality was significantly lower in PPCM group (p = 0.03, Figure 1). Causes of death are shown in Table 3. Major causes of one-year mortality after HT were rejection, hemorrhagic complications and infections; major causes of long-term mortality (> 1 year) after HT were rejection, CAV, and infections. Both early and late rejection rates were similar in both groups (p = 0.5 and 0.6 respectively). PPCM patients had a similar incidence of infections including cytomegalovirus (CMV) infections compared with control population (p = 0.07). Two patients from control group died within the first year following transplantation from septic shock, none in PPCM group. One more patient in control group died from septic shock > 1 year post transplant, none in PPCM group. PPCM patients had a similar risk of CAV compared with control group (p = 0.4). Pathological study of explanted hearts did not reveal any specific lesion.

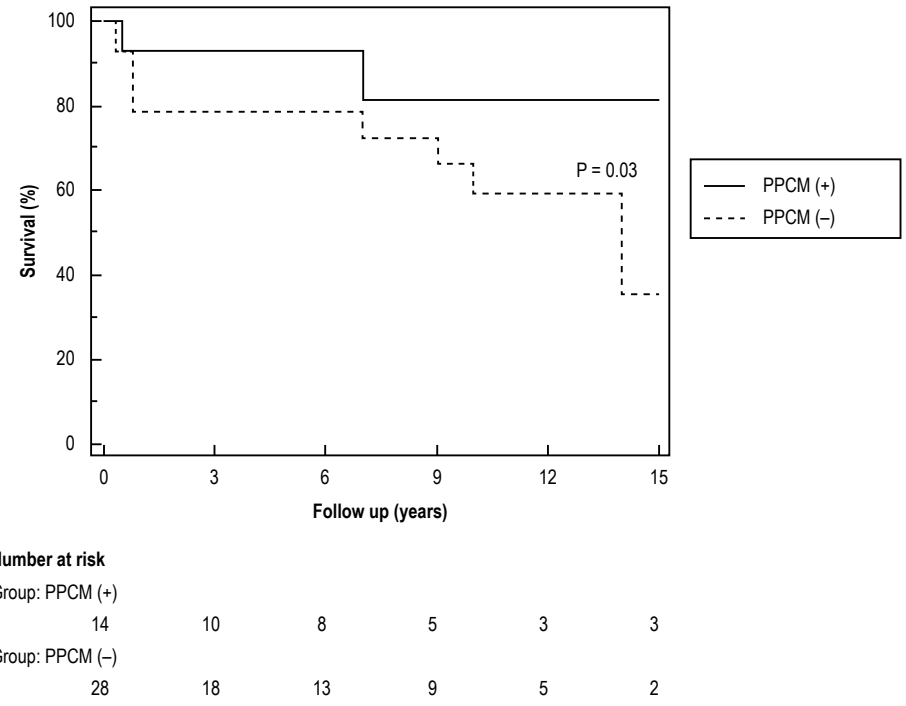

Figure 1 – *Long-term survival after heart transplantation, PPCM group (PPCM (+)) and control patients (PPCM (-)). PPCM: peripartum cardiomyopathy.*

Table 3 – Transplant-related complications and causes of Death

Transplant-related complications	PPCM group (n = 14)	Control group (n = 28)	p
Rejection:			
Treated rejections < 1-year post transplant	50% (n = 7)	50% (n = 14)	p = 0.5
Treated rejections > 1-year post transplant	71% (n = 10)	50% (n = 14)	p = 0.6
Infection rate	35.7% (n = 5)	64.3% (n = 18)	p = 0.07
CAV	50% (n = 7)	35.7% (n = 10)	p = 0.4
Death: Early all-cause mortality (< 1 year)	7% (n = 1)	21.4% (n = 6)	
Rejection	n = 0	n = 1	
Infection	n = 0	n = 2	p = 0.06
CAV	n = 0	n = 0	
Hemorrhagic complications	n = 1	n = 2	
Thromboembolic complications	n = 0	n = 1	
Death: Late all-cause mortality (> 1 year)	21.4% (n = 3)	46.4% (n = 13)	
Rejection	n = 1	n = 2	
Infection	n = 0	n = 3	
CAV	n = 1	n = 4	p = 0.07
Hemorrhagic complications	n = 1	n = 2	
Thromboembolic complications	n = 0	n = 1	
Neoplasia	n = 0	n = 1	
Unknown	n = 1	n = 0	

CAV: Cardiac Allograft Vasculopathy (Comparisons between groups for continuous variables were performed using the Student t-test or the Mann Whitney U test as appropriate).

Discussion

In this retrospective single-center study, we assessed post-transplant outcomes in a population of patients transplanted for severe HF in the setting of peripartum cardiomyopathy. Median follow-up was 7.7 years. We demonstrate upon our population that post-transplant mortality is significantly lower in patients transplanted for PPCM. Patients transplanted for PPCM did not display a significantly higher rate of transplant-related complications compared with control subjects matched for age and transplantation period.

Pre-transplant characteristics

In the pre-transplant setting, we significantly used more inotropes at the time of HT in PPCM patients compared with control subjects. The frequent need of medical intensive cardiovascular support in PPCM patients awaiting heart transplantation has also been demonstrated by others.[13] Importantly, potential deleterious cellular alterations related to Dobutamine have recently been pointed in PPCM patients,[21] and recent guidelines recommend a cautious use of inotropes for critically-ill PPCM patients.[22]

Data related to MCS in the management of PPCM patients are scarce.[23, 24] It seems however that MCS is an option for patients who deteriorate despite maximal therapy, in a strategy of bridge to transplantation or to recovery.[6,22-25] Noticeably, one major concern in the setting of long-term MCS in PPCM patients relates to a possibly higher risk of thrombotic complications in a prothrombotic condition such as the peripartum period.[26]

Medical management of HF might be considered as non-optimal in our population, particularly among PPCM patients, as only one half received beta-blockers and ACE inhibitors. Importantly, under-treated patients were, in both groups, those requiring inotropic and mechanical circulatory support.

Seven percent (7%) of patients had CRT/ICD implantation. Recent data suggest that CRT is crucial in the management of PPCM patients presenting with persistent systolic dysfunction. It has indeed been demonstrated a rapid and significant LV recovery under CRT in PPCM patients with severe systolic dysfunction despite optimal medical therapy.[27]

Patients Outcomes after Heart Transplantation

We assessed post-transplant outcomes in patients transplanted for PPCM. Again, we demonstrated a significantly lower post-transplant all-cause mortality in patients transplanted for PPCM, with a similar rate of transplant-related complications as compared with control subjects. Data on long-term outcomes after HT for PPCM are contradictory, reporting either favorable outcomes,[11] or higher rejection rates and poorer outcomes.[12-14] Current practice is however favorable to HT for PPCM. As we did, a long-term survey of a small cohort of patients transplanted for PPCM has also shown favorable outcomes.[23]

Limitations

The major limitation of our study is the small number of patients, prohibiting definitive conclusions. We arbitrarily adjudicated rejection in a binary way (present: yes, or no), which might therefore be considered as simplistic and of limited value.

Conclusion

We assessed long-term post-transplant outcomes in the setting of PPCM. Upon the studied population, we demonstrate a significantly lower long-term post-transplant mortality in patients transplanted for PPCM, with a similar rate of transplant-related complications as compared with control subjects. We show that heart transplantation for PPCM patients who did not significantly recover under maximal medical treatment remains appropriate. The overall impact of heart transplantation for PPCM is yet to be determined at a larger scale in well characterized population.

Author contributions

Conception and design of the research: Bouabdallaoui N; Acquisition of data: Bouabdallaoui N, Demondion P; Analysis and interpretation of the data: Marechaux S; Statistical analysis: Marechaux S; Writing of the manuscript: Bouabdallaoui N; Critical revision of the manuscript for intellectual content: Varnous S, Lebreton G, Mouquet F; Supervision: Leprince P.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

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

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High-Intensity Interval Training in Heart Transplant Recipients: A Systematic Review with Meta-Analysis

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Abstract

Heart transplantation (HTx) is considered an efficient and gold-standard procedure for patients with end-stage heart failure. After surgery, patients have lower aerobic power (VO_2max) and compensatory hemodynamic responses. The aim of the present study was to assess through a systematic review with meta-analysis whether high-intensity interval training (HIIT) can provide benefits for those parameters. This is a systematic review with meta-analysis, which searched the databases and data portals PubMed, Web of Science, Scopus, Science Direct and Wiley until December 2016 (pairs). The following terms and descriptors were used: "*heart recipient*" OR "*heart transplant recipient*" OR "*heart transplant*" OR "*cardiac transplant*" OR "*heart graft*". Descriptors via DeCS and *Mesh* were: "*heart transplantation*'' OR "*cardiac transplantation*". The words used in combination (AND) were: "*exercise training*" OR "*interval training*" OR "*high intensity interval training*" OR "*high intensity training*" OR "*anaerobic training*" OR "*intermittent training*" OR "*sprint training*". The initial search identified 1064 studies. Then, only those studies assessing the influence of HIIT on the post-HTx period were added, resulting in three studies analyzed. The significance level adopted was 0.05. Heart transplant recipients showed significant improvement in VO_2peak, heart rate and peak blood pressure in 8 to 12 weeks of intervention.

Introduction

Heart transplant (HTx) is considered the gold-standard treatment for patients with heart failure refractory to clinical therapy and/or intervention procedure.[1,2] The bicaval technique is currently used in surgical centers, consisting in cardiac denervation via complete dissection of the right atrial appendage and interauricular septum, saving a small portion of the left atrial appendage containing the pulmonary veins.[3] The major advantage of that technique over the others is atrial geometry preservation, lower transpulmonary gradient and lower incidence of post-surgical tricuspid regurgitation.[4]

Keywords

Exercise; Heart Failure/physiopathology; Life Style; Cardiac Rehabilitation; Meta-Analysis as Topic.

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Cardiac denervation causes cardiorespiratory (maximum oxygen uptake - VO_2max) and hemodynamic (heart rate - HR, cardiac output - CO and blood pressure – BP) controls to depend initially on the Frank-Starling mechanism (the law states that preload depends on venous return) and, later, on the concentrations of circulating catecholamines and ejection fraction, because of the lack of sympathetic and parasympathetic stimulation and baroreflex.[5–7] Therefore, transplant recipients have a lower VO_2max (70-80% of the value predicted for age as compared to healthy individuals),[8] high levels of HR, BP and vascular resistance at rest. However, physical exercise causes depressed increase in HR and BP, accompanied by an increase in vascular resistance.[9] This behavior is similar in conditions of submaximal and close-to-peak efforts, causing lower peak HR (HRpeak) and peak BP (BPpeak), with good reproducibility for VO_2peak. In addition, the post-exercise recovery is slow compared to that of healthy individuals of the same age group.[10,11]

The physiological changes previously mentioned and the immunosuppressive therapy cause cardiorespiratory and hemodynamic damage over time, and transplant recipients often develop diseases, such as systemic arterial hypertension (95%), hyperlipidemia (81%), vasculopathy (50%), kidney failure (33%) and type 2 diabetes mellitus (32%).[12,13] Thus, cardiac rehabilitation programs have been recommended since the first guidelines of the American Heart Association and American College of Sports Medicine. The major objective of such programs is to re-establish the patients' daily activities and to change their lifestyle, by adding activities that improve their physical, psychological and social conditions. Those activities should be structurally and continuously performed, focussing on developing the patient's major deficient variables.[14] The current guideline recommends that cardiac rehabilitation be composed partially of physical training, consisting of three to five sessions of continuous exercise (walking, jogging, cycling) per week, at mild to moderate intensity, for at least 30 minutes daily.[15,16] The sessions should begin and end with short warm-up and cool-down periods (5-10 minutes) at low intensity, respectively. Post-HTx physical exercise is safe and effective to promote significant improvement in cardiorespiratory, metabolic, hemodynamic, endothelial and morphological variables.[14,15]

However, studies of systematic review with meta-analysis conducted in patients with coronary artery disease,[16,17] type 2 diabetes mellitus[18] and metabolic syndrome[19] have shown that, in contrast to moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) enables patients to reach similar and/or superior benefits regarding the variables decompensated by those diseases.[20] The HIIT is

characterized by sets of short- or long-lasting exertion periods (30s – 4min) at high intensity (> 85% VO_2max), followed by short- or long-lasting recovery periods (30s – 4 min).[21]

Although some studies have shown greater progress with HIIT practice as compared to MICT, HIIT is still cautiously prescribed for individuals diagnosed with cardiovascular and metabolic diseases or those who underwent an organ transplantation. In addition, little is known about the dose-response ratio of the improvement in cardiorespiratory, endothelial and hemodynamic parameters caused by HIIT in HTx recipients. Thus, this study was aimed at assessing by use of a systematic review with meta-analysis whether HIIT can benefit those parameters.

Methods

A systematic review was conducted following the recommendations and meeting the criteria determined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline (PRISMA).

Search strategy

The search for articles in English was conduct in the PubMed, Web of Science, Scopus, Science Direct e Wiley databases up to December 2016. The terms and descriptors used in the searching process were selected based on the keywords available in previous studies and via DeCS and Mesh, respectively (Table 1). The terms identified in the literature were: "*heart recipient*" OR "*heart transplant recipient*" OR "*heart transplant*" OR "*cardiac transplant*" OR "*heart graft*". The descriptors of DeCS and Mesh were: "*heart transplantation*'' OR "*cardiac transplantation*". The words used in combination (AND) were "*exercise training*" OR "*interval training*" OR "*high intensity interval training*" OR "*high intensity training*" OR "*anaerobic training*" OR "*intermittent training*" OR "*sprint training*". Data extraction and all processes of search, selection and assessment of articles were performed in pairs.

Selection criteria

The inclusion criteria were as follows: a) randomized studies assessing VO_2peak (based on a maximum incremental test) and/or HRpeak as primary outcome; b) sample comprised exclusively of HTx recipients; c) studies assessing the HIIT effect; and d) studies with an intervention period longer than 4 weeks.

The exclusion criteria were as follows: a) studies without a control group; b) studies with acute analysis; and c) case studies.

Identification and selection of studies

Initially the references were reviewed based on the titles and abstracts. Then, the relevant articles according to the selection criteria were fully read and assessed regarding their methodological quality by use of the Testex scale.[22]

Data analysis

The variables analyzed (VO_2peak and HRpeak) were classified as continuous, and data were presented as mean and standard deviation. Data were combined to obtain the size of the general effect, 95% confidence interval (CI) and significance level, using the Review Manager (RevMan) software, version 5.3, Copenhagen: The Nordic Cochrane Centre. The HIIT group was compared with the control group (post-entrance) by use of weighted mean difference (WMD). For each result, heterogeneity (I^2) was calculated, adopting the fixed effects model. The significance level adopted was $p < 0.05$.

Results

Figure 1 shows the flowchart of the search and selection process of the articles included in this review.

In the initial electronic search, 1064 potentially relevant studies were identified. After reading their titles, 994 articles were ruled out because they did not have a primary outcome related to the objective of the present review. Then, after reading the abstracts of the remaining studies, 14 were excluded because they did not meet the selection criteria of this study. Three articles with a mean score regarding methodological quality of 10 points, according to the Testex scale, were included in the final analysis.

Major information regarding sample characteristics, methodology, qualitative analysis and results from the studies on HTx recipients are shown in chronological order in Tables 2 and 3. A total of 118 patients (90 men and 28 women) who had undergone HTx 5.3 ± 3.7 years before were included in the analysis of this systematic review, 60 in the HIIT group (49.3 ± 12.7 years) and 58 in the control group (53 ± 14.3 years), maintaining their usual activities. The HIIT sessions were conducted on cycle ergometers[23,24] and treadmills,[25] reaching an intensity of 80-100% of VO_2peak or 85-95% of HRmax. Such training sessions were performed three to five times per week for 8 and 12 weeks.

All studies included had VO_2peak as the major outcome of the analysis. Figure 2 shows the increased effect on VO_2peak [95%CI: 4.45 (2.15 - 6.75), p = 0.0001, N = 118] of HIIT (24.3 ± 6.5 – 28.0 ± 6.7 mL/kg.min; 15%) as compared to that of the control group (23.8 ± 6.0 – 23.2 ± 5.9 mL/kg.min; -2%).

Table 1 – Strategy of the bibliographic search in data bases and portals.

#1 "*heart recipient*"[tiab], OR "*heart transplant recipient*"[tiab], OR "*heart transplant*" [tiab], OR "*cardiac transplant*" [tiab], OR "*heart graff*" [tiab], OR"*heart transplantation*"[Mesh], OR "*cardiac transplantation*" [Mesh]	**#2** "*exercise training*" [tiab], OR "*interval training*" [tiab], OR "*high intensity interval training*" [tiab], OR "*high intensity training*" [tiab], OR "*anaerobic training*" [tiab], OR "*intermittent training*" [tiab], OR "*sprint training*" [tiab]
#1 AND #2	

Mesh: Medical Subject Headings

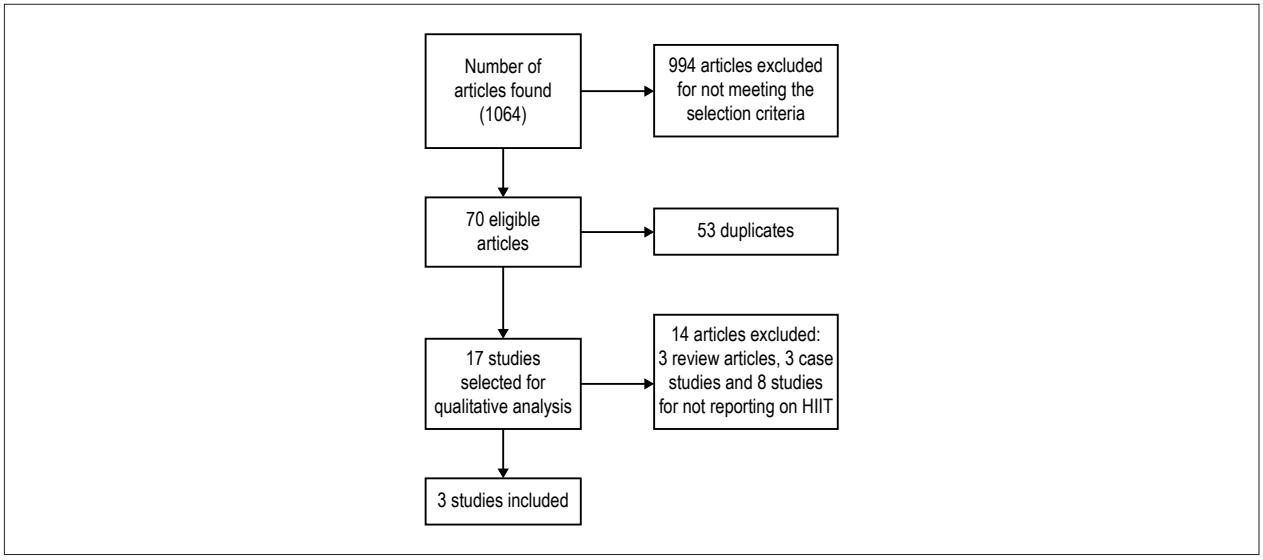

Figure 1 – *Flowchart of the search and selection process of the articles included in this review.*

Regarding HRpeak, based on the comparative analysis of the groups, two studies reported a favorable effect [95%CI: 0.74 (0.31 - 1.16) p = 0.0007, N = 46] in the HIIT group (Figure 3).

The studies that were not statistically analyzed (forest plot) showed, in the HIIT group, a positive effect on BP at rest and BPpeak (systolic and diastolic), brachial flow velocity, maximal muscle strength (1 RM), lean mass maintenance, and inflammatory markers. Some of those results are shown in Table 3. In addition, none of the studies reported a cardiovascular event and/or mortality associated with training, showing it to be a safe practice to be included in cardiac rehabilitation programs.

Discussion

The present systematic review with meta-analysis is the first to analyze the effect of HIIT on some health-related parameters of HTx recipients. The three studies included showed that HIIT improved VO_2peak by 15%. Such increase is greater than that found in two systematic reviews with meta-analysis that assessed the effect of different types of exercise[26] and of MICT[27] on the VO_2peak of those patients.

Although HIIT improves VO_2peak, sometimes it is not indicated for HTx recipients because they have chronotropic insufficiency developed from cardiac denervation.[28] That incompetence hinders HR at rest (increase) and during close-to-peak exercise (decrease - HRpeak), decreasing the chronotropic reserve values. Thus, according to the studies assessed in this review, 8 to 12 weeks of HIIT intervention can decrease HR at rest and increase HRpeak. High-intensity exercise (> 80%VO_2peak or > 85%HRmax) might have improved the cardiocirculatory function, stimulating the sinus node faster, facilitating faster and better responses on HR at rest and HRpeak.[29]

Although the literature shows an insufficient number of studies on HIIT and HTx recipients, that type of training can provide significant central and peripheral benefits to improve the clinical findings after surgery.[30] In addition, recent studies comparing the contribution of HIIT and MICT to the deficient variables of HTx recipients have shown the superior effect of HIIT.[31,32] Such results can indicate a possible change in paradigm regarding the recommendation of exercise prescription for HTx recipients. Thus, further studies are required to identify which training protocol better improves the deficient variables of those patients.

Conclusion

Our results showed that 8 to 12 weeks of cardiac rehabilitation with HIIT were sufficient to significantly increase HRpeak and aerobic power of HTx recipients (men and women).

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Perrier-Melo RJ, Costa MC; Acquisition of data, Statistical analysis and Obtaining financing: Perrier-Melo RJ; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Perrier-Melo RJ, Figueira FAMS, Guimarães GV, Costa MC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Raphael José Perrier-Melo, from Universidade de Pernambuco.

Ethics approval and consent to participate

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

Table 2 – Characteristics of the sample, methodological quality and major results of the studies assessing the effect of high-intensity interval training (HIIT) on heart transplant (HTx) recipients.

Study	GROUPS		HIIT protocol	Duration (weeks)	Major results	Testex											
	HIIT	CONTROL				1	2	3	4	5	6	6	7	8	8	9	10	11	12
Haykowsky et al., 2009	N = 22 17M/5F 57 ± 10 Post-HTx time = 5.4 ± 4.9 years	N = 21 18M/3F 59 ± 11 Post-HTx time = 4.4 ± 3.3 years	Cycle ergometer and treadmill **1-8 weeks** 5x/week 30-45 min: 60-80%VO_2peak **9-12 weeks** 3x/weeks 30-45 min: 60-80%VO_2peak 2x/weeks 20-25x (30s: 90-100% VO_2peak/1 min)	5x/week 12 weeks	12 weeks of training significantly increased VO_2peak (21.2 ± 7.3 - 24.7 ± 8.8 mL/kg/min, p = 0.003) of HTx recipients	+	+	+			+	+		+	+	+	+	+
Hermann et al., 2011	N = 14 12M/2F 53 ± 11 Post-HTx time = 6.8 ± 4.0 years	N = 13 10M/3F 47 ± 18 Post-HTx time = 7.0 ± 5.5 years	Cycle ergometer and staircase running 4 min: 80% VO_2peak / ½ min 2 min: 85% VO_2peak / ½ min 30 s: 90% VO_2peak/ ½ min	3x/week 8 weeks	The 8-week HIIT program significantly reduced SBP (p = 0.02) and significantly increased VO_2peak (p < 0.001) and endothelial action	+	+	+			+	+		+	+	+	+	+
Nytroen et al., 2012	N = 24 16M/8F 48 ± 17 Post-HTx time = 4.3 ± 2.4 years	N = 24 17M/7F 53 ± 14 Post-HTx time = 3.8 ± 2.1 years	Treadmill 4 min (85-95% HRmax) / 3 min (11-13 Borg SEP)	3x/week 8 weeks	HIIT significantly improved VO_2peak (p < 0.001) after 8 weeks of training	+	+	+			+	+		+	+	+	+	+

N: sample; M: male; F: female; HRmax: maximum heart rate; SEP: subjective effort perception; SBP: systolic blood pressure.

Table 3 – Major results of the hemodynamic and cardiorespiratory variables found in the studies

	HIIT		CON		
VARIABLES	**Pre**	**Post**	**Pre**	**Post**	**Studies**
	-	-	-	-	Haykowsky et al., 2009
HR at rest	76 ± 11	76 ± 7 (NS)	78 ± 7	78 ± 11 (NS)	Hermann et al., 2011
	85 ± 11	83 ± 11 (NS)	79 ± 11	81 ± 13 (NS)	Nytroen et al., 2012
	147 ± 18	154 ± 15 (0.06)	139.6 ± 19	139 ± 20 (NS)	Haykowsky et al., 2009
HRpeak	-	-	-	-	Hermann et al., 2011
	159 ± 14	163 ± 13 (< 0.05)	154 ± 15	153 ± 17 (NS)	Nytroen et al., 2012
	21.2 ± 7.3	24.7 ± 8.8 (0.03)	18.2 ± 5.9	18.2 ± 5.3 (NS)	Haykowsky et al., 2009
VO_2peak	23.9 ± 6.7	28.3 ± 6.1 (< 0.001)	24.6 ± 5	23.4 ± 5.7 (NS)	Hermann et al., 2011
	27.7 ± 5.5	30.9 ± 5.3 (< 0.001)	28.5 ± 7	28 ± 6.7 (NS)	Nytroen et al., 2012
	4 ± 6.8	5.3 ± 4.9 (NS)	3.2 ± 4	3.9 ± 5.2 (NS)	Haykowsky et al., 2009
FMD	8.3 ± 1.3	11.4 ± 1.2 (0.01)	5.6 ± 1	5.3 ± 1.7 (NS)	Hermann et al., 2011
	-	-	-	-	Nytroen et al., 2012
	-	-	-	-	Haykowsky et al., 2009
SBP	142 ± 17	127 ± 13 (0.02)	141 ± 15	142 ± 23 (NS)	Hermann et al., 2011
	130 ± 17	136 ± 16 (NS)	131 ± 20	129 ± 14 (NS)	Nytroen et al., 2012
	-	-	-	-	Haykowsky et al., 2009
DBP	85 ± 7	82 ± 9 (NS)	82 ± 9	84 ± 14 (NS)	Hermann et al., 2011
	80 ± 10	82 ± 9 (NS)	81 ± 15	82 ± 17 (NS)	Nytroen et al., 2012
	175 ± 26	177 ± 21 (NS)	172 ± 29	180 ± 27 (NS)	Haykowsky et al., 2009
SBPpeak	-	-	-	-	Hermann et al., 2011
	181 ± 33	211 ± 66 (< 0.05)	197 ± 22	191 ± 32 (NS)	Nytroen et al., 2012
	81 ± 9	79 ± 9 (NS)	81 ± 8	80 ± 9 (NS)	Haykowsky et al., 2009
DBPpeak	-	-	-	-	Hermann et al., 2011
	71 ± 15	80 ± 14 (< 0.05)	83 ± 14	91 ± 35 (NS)	Nytroen et al., 2012

HIIT: high-intensity interval training; HR: heart rate; FMD: flow mediated dilation of the brachial artery; SBP: systolic blood pressure; DBP: diastolic blood pressure; NS: nonsignificant.

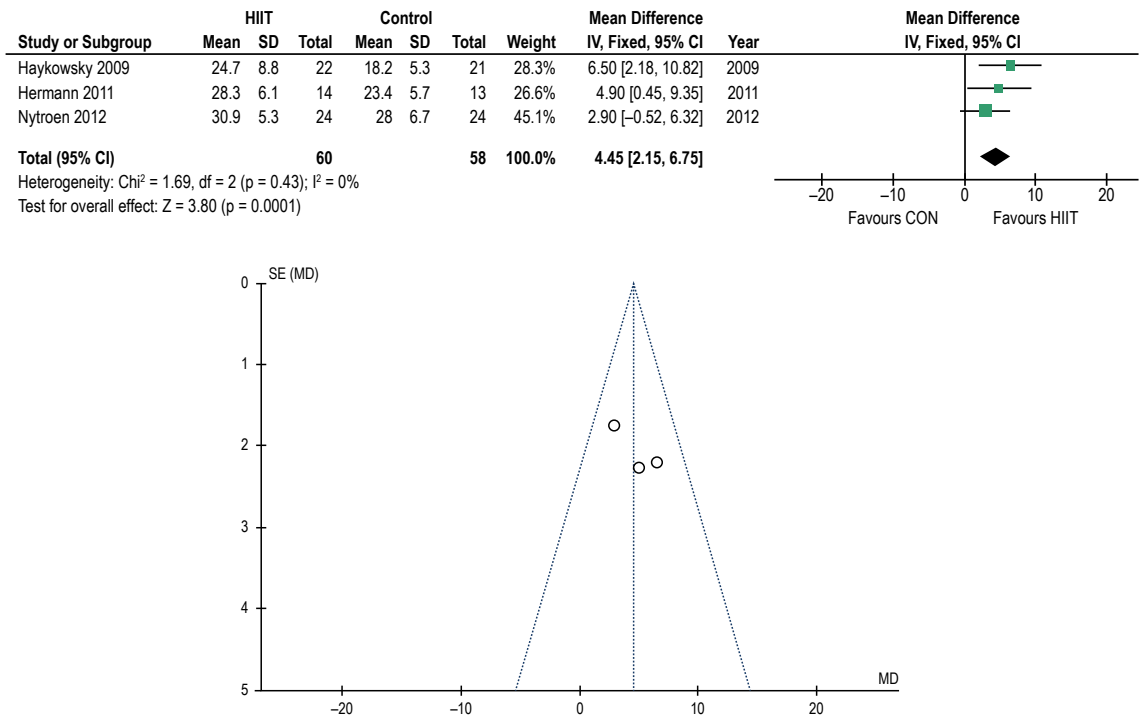

Figure 2 – *Forest plot (A) AND funnel plot (B) showing information about the effect of high-intensity interval training (HIIT) on VO_2peak.*

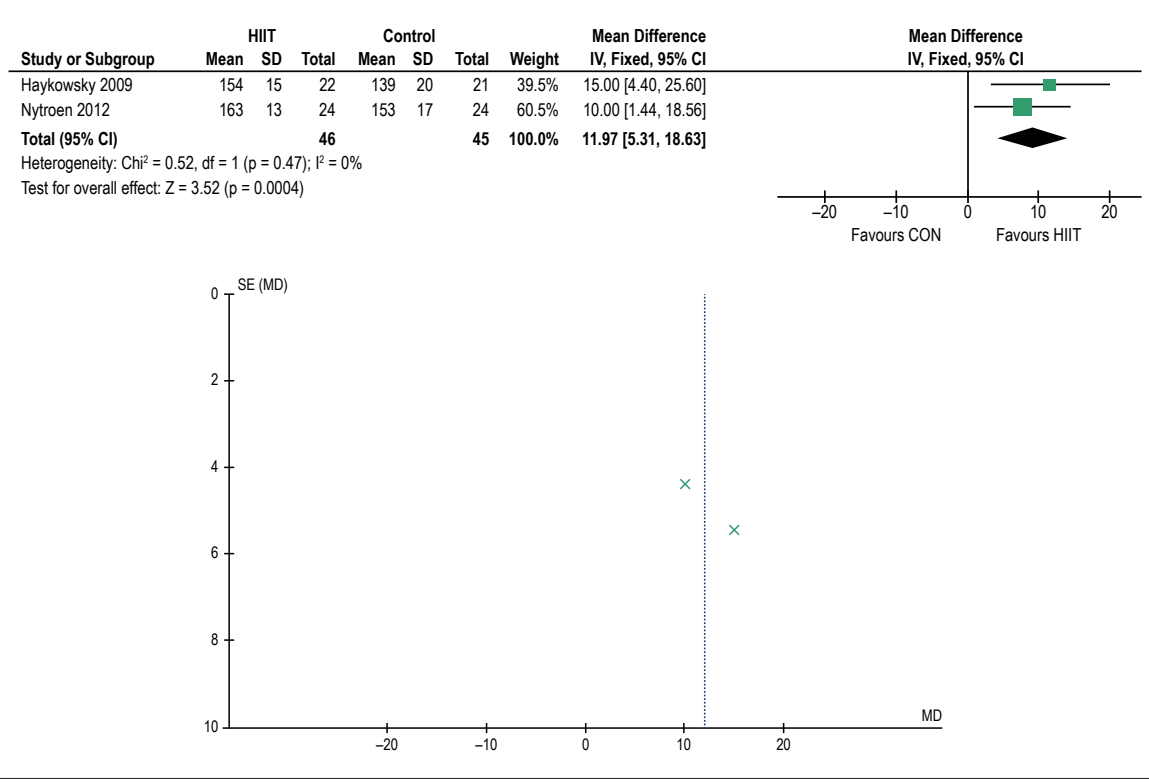

Figure 3 – *Forest plot (A) AND funnel plot (B) showing information about the effect of high-intensity interval training (HIIT) on peak heart rate.*

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Case 1/2018 - Young Male with Heart Disease Expressed Mainly as Ventricular Arrhythmia, Right Ventricular Dysfunction and Syncope

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The patient is a 36-year-old male with history of syncope since the age of 20 years and dyspnea since the age of 30 years. He reported marked worsening of those symptoms in the preceding 6 months from the last admission.

His symptoms began with episodes of syncope at the age of 20 years. On the investigation, a neurological cause was ruled out, and heart disease with cardiac dilatation and systolic dysfunction of the left ventricle was detected. The patient denied dyspnea at that time.

On ECG (2001), low-voltage complexes in the frontal plane and final conduction delay were observed.

The laboratory tests (April 2001) revealed: hemoglobin, 14.6 g/dL; hematocrit, 42%; leukocytes, 4900/mm^3 (31% neutrophils, 14% eosinophils, 1% basophils, 37% lymphocytes and 17% monocytes); platelets, 170000/mm^3; potassium, 4 mEq/L; sodium, 134 mEq/L; creatinine, 1 mg/dL; urea, 39 mg/dL; PT(INR), 1.0; aPTT (rel. times), 1.16.

Magnetic resonance angiography (April 12, 2001) of the internal carotid, anterior, middle and posterior cerebral and vertebral arteries was normal.

The echocardiogram (June 5, 2001) revealed the following: diameters of the aorta and left atrium, 32 mm, and of the left ventricle (diastolic/systolic), 65/52 mm; ejection fraction (Simpson), 40%; septal and posterior wall thickness, 10 mm; right ventricle, 23 mm. In addition, there were indirect signs of pulmonary hypertension, estimated as 40 mmHg. The left ventricle showed diffuse hypokinesia, and there was marked calcification of the mitral valve leaflets.

The exercise test (July 2, 2001) up to 70% of the predicted maximal heart rate showed no change suggestive of ischemia. The blood pressure curve had a depressed pattern. Isolated and paired ventricular extrasystoles were frequent, as were short-duration nonsustained ventricular tachycardia episodes. The test was interrupted because of exhaustion.

Keywords

Arrhythmias, Cardiac; Ventricular Dysfunction, Right; Syncope; Diagnostic Imaging; Defibrillators, Implantable; Catheter Ablation; Heart Transplantation.

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The management consisted in heart failure treatment and cardioverter defibrillator implantation, the cardiac findings being attributed to sequelae of myocarditis. His daily prescription was as follows: losartan 50 mg, amiodarone 400 mg, spironolactone 25 mg, and metoprolol succinate 75 mg.

His laboratory tests (Dec 2002) showed: cholesterol, 167 mg/dL; TSH, 6.8 μg/mL; free T4, 1.6 ng/mL; triglycerides, 43 mg/dL; glycemia, 90 mg/dL; uric acid, 4.3 mg/dL.

His new echocardiogram (March 2004) revealed the following diameters: aorta, 31 mm; left atrium, 34 mm; left ventricle (diastolic/systolic), 60/50 mm. His ejection fraction was 42%, and the septal and posterior wall thickness, 7 mm. The left ventricle was dilated and diffusely hypokinetic. The right ventricle was 31-mm thick, dilated and hypokinetic. The right atrium was dilated. Pacemaker electrodes were identified in the right chambers. Neither atrioventricular nor ventriculo-arterial valves had changes.

The patient developed dyspnea on maximal exertion, but no syncope. There was an episode of inappropriate shock from the cardioverter defibrillator in 2005, due to problems in the ventricular electrode, which was replaced. The disease course was uneventful until 2012.

Cardiopulmonary exercise test showed variation of heart rate from 57 bpm to 122 bpm, and of blood pressure from 120/80 mm Hg to 185/70 mm Hg, and maximal oxygen consumption of 28.4 mL/kg/min.

During that time, the echocardiography showed ejection fraction ranging from 44% (2001) to 39% in 2006, and of 28% in 2011, while the diastolic diameter of the left ventricle remained constant (65 mm in 2001, 66 mm in 2006 and 2011).

The patient was referred for surgical treatment assessment for heart failure, but, because he had few symptoms and good physical capacity, clinical and pharmacologic management was maintained (2012).

Computed tomographic angiography of the coronary arteries (February 5, 2014) showed neither calcifications nor obstructive lesions.

In February 2014, the cardioverter defibrillator delivered a shock, and the patient underwent radiofrequency ablation of the arrhythmia.

During the electrophysiological study (February 3, 2014), atrial stimulation triggered atrial fibrillation, which organized as flutter arising from the cavotricuspid isthmus, which was blocked. On the electrical mapping of the right ventricle, areas of scar and low-voltage late potentials were observed in the basal posterior and lateral walls, and radiofrequency pulses were applied, eliminating them.

During left ventricular epicardial mapping, a non-dense scar area was identified in the basal portion of the posterolateral wall, as were late potentials. No radiofrequency pulse was applied to those sites.

During the study, poorly-tolerated sustained ventricular tachycardia of epicardial origin was observed and reversed with electrical cardioversion. The procedure was successful.

In March 2014, the patient sought the emergency unit reporting three shocks of the implantable cardioverter defibrillator in the morning while walking on the beach, the first being preceded by tachycardia. The patient had bradycardia (40 bpm) while receiving intravenous amiodarone. He remained asymptomatic during hospitalization (March 3 to 14, 2014). The patient was discharged with the following prescription: 50 mg of losartan, 200 mg of amiodarone, 25 mg of spironolactone and 75 mg of metoprolol succinate, in addition to programming of the implantable cardioverter defibrillator to pacemaker capture threshold of 40 bpm.

His catheterization (September 29, 2015) revealed: mean right atrial pressure, 14 mm Hg; right ventricular pressures (systolic/initial diastolic/final diastolic), 28/06/14 mmHg; pulmonary artery pressures (systolic/diastolic/mean), 28/18/21 mmHg; pulmonary occlusion pressure, 18 mmHg; aortic pressures (systolic/diastolic/mean), 93/60/71 mmHg; cardiac output, 3.78 mL/min; pulmonary vascular resistance, 0.79 woods; arterial O_2 saturation, 99.1%; venous O_2 saturation, 70.4%.

A new electrophysiological study was performed (September 29, 2015). At the beginning of the procedure, the patient was in sinus rhythm, and had periods of atrioventricular block 2:1 and total atrioventricular block during the procedure. To desfibrillitor was summed a pacemaker elecatrode programmed to VVI pacing for 40 bpm. Electrophysiological mapping and voltage mapping of the right ventricle (endocardial) were performed, evidencing a scar area in the lateral region of the right ventricular outflow tract, extending to the tricuspid annulus. The extra stimuli induced type I ventricular tachycardia (VT1) with positive complexes in I and aVL leads, with negative superior axis in V_1 and no transition. The activation mapping during tachycardia evidenced mesodiastolic potential in the scar area of the lateral region of the right ventricular outflow tract. Radiofrequency application in that site terminated the VT1. In addition, the scar area was homogenized from the lesion to the tricuspid annulus. New tests with extra stimuli failed to induce arrhythmias.

The patient had no arrhythmia and only a few symptoms of dyspnea.

During a medical visit in January, 2016, the patient reported worsening of symptoms, with dyspnea occurring while taking a bath or walking less than two blocks, in addition to weight loss, although his appetite was preserved. His daily prescription was as follows: amiodarone 400 mg, spironolactone 25 mg, metoprolol succinate 50 mg, losartan 50 mg, levothyroxine 75 mcg, magnesium 400 mg, and furosemide 20 mg.

His physical examination revealed blood pressure of 100/80 mm Hg, heart rate of 60 bpm, regular perfusion, and signs of neither hypervolemia nor pulmonary congestion. His daily dose of losartan was increased to 75 mg.

The patient continued very limited regarding his daily activities, being placed on the waiting list for cardiac transplantation, which was performed on April 12th, 2016.

Clinical aspects

The patient had syncope episodes since the age of 20 years, and heart failure since the age of 30 years, undergoing cardiac transplantation at the age of 36 years.

Since symptom onset, heart disease with marked left ventricular dilatation and moderate dysfunction was detected. The exercise test revealed frequent ventricular arrhythmia. His syncope episodes were attributed to malignant ventricular arrhythmias, and a cardioverter defibrillator was implanted.

The patient remained stable and with no syncope episode for 11 years, when marked decrease in ventricular ejection fraction was detected.

At the age of 34 years, the cardioverter defibrillator delivered an appropriate shock during an episode of ventricular tachycardia, and the patient was submitted to an electrophysiological study, which triggered atrial fibrillation and the cavotricuspid isthmus was blocked. During the same procedure, areas compatible with scars and low-voltage late potentials in the basal posterior and lateral walls of the right ventricle were observed, undergoing ablation, which eliminated the potentials. However, during the procedure, poorly-tolerated sustained ventricular tachycardia of epicardial origin was observed and reversed with electrical cardioversion.

One year later, the patient had a new episode of tachycardia and appropriate cardioverter defibrillator discharge, undergoing then a new electrophysiological study, which evidenced a scar in the right ventricular outflow tract, extending to the tricuspid annulus. The extra stimuli triggered VT1 arising in the right ventricle, which was terminated with ablation with radiofrequency application.

A few months later, the patient was hospitalized due to NYHA functional class III heart failure, being placed on the waiting list for cardiac transplantation.

This is a case of heart disease, presenting as episodes of syncope due to ventricular arrhythmias and mild left ventricular dysfunction, despite left ventricular dilatation.

Some of the heart diseases that progress mainly with ventricular arrhythmias are as follows: Chagas heart disease, sarcoidosis, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.

Regarding Chagas disease, it is known to cause frequent arrhythmias, heart failure and sudden death, but the patient had neither a typical ECG nor a typical echocardiogram. His ECG showed neither right bundle branch block nor left anterior hemiblock, and his echocardiogram revealed neither diffuse marked hypokinesia nor an apical aneurysm. In addition, apparently there was neither positive epidemiology for that disease, nor predominance of right heart failure signs.[1,2]

In sarcoidosis, heart impairment is mainly characterized by atrioventricular blocks, malignant arrhythmias and sudden death, all caused by infiltration of the conduction system and myocardium by noncaseous granuloma. Some studies on pulmonary or systemic sarcoidosis have reported cardiac impairment in 5% of the patients and in up to 25% of postmortem examinations. However, imaging tests have shown impairment in up to 50% of the patients. Individuals with extracardiac sarcoidosis diagnosis confirmed on biopsy should

Anatomopathological Correlation

be asked about the symptoms of syncope, presyncope and heart palpitations. The ECG is mandatory in all patients with sarcoidosis, and if any abnormality is found, echocardiography and other imaging tests, such as magnetic resonance imaging and 14-fluorodeoxyglucose PET, can be useful.[3]

The present case could be perfectly diagnosed as sarcoidosis, except for the lack of extracardiac sarcoidosis findings, mainly pulmonary impairment, which is the most common finding.

Hypertrophic cardiomyopathy can cause syncope and sudden death. However, our patient showed no cardiac hypertrophy with at least one wall with minimal thickness of 15 mm.[4]

Arrhythmogenic ventricular cardiomyopathy is a genetic disease due to mutations in the genes encoding desmosine, characterized by fibrofatty infiltration of the right ventricular myocardium. The changes can begin in three regions of the right ventricle: ventricular inlet, outflow tract and tip.

The diagnostic criteria of arrhythmogenic ventricular cardiomyopathy were reviewed by a Task Force in 2010. They comprise electrocardiographic, echocardiographic, magnetic resonance imaging and right ventriculographic findings, family history, and histologic changes on endomyocardial biopsy.

On ECG at rest, the major criteria are: T-wave inversion in V_1 to V_3 in individuals aged over 14 years, in absence of right bundle branch block (QRS ≥ 120 ms), epsilon waves at the end of the QRS complex in V_1 to V_2. The minor criteria are: T-wave inversion in V_1 and V_2, in absence of right bundle branch block, or in V_4 to V_6; or T-wave inversion in V_1 to V_4 at that same age group with right bundle branch block, high-resolution ECG lasting ≥ 114 ms, and low-voltage late potentials (< 40 μV), at the end of the QRS complex, > 38 ms.

Regarding the presence of arrhythmia, a major criterion is the occurrence of sustained or nonsustained ventricular tachycardia with morphology of left bundle branch block with superior axis. The minor criteria are: ventricular tachycardia with QRS morphology of left bundle branch block with inferior axis or frequent ventricular extrasystoles > 500/24 hours.

On two-dimensional echocardiography, the major criteria are regional right ventricular akinesia, dyskinesia or aneurysm, accompanied by one of the following changes: ventricular outflow tract dilatation (≥ 32 mm) or with correction for body surface ≥ 19mm/m² in parasternal long-axis view; ≥ 26 mm or with correction for body surface ≥ 21 mm/m² in parasternal short-axis view or ejection fraction ≤ 33%. The minor criteria are: regional right ventricular akinesia or dyskinesia and one of the following changes: ventricular outflow tract dilatation ≥ 29 and < 32 mm or with correction for body surface ≥ 16 and < 19 mm/m² in parasternal long-axis view; or ≥ 32 and < 36 mm in parasternal short-axis view or with correction for body surface ≥ 18 and < 21 mm/m²; or ejection fraction > 33% and ≤ 40%.

On magnetic resonance imaging, the major criteria are akinesia or dyskinesia or dyssynchronous right ventricular contraction, in addition to one of the following changes: right ventricular end-diastolic index ≥ 110 mL/m² (male) and ≥ 100mL/m² (female); right ventricular ejection fraction ≤ 40%. The minor criteria are the motion changes already described as major criteria accompanied by right ventricular end-diastolic index ≥ 100 and < 110 mL/m² (male) and ≥ 90 and < 100mL/m² (female), or ejection fraction > 40% and ≤ 45%.

The family history has the strength of a major criterion when arrhythmogenic right ventricular cardiomyopathy is diagnosed in first-degree relatives both by meeting the above-mentioned criteria and by a positive biopsy or postmortem examination, or even when mutations related to the development of cardiomyopathy are confirmed. The minor criteria are: suspected disease in a first-degree relative that cannot be confirmed; sudden death probably due to that cardiomyopathy in a first-degree relative before the age of 35 years; or confirmed diagnosis in a second-degree relative.

Regarding endomyocardial histopathology, the major criterion is less than 60% of the myocardial area occupied by cardiomyocytes at morphometric analysis (or <50% if estimated) with fibrous replacement of the right ventricular free wall in at least two endocardial samples, with or without fatty replacement. The minor criteria comprise the same changes described above and a residual myocyte rate between 60% and 75% by morphometric analysis (or between 50% and 65% if estimated).[5]

In our patient, we had no access to the original ECG tracing, and, thus, could not use it as a diagnostic method.

However, on the electrophysiological study, ventricular tachycardia with morphology of left bundle branch block and superior axis was triggered, a major criterion for that disease diagnosis.

The echocardiogram evidenced a dilated and hypokinetic right ventricle, but provided no detail to confirm the diagnosis.

Magnetic resonance imaging could not be performed because of the presence of the cardioverter defibrillator, implanted on the beginning of the clinical findings, when syncope was attributed to arrhythmia, which, along with left ventricular dysfunction, would be sequelae of a previous episode of myocarditis.

Although magnetic resonance imaging is considered the gold-standard test for the non-invasive diagnosis of that disease, the false-positive rate has been very high.[6]

The therapy of choice for patients with arrhythmogenic right ventricular cardiomyopathy is cardioverter defibrillator implantation, because neither the use of antiarrhythmic agents nor ablation on electrophysiological study proved to be reliable alternatives to reduce sudden death.[7] (Desiderio Favarato, MD)

Diagnostic hypothesis: arrhythmogenic right ventricular cardiomyopathy. (Desiderio Favarato, MD)

Anatomopathological examination

The explanted heart weighed 576 g, lacked a large part of the left atrium, was very enlarged and ball-shaped, and had abundant subepicardial fat. There was a bulging area of imprecise limits in the right ventricular outflow tract, corresponding to an aneurysmal formation (Figure 1). The right ventricle was markedly dilated and exhibited a metallic lead (cardioverter defibrillator lead) anchored in its apex, focally adhered to the free margin of the tricuspid valve. Extensive, diffuse fatty

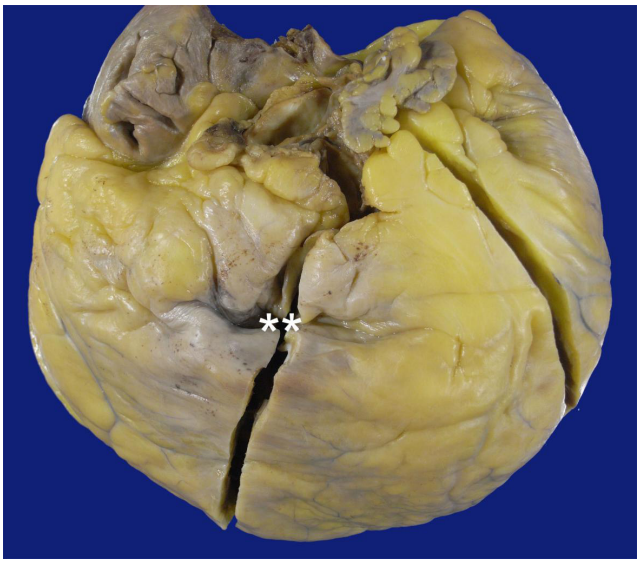

Figure 1 – *External view of the anterior face of the explanted heart. The epicardial fat is abundant, and a collapsed aneurysmal formation can be seen in the right ventricular outflow tract (asterisks).*

infiltration of the compacted portion of the right ventricular free wall in its inlet, apex and outflow tract was seen (Figure 2). The left ventricle showed moderate dilation and hypertrophy, with isolated foci of subepicardial fibrofatty infiltration (Figure 3). The microscopic exam confirmed the gross aspect of myocardial fatty infiltration, in addition to fibrosis (Figure 4). The most preserved areas of the myocardium showed hypertrophic cardiomyocytes, fibrosis foci, and interstitial mild lymphohistiocytic inflammatory infiltrate. The endocardium was thickened and whitish in the region of the aneurysmal formation of the right ventricular outflow tract. The heart valves and epicardial coronary arteries showed no abnormality. No cavitary thrombus was seen. (Luiz Alberto Benvenuti, MD)

Anatomopathological diagnosis: arrhythmogenic right ventricular cardiomyopathy. (Luiz Alberto Benvenuti, MD)

Comments

The patient is a 36-year-old male with heart disease characterized by syncope episodes since the age of 20 years, cardiomegaly and ventricular dysfunction. He underwent cardioverter defibrillator implantation in 2001. His electrophysiological study evidenced scars and late potentials in several regions of the right ventricle, ventricular tachycardia being triggered during the exam in 2015. Because of progression of the ventricular dysfunction and heart failure, the patient underwent cardiac transplantation in 2016. The anatomopathological exam of the explanted heart revealed arrhythmogenic right ventricular cardiomyopathy, with marked fatty infiltration of the compacted portion of that ventricle, with aneurysmal formation in the outflow tract. In addition, there was impairment of the left ventricle, which showed foci of subepicardial fibrofatty infiltration. Arrhythmogenic right ventricular cardiomyopathy, also known as arrhythmogenic dysplasia, is a primary genetic cardiomyopathy, most commonly of dominant autosomal inheritance. Several mutations related to the disease have been identified, usually in genes encoding desmosomal proteins, the most known being the genes of desmoplakin and plakoglobin. It can be associated with Carvajal syndrome or Naxos disease (palmoplantar keratoderma/wooly hair). Arrhythmogenic right ventricular cardiomyopathy is a frequent cause of sudden death in young individuals, being the major cause of sudden death associated with sports activity in Italy.[8] The disease can be restricted to the right ventricle, with severe arrhythmias, but, in the forms of progressive heart failure, as the present case, the left ventricle is commonly affected. Because both ventricles can be affected, many people advocate the use of the term 'arrhythmogenic cardiomyopathy'. The diagnosis of the disease is complex and multifactorial, and several elements should be considered, such as electrocardiographic changes, presence and type of arrhythmias, echocardiographic and magnetic resonance imaging changes, family history and even histological changes of the ventricular wall. Since 1994, and modified in 2010, there has been consensus about the diagnostic criteria, some considered major and others, minor.[9] Although invasive, endomyocardial biopsy is indicated in selected cases to assess myocardial histology, and myocardial fibrofatty infiltration is considered a major criterion when the residual myocardium corresponds to less than 60%, and a minor criterion when the residual myocardium corresponds to 60% to 75% of the sample.[10] (Luiz Alberto Benvenuti, MD)

Anatomopathological Correlation

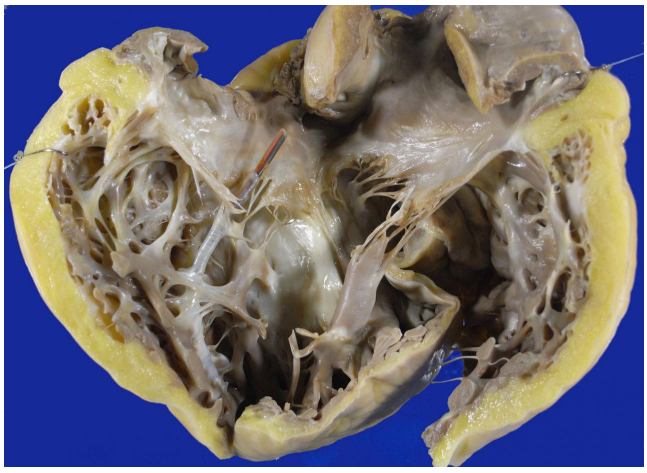

Figure 2 – *Right ventricular inlet. The cavity is markedly dilated, and the fatty infiltration of the compacted portion of the wall is evident, remaining only the trabecular musculature. Note the metallic lead of the cardioverter defibrillator in the ventricular apex.*

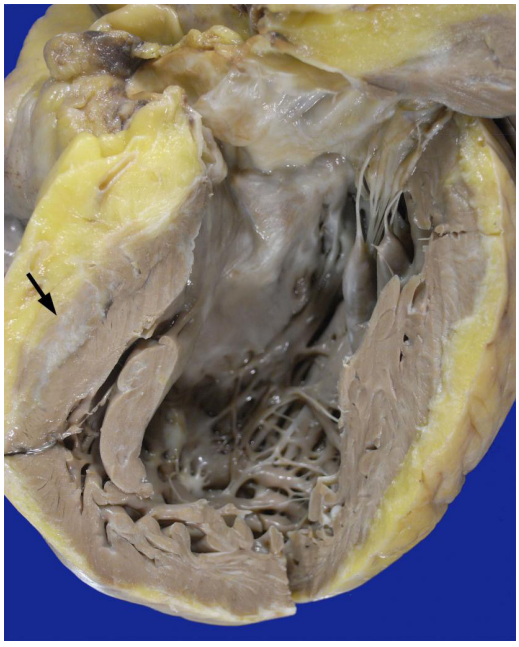

Figure 3 – *Left ventricular outflow tract. Note the moderate dilatation of the cavity, hypertrophy of the wall and area of subepicardial fibrosis (arrow).*

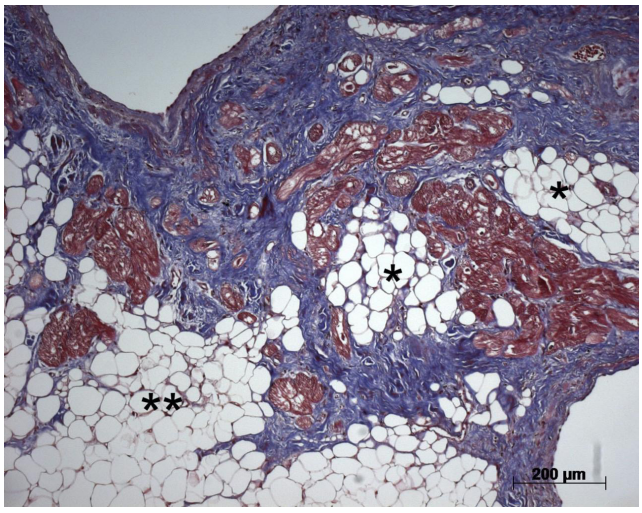

Figure 4 – *Histological section of the right ventricular inlet. The myocardium shows replacement with adipose cells (asterisks), and deposition of collagen (stained in blue) amid the cardiomyocytes (stained in red). Masson's trichrome staining.*

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A Prenatal Case of Arrhythmogenic Right Ventricular Dysplasia

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Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) is a heart muscle disorder that is characterized pathologically by fibrofatty replacement of the right (and sometimes left) ventricular myocardium.[1] In 30-90% of cases, it is an inherited condition, with an autosomal dominant form of transmission.[2] Disease expression is variable. In this article, we discuss a rare case of fetal ARVD and its difficult prenatal diagnosis, only confirmed at post-natal autopsy.

Case Report

A healthy 33-year-old woman (gravida 4, para 2) was referred to our tertiary center at 27 weeks' gestation because a previous fetal echocardiography showed an unexplained progression of congestive heart failure after tachyarrhythmia control with digoxin associated with amiodarone. The mother had been seen at another private clinic since 18 weeks' gestation, when the diagnosis was made of a structurally-normal fetal heart, premature atrial contractions, and supraventricular tachycardia with heart rate of 180bpm, treated with digoxin, initially.

The patient was then referred to our unit, and fetal echocardiography performed at 27 weeks' gestation showed sinus rhythm with ventricular premature contractions, evidence of global dilatation of all chambers with lower limit shortening fraction of the left ventricle (28%, normal >28%) and a functionally akinetic right ventricle (8%, normal >28%). The presence of a low tricuspid regurgitation velocity of 0.80 m/sec and a reversal flow at the ductus arteriosus level with pulmonary insufficiency suggested a somewhat lower right ventricular systolic pressure (Figure 1). There was fetal hydrops with ascites, pleural effusion, pericardial effusion, and skin edema. The umbilical Doppler indices and ductus venosus flow pattern were within normal ranges, but abnormal umbilical venous pulsations were present. The cardiovascular profile score[3] was six. Heart failure became worse in the subsequent days, and at 28 weeks' gestation, the patient was hospitalized to investigate other possible causes of fetal heart failure, such as infections, syndromes, and genetic disorders.

Keywords

Arrhythmogenic Right Ventricular Dysplasia; Fetus / echocardiography; Prenatal Care; Pregnancy.

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The patient's family medical history was unremarkable, and there were no clinical or serological signs of infection. This patient had experienced fetal death at 20 weeks' gestation in her first pregnancy , and her second pregnancy resulted in miscarriage. In the same year, her third pregnancy evolved to biventricular dysfunction, fetal hydrops, and intermittent tachyarrhythmia, again interpreted by another team as supraventricular. Transplacental medication with digoxin was tried at 25 weeks' gestation but did not prevent heart failure progression. At 29 weeks' gestation, the neonate was delivered by cesarean delivery and lived for 14 hours. Fetal autopsy was not performed.

Considering the previous fetal losses, the similarities of the medical history of this pregnancy with the third pregnancy in terms of arrhythmias and the striking finding of right ventricular akinesia in the current fetal echocardiogram, an inherited condition was suspected, and the diagnosis of arrhythmogenic right ventricular dysplasia was considered. At 29 weeks' gestation, diminished fetal movement was observed in the ultrasonographic examination and a cesarean delivery was indicated. A 1,790g male stillbirth was delivered, and histological examination revealed moderate ascites and pleural effusion. Cardiac chambers were greatly dilated, the right ventricular walls were very pale and thin, the left ventricle had an aneurysm at the apex, and the right ventricle showed fibrous tissue and clusters of adipocytes interspersed with myocardial fibers.

Discussion

Marcus et al.,[4] described an entity called arrhythmogenic right ventricular dysplasia, characterized by localized deficiency or fibrofatty tissue replacement of the right ventricular myocardium, in the so-called "triangle of dysplasia" (inflow, outflow, and apical regions of the right ventricle), resulting in functional and morphological changes that provide a substrate for both arrhythmias and heart failure,[4] different from Uhl's disease, which is characterized by a right ventricle wall as thin as a paper and almost devoid of muscle fibers, even though confusion between the two terms has occurred in recent years. Moreover, arrhythmia is more frequent in ARVD, which usually has a right ventricular origin, ranging from frequent premature ventricular contractions (PVCs) to ventricular tachycardia[5] (VT). Even though our patient had some of the cardinal features of ARVD[6] (RV dilation/dysfunction and arrhythmia), the diagnosis was only confirmed after the histological findings, as fetal presentation of this disease is rare and literature covering this scope is scarce.[2]

Since ventricular arrhythmias are much more common in ARVD, the diagnosis of supraventricular tachycardia in the third and current pregnancy before referral to our unit was probably misleading, with consequent drug treatment (digoxin) that was not the ideal one. Despite the chosen drug, it seems that in

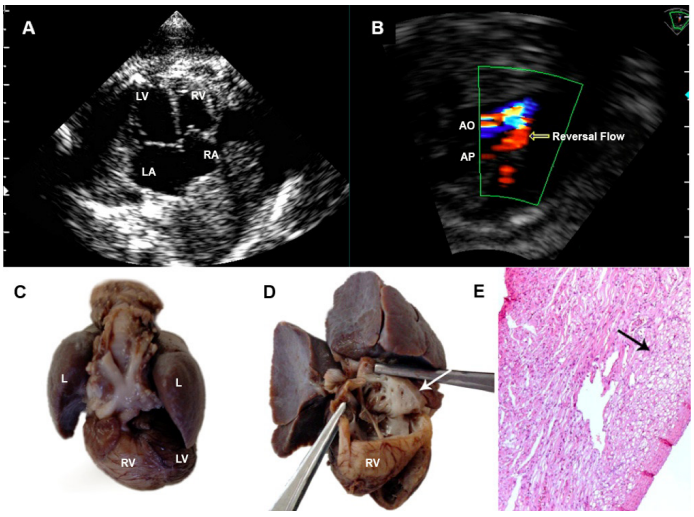

Figure 1 – *Fetal echocardiography and anatomic features observed at the autopsy. (a) Four-chamber view at 36 weeks showing cardiac enlargement and left atrial dilatation. (b) Three-vessel view showing reversal flow at the ductus arteriosus level (arrow). (c) Heart and lungs with pale, enlarged right ventricle. (d) Right ventricular wall is thin and almost devoid of muscle fibers. (e) A hematoxylin-eosin stain demonstrating absence of myocardial fibers and fibrofatty tissue replacement of the anterior free wall of the right ventricle. RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle; L: lungs.*

this case the evolution to cardiac failure and death could not be prevented, but we should be very careful when analyzing fetal rhythm, since a correct prenatal diagnosis is crucial for selecting the correct antiarrhythmic treatment and improve chances of survival. This article not only teaches us about the importance of echocardiographic ventricular function evaluation, especially in case of ventricular arrhythmia, but also highlights ARVD as a possible diagnosis in the fetus in early pregnancy.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Lopes LM; Acquisition of data: Lopes LM, Pacheco JT, Schultz R; Writing of the manuscript: Lopes LM, Pacheco JT; Critical revision of the manuscript for intellectual content: Lopes LM, Schultz R, Francisco RPV, Zugaib M.

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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Cardiac Lymphoma: A Rare Cause of Acute Heart Failure with Restrictive Physiology

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A 74-year-old woman with a history of membranous glomerulonephritis and a recent diagnosis of mediastinal adenopathy was admitted to the emergency department with acute heart failure. She complained of progressive dyspnea and weakness in the last week. Physical examination revealed hypotension, tachypnea, jugular vein distention, and desaturation. The most relevant laboratory findings were: anemia, lymphocytopenia, lactic acidosis, and increased lactate dehydrogenase. An electrocardiogram showed rapid atrial fibrillation and low-voltage QRS complexes. An echocardiogram revealed severe pericardial effusion and diffuse heterogeneous thickening of the ventricular and atrial walls. The patient required mechanical ventilation and inotropic support. Therapeutic pericardiocentesis was performed without clinical improvement. Cardiovascular magnetic resonance imaging (CMR) showed septal bounce (compatible with restrictive physiology) and a heterogeneous isointense mass surrounding the ventricular and atrial walls with late gadolinium enhancement of the myocardium and hypoenhancement of the tumor (Figure 1), compatible with primary cardiac lymphoma.

Keywords

Cardiovascular Diseases; Lymphoma; Heart Failure / physiopathology; Magnetic Resonance Imaging.

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A diagnosis of large B-cell lymphoma was confirmed by flow cytometry of the pericardial fluid. The patient died before starting chemotherapic treatment.

Secondary involvement of the myocardium in patients with systemic lymphoma is relatively frequent (around 30% in disseminated non-Hodgkin lymphoma) whereas primary cardiac lymphoma is rare (1-2%). We present a case of acute heart failure with restrictive physiology secondary to cardiac lymphoma. In our experience, CMR was key to the final diagnosis.

Author contributions

Conception and design of the research: Garagoli F, Guzzetti E, Lillo E, Lucas L, Belziti C; Acquisition of data: Garagoli F, Guzzetti E, Lillo E; Analysis and interpretation of the data: Garagoli F, Guzzetti E, Lucas L; Statistical analysis: Garagoli F, Guzzetti E, Belziti C; Critical revision of the manuscript for intellectual content: Lucas L, Belziti C.

Potential Conflict of Interest

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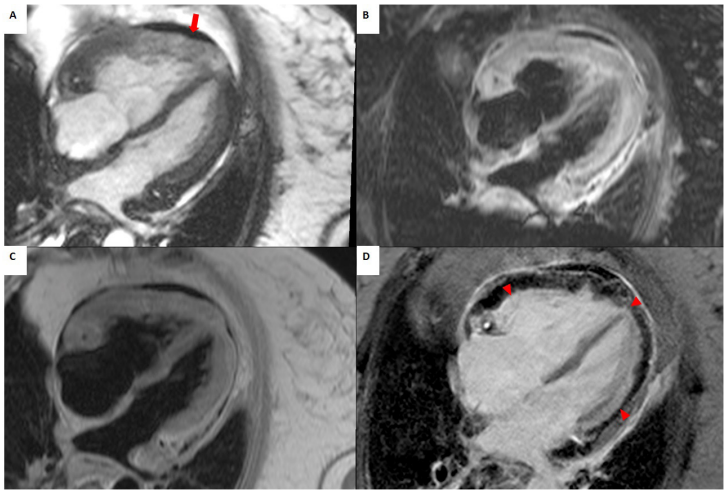

Figure 1 – *a) Steady -state free precession (SSFP)-cine imaging showing an ill-defined, heterogeneous myocardial mass involving all cardiac chambers, particularly the right ventricle wall and right atrioventricular groove, as well as moderate pericardial effusion (solid arrow). b) T2-weighted magnetic resonance imaging showing hyperenhancement of the mass, compatible with edema. c) T1-weighted sequence showing isointensity of the heterogeneous mass. d) T1-weighted inversion recovery showing late gadolinium enhancement of the myocardium (compatible with myocardial fibrosis) and hypoenhancement of the mass, marking the limit between myocardium and tumor (arrowheads).*